THE EVOLVING TREATMENT OF ANKYLOSING SPONDYLITIS
THE EVOLVING TREATMENT OF ANKYLOSING SPONDYLITIS

ACADEMISCH PROEFSCHRIFT

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geboren te Kampen
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CHAPTER 1

Introduction

1. General introduction.
2. History of the disease ankylosing spondylitis.
3. History of therapy in ankylosing spondylitis.
4. Objectives and outline of this thesis.
1 GENERAL INTRODUCTION.

The subject of this thesis is the disease ankylosing spondylitis (AS) and particularly various aspects of drug therapy in AS.

AS is the prototype of a group of diseases, called spondyloarthritides, which have inflammation of the spine and sacroiliac joints as common features. Other diseases belonging to spondyloarthritis (SpA) are psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and a subgroup of juvenile idiopathic arthritis. In the Netherlands AS is often called “ziekte van Bechterew”.

AS is characterised by a chronic sterile inflammation of joints and entheses (entheses are the sites of attachment of tendons, ligaments and joint capsules). The inflammation in AS is localised primarily in the sacroiliac joints and spine, but peripheral joints can be involved as well. The peripheral arthritis is usually an asymmetric oligoarthritis of the lower extremities, including the hips. In contrast to rheumatoid arthritis the inflammation does in a lesser degree lead to destruction (erosions) of bone, but can lead to local ossification. This hyperostosis can lead to ankylosis and in some cases to the characteristic bamboo spine. This has given the disease its name: the Greek \textit{ankylos} means stiff/curved and \textit{spondylos} means vertebra/spine.

In mid-Europe AS affects 0.3-0.5 \% of the population and the prevalence for SpA is 1-2\% [1]. The Human Leukocyte Antigen (HLA) B27 is the most important genetic factor linked to the disease. In more than 90\% of Caucasian AS patients HLA-B27 is present. This explains the familial aggregation of AS and the higher prevalence of AS in the northern countries, where HLA-B27 is more prevalent [2]. Men are affected more often than women (ratio 2-3 to 1) [1, 3].

The pathophysiology of the disease is not fully clarified. Probably, in subjects with genetic susceptibility, auto-inflammatory processes are triggered by environmental factors (for example enteral or urogenital microbes and smoking), mechanical stress and/or HLA-B27 binding peptides [4-6]. Laboratory investigation can show raised acute phase reactants (erythrocyte sedimentation rate (ESR) and C-reactive protein), but often does not [7]. Diagnostic for AS are radiological changes of the sacroiliac joints: sclerosis, erosions and ankylosis. Later in the disease process similar changes can be seen in the rest of the spine at the corners of the spinal corpora, in the intervertebral and costovertebral joints.

In most cases the disease starts in young adults (<30 years), but is diagnosed several years later. General symptoms, like anaemia and tiredness, often occur. The inflammation causes pain and stiffness in the buttocks, the lower back and other parts of the spine. The complaints are worst in the late night and early morning and improve with moving and not with rest. Inflammation and ankylosis can cause limitation of mobility of the spine and thorax. After many years flattening of the lumbar lordosis and increase of the thoracic kyphosis can occur; which produce the characteristic curved and immobile posture. In addition, this posture becomes aggravated by flexion contractures in the hips in case of hip arthritis. Some AS patients can not stand erect, nor see well straight forward (figure 1). The severity of AS can range from mild disease and limited radiological changes to a severe disease with persisting disease activity and disability. Pain and structural damage can cause limitation of mobility, functional impairment, reduction in well being and can lead to absence and disability at work [8]. Predictors of functional impairment are: worse initial features of the disease, older age, smoking, uveitis and peripheral joint disease, especially hip involvement [6, 9-12].

Patients with AS have an increased risk of mortality [10]. In a review the standardized mortality ratio was approximately 1.7 (range 1.5-1.9), which for the most part could be ascribed to cardiovascular diseases [13].

In AS extra-spinal and extra-articular manifestations are observed. AS is associated with skin disease (psoriasis), inflammatory bowel disease (ulcerative colitis and Crohn’s disease) and preceding enteral or genitor-urinal infections (reactive arthritis). One third of the patients with AS experience attacks of inflammation of the eye (acute anterior uveitis) [14]. Problems of the heart (conduction disturbance and aortic root anomaly) and sometimes apical pulmonary fibrosis do occur. The incidence of osteoporosis and vertebral fractures is increased, as well as the incidence of cardiovascular disease [15-18].

In the next paragraph, the historical context of the disease AS will be discussed, including the evolution towards the recognition as a separate disease. In the third paragraph of the introduction the therapy of AS in the past and present will be discussed. At the end of the introduction an outline of this thesis is given.
Figure 1. Progression of ankylosing spondylitis in a patient with severe disease. By 1957, 10 years after the onset of disease, he has very limited extension of his spine as evidenced by the loss of lordosis and exaggeration of thoracic kyphosis (spine is fusing in flexion). By 1967, he is unable to extend his cervical spine. He developed contractures at the knees and hip disease (note the cane) leading to hip replacement in 1973 with subsequent improvement of posture. (ACR Slide Collection)

2 HISTORY OF THE DISEASE ANKYLOSING SPONDYLITIS.

The evolution of ankylosing spondylitis (AS) towards a separate disease entity is described in this paragraph, based on old descriptions, pathophysiological findings in animal and human skeletons and new scientific developments like the invention of X-rays and DNA-sequencing, that unravelled the HLA-B27 association. Classification criteria for AS were developed and later AS was embedded in the broader spectrum of axial spondyloarthritis (SpA).

Old literature and art
Luke, one of the four evangelists, was a Greek physician who wrote around Anno Domini 75 in verse 13 of the Gospel ascribed to him: “Ende siet / daer was eene vrouwe / die hadde eenen geest der kranckheyt achtien jaren / ende sy was krom / ende en konde niet wel op-sien” [19].
Caelius Aurelianus, a Roman physician in the fifth century, described a patient in “De Ischiadicis et Psosadicis”: The patient is seized by pain in the nates, moves slowly, and can only bend or stand erect with difficulty [20].

In old literature and visual arts, people with increased kyphosis were described or depicted and some very interesting publications have covered this subject [21-23]. To some of these cases the diagnosis ankylosing spondylitis (AS) could apply, but without further details a definite diagnosis can not be confirmed. Probably more common in the past were other diseases like infections (for example Pott's disease caused by tuberculosis), rickets, congenital and traumatic deformities and spondylotic kyphosis. In addition, other diseases and some rare phenomena can irreversibly stiffen the spine, for example the Japanese “porter disease” (Lastenträgerkrankheit) in persons who have carried heavy loads on their back for a long time [24].
More certainty about the diagnosis can be obtained by the examination of the remains of old skeletons. Not only human skeletons were searched for signs of AS, but also the remains of animals.

Paleopathology in animals
Many fossils dated 30 to 50 million years ago were investigated. Sacroiliac joint erosions or fusion, suggestive for spondyloarthritis, were seen in 13-50% of three affected mammalian orders (like rhinocerotidae, to which the rhinos belong). Hypothesised was that persistence of this disease may perhaps represent evidence for some unknown host benefit [25]. In addition, more recent skeletons, extending from the largest mammal that ever lived (the whale) to the one of the smaller marsupials, were also investigated for AS. Syndesmofytes and zygapophyseal joint fusion were found in cetacean (for example dolphins), erosions of zygapophyseal vertebral joints in a blue whale and sacroiliac joint fusion in a mouse-like marsupial [26]. Although a systemic inflammatory disease seems more likely than an infection
when polyarticular and symmetrical changes are seen, it remains doubtful what the relation is between these changes in animals and human AS. Even more interesting are studies performed in human skeletons.

**Paleopathology in humans**

Interesting studies were done in remains of Egyptian pharaohs. Calcification of spinal ligaments and ankylosis of the sacroiliac joints, suggestive of AS were seen in mummies of Amenhotep II (reigned 1438-1412 BC), Ramses II (reigned about 1279-1213 BC) and, interestingly, his son Merenptah (reigned 1213-1203 BC) [27]. Ramses’s mummy also showed postinflammatory hip disease. His cervical spine showed a post-mortem fracture of C5-6, probably produced intentionally to straighten his neck before mummification. The mummy of Thutmose I (around 1500 BC) showed an ankylosed spine, caused by another disease with hyperostosis: diffuse idiopathic skeletal hyperostosis (DISH or Forestier’s disease, which is described below) [28]. Other authors stated that the findings in the skeletons of most of the mentioned pharaohs were also more suggestive for DISH than for AS [29, 30].

Bristol investigators reviewed 560 adult skeletons with at least part of the spine intact, gathered from recently excavated sites in England [31]. Most of them (424) dated from the Middle Ages and in about half of the skeletons osteophytes were identified. Bilateral sacroilitis was seen in only one case and unilateral in another case, both with peripheral erosive joint changes more suggestive of another spondyloarthritic than AS. Thirteen specimens showed spinal signs of DISH. Hence, DISH seemed more prevalent despite the fact that people lived shorter and often suffered from hunger in that period, whereas nowadays DISH is seen in middle-aged and older people and related to obesity and hyperglycaemia [32].

However, the examined skeletons probably did not represent the average society, because for example, the remains of seven early medieval bishops were included. The suggestion that a “monastic way of life” may have predisposed to DISH, was also supported in the study of the remains of presumably clergymen and high-ranking citizens buried between 275 and 1795 in the abbey court in the city of Maastricht. The mean age at death for adults was 37 years and in 40% DISH was diagnosed [33].

More indicative for AS were the skeletons of Cosimo de Medici (1389-1464), a banker in Florence, showing ossification and bridging of the vertebral ligaments and that of his son Piero, showing sacroiliac ankylosis [22, 34]. These old skeletons were examined by inspection and radiology, but more recently newer techniques became available.

**HLA-B27 in historical skeletons**

Human Leucocyte Antigen (HLA) B27 is a strong genetic risk factor for AS. Investigated were remains from a church in La Neuville (Switzerland) of a male aged about 62 years living between the year 1300 and 1700. His spine showed extensive syndesmofytes, ossified interspinal ligaments and ankylosed facet joints, suggestive of AS. B27 sequence-specific PCR (polymerase chain reaction) of DNA extracted from two parts of the femur showed confirmative results [35].

The skeleton from a church in Visby (Sweden) showed calcification of the vertebral ligaments and fusion of intervertebral, costovertebral and sacroiliac joints, compatible with AS. The man lived between the years 900 and 1300. HLA-B27 sequences were found in DNA, extracted from 20 mg of bone powder from several samples [36].
In both studies extensive precautions were taken to minimise the risk of contamination. For example, several control samples were studied and genetic typing was done as well of all researchers involved in the first study.

**Early clinical descriptions of AS**


Commonly accepted as the first most extensive description of AS are the reports of Bernard Connor, an Irish medical student attending several medical schools in France and later personal physician of the King of Poland. He described in 1693 a skeleton, which was found in a graveyard, in his letter to the British Royal physician Sir William de Waldegrave (figure 2) [37, 38]. “All these bones, which naturally are separate and distinct from one another were here so straightly and intimately joined, their ligaments perfectly bony and their articulations so effaced, ... The root of the ribs made by one equal smooth and plain superficies with the vertebrae and their apophyses... But when I had sawed two of the vertebrae asunder at the commisure I found that this uniting did not enter above two lines deep... their middles were separated as they usually are and touched each other only at their edge...” [39].

Somewhat amusing are his aetiological ideas: “As to the crooked and bending shape of the skeleton it is reasonable to suppose that it proceeded from the first formation of the foetus in the womb, from the eggs not having sufficient room, or being accidentally pressed by some abscess in the womb or elsewhere, so that the carina of the backbone instead of running straight, was bent into a circle and kept the same figure when at full growth...” [20].

**Descriptions of AS in the nineteen’s century**

Carl Wenzel published in 1824 in Frankfurt-am-Main (Germany) findings in pathological anatomical specimens of spines with spondylotic and spondylitic ankylosis [37]. Patients with pain, stiffness and ankylosed spine were described for example by Lyons (1831), Hare (1849), Wilson (1856), Adams (1857) and Von Thaden (1863) [20].

Brodie described a patient in 1850 having gonarthritis and iritis as well, which might nowadays probably be classified as reactive arthritis. The two cases of Brodhurst (1858) had preceding gonorrhoea [20]. Several physicians published clinical pathological findings, suggestive of AS from the eighties [Fagge 1877, Sturge 1879] [20].

However, in Garrod’s textbook from the year 1890 rheumatic fever was the most important subject and particularly gout was seen as a separate disease [40]. The difference between osteoarthritis, rheumatoid arthritis (RA) and AS was not yet clear. RA was seen as a chronic sequel of rheumatic fever and its “development or recrudescence is greatly favoured by exposure to damp and cold: Rheumatic fever and RA can involve all joints, also the symphysis pubis, sacroiliac synchondroses and the joints of the lumbar spine.”

In the last decade of the century the most well-known early descriptions of AS were published by Bechterew (in 1892-99), Strümpell (in 1884-97) and Pierre Marie (in 1896).

Wladimir Michailowitsch Bechterew (1857-1927) was a Russian neurologist and psychiatrist. Some are convinced he was murdered, commissioned by Joseph Stalin several days after he had diagnosed Stalin as having paranoid psychosis [41]. Bechterew described patients with “Steifigkeit der Wirbelsäule und Verkrümmung” and several neurological signs like paresthesias, neuralgia and muscle weakness. He assumed that the primary lesion was located in the meninges, descending from the neck to caudal. It is not clear why in several countries especially the name of Bechterew was associated with the disease AS, because the cases he described where not the most classic ones of the disease as we know nowadays [42].

Adolf Strümpell (1853-1925) was a German neurologist. He described an illness in which, very gradually and without pain (!), from caudal to cranial the entire vertebral column and hips became ankylosed completely [43].

Pierre Marie (1853-1940) was a French neurologist and pupil of Charcot. He described six male cases with spines “rigide comme un baton”, supplemented with photographs and analysis of costovertebral specimens. The cases described by Strümpell and Marie were soon considered to be caused by the same disease (the Strümpell-Marie type of arthropathy) [22, 43].

**Figure 4.** Correction with pelottes (Barwell).
In the Netherlands in 1898 two cases from the Amsterdam clinic of neurology were published in a Dutch magazine for psychiatry and neurology by Jacobi and Wiardi Beckman [44]. In 1899 the Amsterdam family practitioner Martein Menko presented for the society of physicians in Amsterdam a case of “spondylosis rhizomelica”, illustrated with photographs. He also quoted a case of André Leri in which the guard of the pathology room was frightened by the sudden sight of a corps in sitting position. After the spine was dissected, the widow was surprised by the lying position of the corps, while she just ordered to make a coffin particularly constructed for a sitting position [44].

Was the medical world at the beginning of the new century ready to accept AS as a distinct disease?

**AS in the first half of the twentieth century: the invention of X-rays.**

In addition to Bechterew’s disease several other names were used for illnesses that were initially not always thought to be identical, like kyphosis heredo-traumatica, syndesmitis ossificans, spondylose rhizomélique, chronic ankyllosing inflammation of the large joints and vertebral column, Marie-Strümpell disease, rheumatoid spondylitis, spondylitis deformans and spondylarthritis anklyopéotica. In 1905 the assumed differences between these diseases were also discussed in the Netherlands by W Huet, neurologist/psychiatrist in Haarlem [45].

In 1903 Eugen Fraenkel, a German pathologist, differentiated AS from osteoarthritis by anatomic dissection. He also noted the involvement of the costovertebral joints in AS [43].

Gradually X-rays became available for diagnosis and differentiation. The German Wilhelm Röntgen, who grew up in the Netherlands, developed X-rays in 1895. Already in 1897 spondylitis was studied radiographically [43]. In 1934 Walter Krebs, a German radiologist, pointed out the significance of radiologic examination of the sacroiliac joints and of signs of periostitis on the pelvis [43].

Ralph Pemberton (USA) distinguished in his textbook (1929) two types: Bechterew and Marie [46]. “However, there seems to be no adequate reason to regard the spondylitides as representing anything more than the extension of the atrophic or hypertrophic type of arthritis to the vertebral column and associated structures.” In the 1938 edition, Osler’s textbook (USA) dealt with rheumatoid spondylitis as one form of chronic arthritis which included both osteoarthritis and RA, both included under the term “arthritis deformans” [47].

In 1936 Henri Tempelaar made a review of 54 cases of “spondylosis rhizomelica”, examined and treated in the Consulting Bureau at Amsterdam (Medical Director: Dr. Jan van Breemen) [48]. The writer shared the opinion of others that the disease was an infective form of rheumatism. Only five of the described patients were female. Emphasizing the male predominance he noted that one of these women had a calcified ovary and another was “somewhat masculine”, but the other three were “true feminine”. Thirteen patients suffered from “iritis rheumatica”, which we now consider as anterior uveitis, strongly associated with AS. The characteristic posture of the patient was called “a sitting trunk on standing legs”. Interestingly, this typical posture was noted especially in patients with physically light jobs. On the contrary, later more strenuous work was considered as a risk factor for worse prognosis [49].

Jacques Forestier, a French specialist in internal diseases, described in 1950 the “senile ankylosing hyperostosis of the spine”, which was named after him as Forestier’s disease and was later called diffuse idiopathic skeletal hyperostosis (DISH). Cases were already reported since 1897 under names like “heredo-traumatic kyphosis of Bechterew” and “moniliform hyperostosis”: The distinction with AS was not fully accepted until then. However, Forestier showed the differences with AS in age of onset, symptoms, clinical and radiological examinations. Most important Forestier’s disease is a non-inflammatory disease of old age and radiologically the “candle-flame” hyperostoses are entirely different from the syndesmofytes in AS [28].

Jan van Breemen (1874-1961) was the pioneer of rheumatology in Amsterdam and in the Netherlands. He was also one of the founders of the International Organisation for the Investigation of Rheumatism (ICIR) in 1919, which evolved into the International League Against Rheumatism (ILAR) in 1925 and the European League Against Rheumatism (EULAR) in 1947 [50, 51]. In his Dutch textbook from the year 1942 Jan van Breemen emphasized the importance to diagnose AS in an early phase [39]. He noted that patients could have symptoms for 10-20 years before diagnosis. For early recognition he advised to detect the following early symptoms: pain in spine and pelvis, X-ray anomaly of sacroiliac joints, very limited chest expansion, limited mobility of spine and elevated erythrocyte sedimentation rate (ESR). Apparently, until then patients were often not diagnosed before they were quite ankylosed.

Another European rheumatologist, Copeman (from Great Britain) agreed in his textbook (1948) with Jan van Breemen that AS should be considered as a separate disease, in contrast to their colleagues in the USA [52].

**From the second half of the twentieth century: HLA-B27 and classification criteria.**

More and more, AS was recognized as a disorder distinct from RA, because clinicians observed differences in age, sex, peripheral joint involvement, uveitis, agglutination of sheep erythrocytes (Rose-test, the old test for rheumatoid factor), response to chrysotherapy (gold) and response to radiotherapy [53].
However, even in 1956 in American literature AS was considered as an extension of chronic RA, despite the fact that for years physicians had noticed another characteristic of AS: a hereditary factor [20]. Already in 1912 the appearance of similar complaints in family members of AS patients was described by G Bolten, neurologist in Den Haag. [54]. In 1949 and 1951 Jan de Blécourt, from Groningen, reported that 6-19% out of 116 Bechterew patients had one or more relatives with the same disease [55, 56]. In 1961 he published his investigation of 7405 family members of patients with RA or AS and controls. The relative risk for having AS was 22.6 in families of AS patients and for having RA 2.8 in families of RA patients [57]. In 1973 the high association of the W27 Human Leucocyte Antigen (HLA) with AS was shown by Schlosstein [43]. Not much later, it was shown that HLA-B27 (as it was named) was also associated with anterior uveitis (iritis) and reactive arthritis [58, 59]. It also explained the higher prevalence of AS in northern countries, as HLA-B27 is more frequent there [2]. Although HLA-B27 is still the most important genetic factor in AS, in later years it became clear that many other genetic factors are involved [4, 60].

With the discovery of the strong association with HLA-B27, AS was definitely accepted as a separate disease. A disease needs a definition or criteria, particularly when symptoms or signs are not pathognomonic. The first diagnostic criteria for AS were published after a meeting in Rome (1963) and the New York criteria were formulated in 1966. In 1984 these criteria were revised to the now commonly used modified New York criteria (table 1) [61]. In 1974 Moll and Wright introduced the term seronegative spondarthritis [62]. Several diseases that had been segregated from RA as separate entities in the preceding decades were now grouped together as spondarthritides, because of their clinical, radiological, serological and genetic resemblances. It concerned especially AS, psoriatic arthritis, reactive arthritis and arthritis in inflammatory bowel disease [63]. Classification criteria for SpondyloArthritis (SpA) were published by Amor in 1990 and in 1991 by the European Spondyloarthropathy Study Group (ESSG) [64].

Before World War II limited chest mobility was considered as a major clinical symptom to diagnose AS in the “praespondylitic phase” (X-ray abnormalities limited to the sacroiliacal joints) and called an important “Frühsymptom” [48, 65]. In later years, the SpA criteria covered the whole spectrum of SpA, including the true early phase of the disease without chronic X-ray changes. Recently, Magnetic Resonance Imaging (MRI) made it possible to show active inflammation before X-ray structural damage become visible [66]. Therefore MRI was incorporated in the classification criteria for axial SpA by the Assessment of SpondyloArthritis international Society (ASAS) in 2009 (table 2) [67]. ASAS was initiated in 1995 to bring evidence-based unity in the existing assessments in AS and later broadened its scope to all aspects of SpA [68]. According to the new criteria it is possible to be classified as having so called “non-radiographic axial SpA” based on HLA-B27 and clinical symptoms, even without MRI changes. This raises new questions, as for example about the prediction of the long term outcome of non-radiographic SpA. Not all cases with non-radiographic SpA will develop to sacroiliitis in the end, as was recently shown [69].

The recognition of AS, the concept of SpA, the international criteria and the ASAS helped to come nearer to the ultimate goal: to improve the well-being and outcome of patients with SpA [68]. This is pursued by a tremendous amount of investigations in SpA all over the world, in particular in epidemiology, etiology, pathogenesis, genetics, pathology, radiology, clinical outcome, etcetera, and last but not least in therapy.

In the next paragraph an overview of treatment of AS during the past hundred years is given.

**Table 1. Modified New York criteria for ankylosing spondylitis (AS) (1984)**

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<tr>
<th>Clinical criteria:</th>
<th>Radiologic criterion:</th>
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<td>Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.</td>
<td>Sacroiliitis grade 2-4 bilaterally or grade 3-4 unilaterally.</td>
</tr>
<tr>
<td>Limitation of motion of the lumbar spine in both the sagittal and frontal planes.</td>
<td>Limitation of chest expansion relative to normal values corrected for age and sex.</td>
</tr>
<tr>
<td>Limitation of chest expansion relative to normal values corrected for age and sex.</td>
<td>Definite AS if the radiologic criterion is associated with at least one clinical criterion.</td>
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Table 2. ASAS criteria for classification of axial spondyloarthritis (SpA)

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<th>Sacroiliitis on imaging*</th>
<th>OR</th>
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<td>≥ 1 SpA feature**</td>
<td>≥ 2 other SpA features</td>
</tr>
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* Sacroilitis on imaging:
  Active (acute) inflammation on MRI highly suggestive of sacroilitis associated with SpA. OR
  Definite radiographic sacroilitis according to modified New York criteria.

** SpA features:
- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's disease, ulcerative colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated C-reactive protein (CRP)

3 HISTORY OF THERAPY IN ANKYLOSING SPONDYLITIS.

General and various treatment
In the time that the discrimination between ankylosing spondylitis (AS) and rheumatoid arthritis (RA) was not yet accepted or not always possible, the same therapies were used for both diseases. Gradually differences in response, but also similarities between these diseases became obvious.

In the decades after the first descriptions of AS the following therapies were most described:
salicylates, potassium iodide, antipyrin, arsenic, strychnin, application of iodine tincture above the vertebra with a pencil, corsets and several forms of physiotherapy [44, 70] Rest, diet, cod-liver oil and tonic measures were meant to raise the general resistance and improve the calcium metabolism [52]. Other forms of therapies included cupping (local suction on the skin by a device), vaccination (polyvalent immune stimulation by for example Warren Crowe's or Pondorff's vaccin) and treatment with testosteron (neo-hombreol syntheticum) [38, 71].

Following observations of increased calcium levels in AS, hemi-parathyroidectomy seemed to give short term, but temporarily improvement in two-third of 49 operated patients [47, 48].

In later years patients often used alternative or complementary medicine, but in AS hardly any studies were done. In a study with simplified methods in 141 AS patients no evidence was found for Ayurvedic treatment (old traditional Indian healing method) in AS [72]. Since decades a low starch diet is advocated by Alan Ebringer, based on his hypothesis that Klebsiella bacteria in the gut are involved in triggering AS. However, the efficacy of this treatment was never proven [73].

Figure 5. Violent mobilisation (Beely).
Physiotherapy
Massage was used frequently, but in the past discouraged in case of active inflammation [39].
Abnormal posture and limited mobility were supposed to be due to the “sleeping” condition of the muscles, because patients avoided to move. Therefore, exercises were considered as very important. Chest exercises, for instance, could be supported by a tight pelotte on the abdomen (Krebs’ method of coercion) and a sling was supposed to be used for passive stretching of the spine (figures 3-6) [48, 74]. Jan van Breemen, however, concluded that gymnastics were not successful in correcting the posture of the spine [39]. In contrast to exercises, rest was advocated by others in 1948: “The patient should spend the greater part of the day in bed or lying on his back” [52].
For many years several types of physiotherapy were used, such as hydrotherapy, spa, (Priessnitz’s) cold packs, methylsalicylate containing liniments, application of warmth, light and electricity (figures 7-10). Temporary symptomatic relief of AS was achieved by exposition to a quartz lamp, an ultraviolet light source, twice a week [39, 75]. Since 1987 several controlled trials of individualized and group physical therapy in AS were reported and showed favourable effects on mobility, fitness and function [76-78].

Orthopaedic therapy
Strümpell applied forced correction of spine and joints in deep narcosis (redressement forcé), associated with fracturing of ankylosed ligaments. It resulted in temporary excruciating pains and high fevers [44, 79]. Dissection of the spinous processes and curettage of the sacroiliacal joints was also attempted, but not successful. The suggestion to disrupt the rectal abdominal muscles in order to improve the kyphotic posture, was probably never applied [48]. Braces were used for relaxation, but long-term negative effect on muscle strength was emphasized [48]. A corset was also used for correction by using a hinged plaster. The patient had to tighten the swivel every day for a bit in order to correct his posture. Improvement of 10-14 degrees of kyphosis and 2-3 cm increase in body length was reported in 1947 (figure 11) [79].

From 1945 on corrective operative treatment was reported by means of vertebral osteotomy (the Norwegian-born Marius Smith-Petersen) [79]. In case of disabling kyphosis lumbar and sometimes cervical wedge osteotomy can still be an advantageous treatment in highly specialised orthopaedic centres [80]. In addition, the technique of joint replacement by a prosthesis made it possible to treat secondary osteoarthritis of the hip, which often partly corrects the kyphotic posture of the AS patient (figure 1). Total hip replacement is performed since 1966 (McKee, Watson-Farrar and Charnley) [81-83].

Radiotherapy
Radioactive elements were used, like radon (product of radium) in hydrotherapy and thorium (mesothorium X) as weekly injections. In recent years, just before the breakthrough of the Tumour Necrosis Factor-alpha (TNF) blockers, radium was again applied as intravenous injections in Germany [84, 85]. Radiation therapy has been used for several rheumatic diseases and seemed especially efficacious in AS [86]. In fact, the existence of an effective treatment was the reason early diagnosis of AS was advocated. From about 1935 to 1955 radiation was the most important therapy for AS when the effect of physiotherapy and
Antiflogistics

From old times salicine, extracted from the bark of willow (Salix), has been used to reduce symptoms of inflammation [92]. Salicylate was isolated from salicin in 1838 and came into use in rheumatology in the late 1870s [93, 94]. Several salicylates were used in AS, for example phenyl salicylate (Salol) 3 gram a day orally and acetyl-salicylacid (Aspirin) 5-6 gram a day, for their analgetic and anti-inflammatory effects [39, 44].

From 1929 dimethyl-amido-antipyrine (pyramidon) was available and was used in all inflammatory rheumatic disorders in doses of 1500-4000 mg per day. Related drugs were metamizol (known as novalgin, novaminsulfon and dipyrone) and from 1952 phenylbutazone (butazolidin; 200-1200 mg a day, mostly 400 mg) and irgapyrine (combination of pyramidon and phenylbutazone) [39, 95].

Most important adverse events of these antiflogistics, as in newer nonsteroidal anti-inflammatory drugs (NSAIDs), were gastro-intestinal ulceration, hypertension, fluid retention, nephrotoxicity and hemorrhagic diathesis. Life threatening was the occurrence of agranulocytosis in the group of pyrazolones, which was reported from 1933 [95, 96]. Fifty years later, in 1983 this led to a medical debate in the Netherlands about the risks and benefits of phenylbutazone [97-99]. The prescription of phenylbutazone became limited to rheumatologists for treatment of AS, because phenylbutazone seemed to have a special role in this disease and the risks could be limited in this way [100, 101].

However, studies directly comparing different NSAIDs were scarce or included small numbers of patients. Most of these studies showed comparable efficacy [94, 102, 103].

Phenylbutazone is still being used in AS, but gradually newer NSAIDs were used more frequently and from 1999 the COX-2 selective inhibitors (COXIBs) were introduced, because of their lower risk for gastric ulceration [104]. One of the COXIBs, rofecoxib (Vioxx), was withdrawn in 2004 because of an increased
cardiovascular risk [105]. Thereafter, it was discussed that many NSAIDs might increase this risk, probably with the exception of naproxen [106].

In 1976 it was shown in a retrospective study that, apart from the beneficial effects on pain and stiffness, continuous use of phenylbutazone also seemed to delay radiological ossification of the lumbar spine [107]. Interestingly, recent controlled studies confirmed radiographic retardation by continuous NSAID use in contrast to on-demand NSAID use, especially in patients with elevated acute phase reactants [108-110]. Therefore, it seems that in addition to symptom modification, NSAIDs might also have disease modifying properties. The question is whether other disease modifying antirheumatic drugs (DMARDs) are effective in AS.

**DMARDs**

In the past, the difference between AS and RA was not always accepted and not always possible in case of peripheral arthritis and therefore, even chrysotherapy (intramuscular gold injections) was employed in AS. However, soon it was generally accepted that gold was not effective in AS, in contrast to RA [39, 65].

The results of a very small double-blind placebo-controlled trial with D-penicillamine in AS were also negative [111].

Soon after the discovery of cortisone (by Nobel prize winner in 1950 Philip Hench, a rheumatologist), cortisone (compound E) and Adrenocorticotropic hormone (ACTH), were tried in AS, but the effect was temporary because medication was given shortly [90, 93, 112]. Currently, corticosteroids are mainly locally used in AS for uveitis (eye drops), enthesitis (injection) and as intra-articular injection, especially in peripheral joints and sometimes in the sacroiliac joints [91, 113]. A recent placebo-controlled trial showed short-term response of a short treatment with a high oral dose prednisolone [114].

In the late 1930s sulfasalazine (SSZ) was designed by Nanna Svartz, in Stockholm, for treatment of RA, combining the antibacterial properties of sulfonamide with the anti-inflammatory properties of salicylate [115]. However, the results of a small controlled study in 1948 seemed disappointing and SSZ became primarily popular in treating inflammatory bowel diseases. In the late 1970s a revival for the interest in SSZ for RA was seen and in the 1980s also in AS small placebo-controlled studies were done, showing moderate effects [115, 116]. Later, larger studies were done and in 1995 SSZ proved to have favourable effect in AS with peripheral arthritis [117, 118]. In this subgroup of AS SSZ 2000-3000 mg a day is still indicated [119].

Levamisole was studied in a small double-blind trial in a mixed group of spondyloarthritides with some positive effects, but also often adverse events [120]. Results of studies with methotrexate, azathioprine, thalidomide and pamidronate in AS were conflicting and in most instances these studies were small and open [121]. Possibly methotrexate can have a role in peripheral arthritis in AS, but there is not enough evidence to recommend this [122].

**Biologics**

Around 1985 blocking of the pro-inflammatory cytokine Tumour Necrosis Factor-alpha (TNF) was studied in bacterial sepsis in animals, but in patients this therapy was not successful for this indication [123]. Later, TNF-blocking proved to be effective in RA and the first experiences in AS were very encouraging [124]. From 2002 onwards TNF-blocking therapy proved to be efficacious in large multicentre double-blind placebo-controlled trials in AS [125]. This applied for the intravenously administered infliximab, as well as the subcutaneously given etanercept, adalimumab, golimumab and certolizumab [126-130]. TNF-blocking in general has favourable effects on axial symptoms and inflammatory Magnetic...
Resonance Imaging (MRI) lesions, as well as on fatigue, quality of life, peripheral arthritis, enthesitis and on extra-articular manifestations like uveitis, psoriasis and colitis [131-134].

The most important adverse events of TNF-blockers are bacterial infections. After the first TNF-blockers were approved for clinical practice, it became clear that life-threatening reactivation of latent tuberculosis did occur [135]. Furthermore, in RA the risk for non-melanoma skin cancer seems to be increased [136].

About 60-80% of the AS patients respond to treatment with a TNF-blocker, but only 30% show a very good response. Therefore, other treatment options remain desirable and other biologicals have been and are being studied [137]. Until now inhibition of the interleukin-12/23 and interleukine-17 pathways show promising results in AS (ustekinumab and secukinumab) [138, 139].

After the acceptance of the concept of axial SpA and non-radiographic SpA, it was obviously questioned if TNF-blocking would be useful in these patients. The first studies showed favourable results [130, 140-143]. On the basis of these studies TNF-blocking therapy is now approved in clinical practice for non-radiographic axial SpA in some countries, provided that active inflammation is demonstrable by the presence of bone oedema on MRI or increased C-reactive protein levels.

Currently, physiotherapy and NSAID therapy maintain the cornerstones of therapy in AS and axial SpA [119]. However, the disease can remain active even when this treatment is given for an adequate period of time. Fortunately, for those patients since around 10 years a successful treatment is available in the form of TNF-blocking agents.

Some studies described in this thesis started just before the availability of TNF-blocking therapy and some started thereafter. In the latter ones, several aspects of the TNF-blocking therapy were studied. In the next paragraph the aims and outline of this thesis are described.

4 OBJECTIVES AND OUTLINE OF THIS THESIS.

Objectives of this thesis
As demonstrated in the last paragraph, for a long time treatment of ankylosing spondylitis (AS) consisted mainly of physiotherapy and non steroidal anti inflammatory drugs (NSAIDs). In contrast to rheumatoid arthritis, most disease modifying antirheumatic drugs (DMARDs) were not effective in AS. The first part of this thesis concerns studies done just before TNF blockers became available and several drugs with potential DMARD activity in AS were investigated. The availability of the tumour necrosis factor (TNF) blocking agents changed the therapeutic possibilities in AS dramatically and the second part of this thesis covers studies concerning different aspects of treatment with a TNF-blocking agent.

Outline of this thesis
Chapter 1 includes the clinical description of AS and the historical perspectives of the evolution of this disease entity and treatment options.

AS is associated with inflammatory bowel disease for which mesalazine is a registered therapy. Mesalazine has been used in AS with various results. The efficacy of a mesalazine with different pharmacological characteristics was studied in AS and the results of this open study are described in chapter 2.

In AS, the cardiovascular risk is increased and statins (cholesterol lowering agents) have shown anti-inflammatory effects in rheumatoid arthritis. The effect of the statin rosuvastatin on AS disease activity and lipid profile was studied in an open study. The results of this study are shown in chapter 3.

Leflunomide has proven to be effective in rheumatoid arthritis as well as in psoriatic arthritis. In chapter 4 the results of a double blind, randomised, placebo controlled study of the efficacy of leflunomide in AS are shown.

TNF-blocking agents are effective in the majority of AS patients. However, in some patients they lack efficacy from the start or after a period in which the disease responded well. The discovery of antibodies against TNF-blocking agents in rheumatoid arthritis made clear that these antibodies influence the efficacy. Chapter 5 shows the results of a study investigating the role of antibodies against infliximab in AS.

Increased liver enzymes were observed in several AS patients treated with a TNF-blocking agent. In a retrospective study, the incidence of increased liver enzymes in AS patients treated with etanercept was investigated and possible risk factors were studied. The results are reported in chapter 6.
The effectiveness of a therapeutic agent in AS is determined with international accepted outcome measures. However, most of these assessments are based on patient questionnaires. It is well known that patient-based and objective outcome measures can differ. As part of a project to compare functional outcome on basis of questionnaires and performance-based functional tests, the change in performance was studied in AS patients who were treated with a TNF-blocking agent. In chapter 7 the results are shown.

Acute anterior uveitis is a frequent extra-articular manifestation of AS. The effect of TNF-blocking agents is favourable, but the efficacy might differ between the several agents. Chapter 8 shows the results of a study in which the number of flares of uveitis is investigated before and after start of adalimumab.

In AS, like in other inflammatory rheumatic diseases, the incidence of osteoporosis and fractures is increased. The effect of a TNF-blocking agent on bone mineral density and vertebral fractures was studied and reported in chapter 9.

In chapter 10 an overview of the evolving treatment of AS is given. The results of the previous studies are summarized and various aspects of drug therapy in AS are discussed (with Dutch summary).

**REFERENCES CHAPTER 1**

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Efficacy and safety of mesalazine (Salofalk\textsuperscript{®}) in an open study of 20 patients with ankylosing spondylitis.

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Abnormalities of the Gut and the Spine

Mesalazine in AS

Chapter 2

ABSTRACT

Objective
Mesalazine (Salofalk®) was found to be effective and showed low toxicity in patients with inflammatory bowel disease. The association of gut lesions and spondyloarthropathy (SpA) is well known and we studied the efficacy and safety of a relatively high dose of mesalazine in patients with ankylosing spondylitis (AS).

Methods
In an open study, mesalazine (3–4 g/day) was prescribed for 24 weeks to 20 patients (aged 18–70 yrs) with active AS, defined as the presence of at least one clinical criterion (morning stiffness > 30 min, peripheral synovitis, enthesopathy, or pain score > 2 on a visual analog scale of 10 cm) and one laboratory criterion [erythrocyte sedimentation rate (ESR) > 20 mm/h or C-reactive protein (CRP) > 20 mg/l]. Data on toxicity and disease activity variables (ESR, CRP, BASDAI, BASFI, BASMI, global assessment, and joint count) were obtained at baseline and after 4, 12, and 24 weeks, and analyzed on an intention-to-treat basis.

Results
Study patients had a mean age of 41 years, with mean disease duration of 7.9 years and a mean ESR at baseline of 29 mm/h. After a mean of 9.3 weeks (range 2–22), 8 of the 20 patients prematurely stopped the medication because of adverse effects, mainly gastrointestinal complaints. Twelve patients completed the 24 weeks of the study using a mean dose of 3.2 g/day (range 1–4) mesalazine. Analysis of the data showed improvement in ESR, CRP, and physician’s global assessment, but only the change in ESR (29 mm/h on baseline and 25 mm/h at week 24) reached statistical significance (p = 0.03). No change was observed in the other disease activity variables.

Conclusion
No significant improvement in any disease activity variable of active AS was observed during treatment with Salofalk® except for the ESR. Many side effects were seen.

INTRODUCTION

Treatment of patients with ankylosing spondylitis (AS) consists mainly of exercise therapy and nonsteroidal antiinflammatory drugs (NSAID). A considerable number of studies have assessed the efficacy and safety of sulfasalazine (SSZ) in AS [1-8]. SSZ (2–3 g/day) was proven to be more effective than placebo in active spondyloarthropathy (SpA), especially in decreasing the peripheral arthritis [8-8].

SSZ is metabolized in the large intestine into sulfapyridine and mesalazine (5-aminosalicylic acid, 5-ASA). The latter is the active drug in the treatment of inflammatory bowel disease (IBD). Based on the hypothesis that the gut plays an important role in the onset of AS and because mesalazine is less toxic than SSZ, mesalazine seemed to be an attractive candidate in the treatment of AS. Mesalazine was used previously in some AS patients with various results [9-11]. The results of a randomized controlled study of treatment with either SSZ, mesalazine, or sulfapyridine suggested that sulfapyridine and not mesalazine is the active moiety in SpA. [11] However, in that study a very low dose of mesalazine (Asacol® 0.8 g/day) was used. For IBD, it is common practice to use doses up to 6 g/day of mesalazine. Our aim was to assess the efficacy and safety of a relatively high dose (up to 4 g/day) of mesalazine (as Salofalk®) in patients with AS.

MATERIALS AND METHODS

Study design
In an open pilot study, 20 patients with AS were treated with mesalazine over 24 weeks. Patients with active AS were included if they fulfilled the modified New York criteria for AS, were aged between 18 and 70 years, and showed active disease defined as the presence of at least one clinical criterion [morning stiffness > 30 minutes, or peripheral synovitis, or enthesopathy, or pain score > 2 on a visual analog scale (VAS, 0–10 cm)] plus one laboratory criterion [erythrocyte sedimentation rate (ESR) > 20 mm/h or C-reactive protein (CRP) > 20 mg/l].

Previous use of mesalazine, treatment with a disease modifying antirheumatic drug (DMARD), including SSZ, experimental therapy, or corticosteroids in the previous 4 weeks, known allergy to salicylates or SSZ, pregnancy, severe renal and/or hepatic dysfunction, and history or symptoms of IBD were the exclusion criteria.

After inclusion, mesalazine was prescribed as Salofalk® in 500 mg tablets with an initial daily dose of 3 g (1 g tid). We confirmed with the patients’ pharmacy that no other mesalazine formulation was given. In case of intolerance or side effects, the dosage of Salofalk® was decreased to the highest tolerated dose. After 4 weeks the daily dose was increased to 4 g in case of inefficacy, defined as less than 20% improvement in at least 2 of the following variables: VAS morning stiffness, VAS pain, or ESR.
NSAID were continued during the study if they had been taken in a stable dose from 4 weeks prior to study entry. The type, dosage at entry, and change in dosage or type of the NSAID during the study were recorded.

At baseline and at 4, 12, and 24 weeks the following data were obtained by one of us (JC van D): Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), global assessment according to the patient and to the doctor (VAS 0–10 cm), Bath Ankylosing Spondylitis Metrology Index (BASMI, new scoring system) [12], tender joint score (TJS, 42 joints), swollen joint score (SJS, 40 joints), laboratory tests, and adverse events.

The following were used as variables for disease activity: ESR, CRP, BASDAI, BASFI, BASMI, global assessment according to the patient and to the doctor, TJS, and SJS. The Assessments in Ankylosing Spondylitis Working Group (ASAS) response criteria were not used because they were not developed when this study was performed [13]. The mean values of the variables at baseline and after 24 weeks were compared using paired t tests. An intention-to-treat analysis of all 20 patients was performed, as well as a separate analysis of the patients who completed the whole study.

The medical ethical committee of the Slotervaart Hospital, Amsterdam, approved the study.

RESULTS

The mean age of the 20 AS patients was 41 years (range 19–69, median 40), 18 were men and 19 were positive for the HLA-B27 antigen. The mean disease duration was 7.9 years (range 0.4–27). The patients had no history of extraarticular manifestations besides acute anterior uveitis (25%) and psoriasis (10%).

Eight out of 20 patients stopped the medication permanently after a mean period of 9.3 weeks (range 2–22) due to adverse effects, despite dose reduction. Several of these patients were not even able to tolerate a dose as low as 0.5 g/day.

Most patients (75%) reported side effects, consisting mainly of gastrointestinal complaints, especially diarrhea. Five patients reported no adverse reaction due to the medication (Table 1). Laboratory values showed no adverse effects except a > 3–6-fold increase in hepatic enzymes in one patient, necessitating withdrawal of treatment with mesalazine; the levels normalized after drug discontinuation.

Twelve (60%) of the patients completed the 24-week treatment with mesalazine, using a mean dose of 3.2 g/day (range 1–4). Because of adverse effects, 5 of these 12 patients discontinued the medication during a short period (with a mean duration of 3.2 weeks and in one case 10 weeks because of an intercurrent urological analysis), but completed the study. The 12 completers were younger (mean 34 yrs) and had shorter disease duration (mean 6.0 yrs) compared to the 8 dropouts (mean 52 and 10.7 yrs).

| Table 1. Number of reported adverse effects in 20 patients with AS taking mesalazine (adverse effects were seen in 15 patients). |
|----------------------------------|--------|
| Adverse Effect                   | n      |
| GI disorders                     |        |
| Nausea                           | 4      |
| Abdominal pain                   | 4      |
| Diarrhea                         | 7      |
| Increased hepatic enzymes        | 1      |
| Skin disorders                   |        |
| Pruritus                         | 1      |
| Worsening eczema                 | 1      |
| CNS disorders                    |        |
| Dizziness                        | 3      |
| Headache                         | 1      |
| Other                            |        |
| Fever                            | 1      |
| Impotence                        | 1      |
| Arthralgia                       | 2      |

GI: gastrointestinal, CNS: central nervous system.

All patients used NSAID during the study; 3 patients increased the dose, 4 used a lower dose, and 3 switched to another NSAID.

The results of the disease outcome variables at baseline and during followup of the total group of 20 patients and of the 12 patients who completed the study are presented in Table 2. Improvement was observed in ESR, CRP, and physician’s global assessment, but only the change in ESR reached statistical significance (p = 0.03). The other outcome variables did not change favorably.

A secondary analysis of the 12 completers only showed significant improvement of the CRP (p = 0.03) and physician’s global assessment (p = 0.02).
Table 2. Disease activity variables in 20 patients with AS (data in parentheses for the 12 completers only). Values are given as mean.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, mm/h</td>
<td>29 (30)</td>
<td>24</td>
<td>26</td>
<td>25 (27)</td>
<td>0.03 (0.26)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>25 (30)</td>
<td>22</td>
<td>28</td>
<td>22 (23)</td>
<td>0.16 (0.03)</td>
</tr>
<tr>
<td>BASDAI, 0–10</td>
<td>4.4 (4.4)</td>
<td>4.1</td>
<td>4.4</td>
<td>4.2 (3.7)</td>
<td>0.67 (0.31)</td>
</tr>
<tr>
<td>BASFI, 0–10</td>
<td>4.5 (4.1)</td>
<td>4.3</td>
<td>4.5</td>
<td>4.5 (3.8)</td>
<td>0.97 (0.49)</td>
</tr>
<tr>
<td>BASMI, 0–10</td>
<td>4.5 (3.9)</td>
<td>4.6</td>
<td>4.7</td>
<td>4.6 (4.2)</td>
<td>0.54 (0.09)</td>
</tr>
<tr>
<td>Patient global, 0–10</td>
<td>4.8 (4.9)</td>
<td>4.8</td>
<td>5.1</td>
<td>4.7 (4.3)</td>
<td>0.85 (0.35)</td>
</tr>
<tr>
<td>Doctor global, 0–10</td>
<td>5.4 (5.3)</td>
<td>4.8</td>
<td>4.8</td>
<td>4.6 (4.1)</td>
<td>0.09 (0.02)</td>
</tr>
<tr>
<td>SJS, 0–40</td>
<td>0.2 (0.2)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3 (0.3)</td>
<td>0.33 (0.34)</td>
</tr>
<tr>
<td>TJS, 0–42</td>
<td>1.2 (1.2)</td>
<td>1.2</td>
<td>1.5</td>
<td>1.3 (0.8)</td>
<td>0.80 (0.17)</td>
</tr>
</tbody>
</table>

Paired t test comparing week 24 to baseline. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index (new scoring system), SJS: swollen joint score, TJS: tender joint score.

**DISCUSSION**

In our open pilot study, no significant improvement of active AS was observed during treatment with mesalazine for 24 weeks. The ESR was the only disease activity variable that changed significantly, although the clinical relevance of this finding (mean difference –4 mm/h) was doubtful. A striking number of patients did not tolerate mesalazine, mainly due to gastrointestinal complaints, which improved after cessation of the drug. A separate analysis of the 12 patients who completed the whole study did not show any favorable effect.

Another preparation of mesalazine, Pentasa®, performed better in 2 open studies in patients with SpA, with fewer side effects and improvement of most clinical, physical, and laboratory variables [9,10]. The somewhat lower mean age of the patients in these studies (37.6, 39.1, and 34.4 yrs) compared to our population (41 yrs) might be a possible explanation, because in our study the older patients were more likely to drop out. Also, the higher tolerance of Pentasa® can probably be explained by the more gradual increment of the drug and the lower dose used in these studies. However, in some of our patients even a dose as low as 0.5 g/day in rechallenge was not tolerated.

As far as we know there are no studies suggesting that Salofalk® is less tolerated than other formulations of mesalazine. The impaired tolerance of mesalazine in our study, compared to the situation in IBD, is possibly related to the rheumatic disease itself or concomitant use of antiinflammatory drugs.

It can be hypothesized that the apparent difference in efficacy between Pentasa® and Salofalk® could be due to the pharmacological difference between the several preparations of mesalazine. These various preparations are released at different parts of the bowel. The release of Pentasa® starts in the proximal small intestine, whereas Asacol® becomes available only when the pH rises to around 7, typically in the terminal ileum. Salofalk® takes an intermediate place, being released at around pH 6. The mesalazine in SSZ is split from sulfapyridine in the colon by bacterial enzymes. The associations of SpA with enterogenic infection and IBD are well known. Even in undifferentiated SpA and AS, ileocolonoscopic inflammatory lesions in the small and large bowel were found in high frequencies [14]. However, because the exact pathogenic role of the gut in AS is not known, the importance of the differences in delivery characteristics of the forms of mesalazine is not certain, but cannot be excluded.

In summary, we saw no improvement in disease activity variables in patients with AS during treatment with Salofalk®, except for the ESR. There was a high rate of premature discontinuance by patients because of intolerance. Although we cannot exclude the possibility that a lower dose or a different formulation of mesalazine might be better tolerated and more effective, our results suggest that Salofalk® has no role in the treatment of AS.
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Statin therapy might be beneficial for patients with ankylosing spondylitis.

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ABSTRACT

Objective.
There is growing evidence that statins possess anti-inflammatory properties, as indicated by lowering of C reactive protein levels (CRP), and the beneficial effect of atorvastatin on disease activity in rheumatoid arthritis. Therefore, we conducted an open pilot study to investigate the effect of rosuvastatin on disease activity in patients with ankylosing spondylitis (AS).

Methods
Fifteen unselected consecutive outpatients with active AS were treated with rosuvastatin (20 mg/day) for 12 weeks, followed by an observational phase of 12 weeks. Plasma concentrations of CRP, erythrocyte sedimentation rate (ESR), lipid levels and the following clinical measures: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Metrology Index (BASMI), general wellbeing according to the doctor/patient and pain score, were determined.

Results
The mean age was 46 years (range 29–61) and the mean disease duration was 11.5 years (range 2–22). All patients completed the trial, but the dose of rosuvastatin was reduced in two patients owing to side effects. Clinical measures tended to improve during the treatment period. Improvements in BASDAI, BASMI and pain score were sustained, with further improvement, during the observational phase. In addition, treatment with rosuvastatin resulted in significant improvements of CRP and ESR after 12 weeks. Total and LDL-cholesterol were significantly reduced after 6 and 12 weeks and increased during the observational phase.

Conclusion
Treatment with rosuvastatin leads to an improvement of disease activity in patients with active AS and is accompanied by significant reduction of acute phase reactants. Several clinical measures continued to improve during the follow up phase, suggesting longlasting beneficial effects. Confirmatory randomised studies are required.

Therapeutic options for patients with the chronic inflammatory disease ankylosing spondylitis (AS) are limited. Treatment was, until recently, mainly based on non-steroidal anti-inflammatory drugs and physical therapy. The efficacy of disease modifying antirheumatic drugs, such as sulfasalazine and methotrexate, is less beneficial in AS than in other rheumatic diseases such as rheumatoid arthritis [1]. Recently, tumour necrosis factor-α blocking agents, have been proved to be very effective in a high proportion of patients with AS. However, these agents are expensive and their use is sometimes accompanied by severe adverse events, as opportunistic infections. Moreover, tumour necrosis factor-α blocking agents are not effective in about 30% of patients [2]. Hence, there is a continuing need for alternative therapeutic options.

There is growing evidence that statins possess anti-inflammatory properties, as indicated by lowering of C reactive protein (CRP) levels, and recently, the clinically beneficial effect of the statin atorvastatin on disease activity was demonstrated in rheumatoid arthritis [3, 4]. Therefore, we conducted an open pilot study to investigate the effect of rosuvastatin on disease activity in patients with AS.

Fifteen unselected consecutive outpatients with AS, according to the modified New York criteria, were treated with rosuvastatin (20 mg/day) for 12 weeks, followed by an observational phase of 12 weeks. Patients were eligible for inclusion if they had active disease defined as at least four points on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, 0–10) and a pain score of at least four on the visual analogue scale (0–10). The local ethics committee approved the study protocol and all patients gave written informed consent. Main exclusion criteria included cardiovascular events within the previous 3 months, current lipid lowering treatment, and current use of biological agents. No patients were allowed to enter the study who would otherwise have qualified for statins on the basis of calculated risk.

Plasma concentrations of CRP, erythrocyte sedimentation rate (ESR), total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides and the following clinical measures: BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI, 0–10), Bath Ankylosing Spondylitis Metrology Index (BASMI, 0–10), general wellbeing according to the doctor/patient (GWBD/P), and pain score were determined. Statistical analysis was performed with Wilcoxon's signed rank test. Values of p<0.05 were considered significant.

The patients’ mean age was 46 years (range 29–61), nine were men and 14 were HLA-B27 positive. The mean disease duration was 11.5 years (range 2–22). All patients completed the trial. However, the dose of rosuvastatin was reduced in two patients to 10 mg/day after 6 weeks owing to side effects. Clinical measures, such as BASDAI, BASMI, pain score, and GWBD/P, tended to improve during the
treatment period. Improvements in the first three variables were sustained, with further improvement, during the observational phase. In addition, treatment with rosvastatin resulted in significant improvements of CRP and ESR after 12 weeks. Total and LDL-cholesterol were significantly reduced after 6 and 12 weeks and increased during the observational phase (table 1).

The main conclusion is that treatment with rosvastatin leads to an improvement of disease activity in patients with active AS and is accompanied by significant reduction of acute phase reactants. Moreover, several clinical measures continued to improve during the follow up phase, suggesting that rosvastatin has longlasting beneficial effects. Accumulating evidence suggests that statins exert anti-inflammatory properties through modulation of the immune response. The immune response is up regulated in the inflammatory disorder AS and we suggested that suppression of the immune response by statins would lead to clinical improvement accompanied by lower levels of inflammation markers, such as ESR and CRP. The results of our investigation are in line with this hypothesis, but clearly, confirmatory randomised studies are required.

Finally, as AS is associated with an increased cardiovascular risk [5], the use of statins might ultimately lead to reduction of this risk by two pathways: one through the lipoprotein metabolism and the other by beneficial effects on the underlying inflammatory process in AS.

Table 1. Clinical and biological variables (median) in 15 patients at baseline, at weeks 6, 12 (with rosvastatin), and at weeks 18, 24 (without rosvastatin).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>At 6 weeks</th>
<th>At 12 weeks</th>
<th>At 18 weeks</th>
<th>At 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/1st h)</td>
<td>22.0</td>
<td>20.0</td>
<td>15.0*</td>
<td>18.0</td>
<td>15.0</td>
</tr>
<tr>
<td>CRP (log mg/l)</td>
<td>15.0</td>
<td>10.0</td>
<td>10.0*</td>
<td>12.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.8</td>
<td>3.5*</td>
<td>3.6*</td>
<td>5.0**</td>
<td>5.0**</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.3</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.8</td>
<td>1.1*</td>
<td>1.8*</td>
<td>3.3**</td>
<td>3.2**</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4</td>
<td>1.2</td>
<td>1.3</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>BASDAI</td>
<td>6.3</td>
<td>5.6</td>
<td>5.8</td>
<td>5.2</td>
<td>5.6</td>
</tr>
<tr>
<td>BASFI</td>
<td>4.7</td>
<td>5.4</td>
<td>4.9</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>BASMI</td>
<td>4.4</td>
<td>4.0</td>
<td>3.8</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>General wellbeing according to doctor</td>
<td>4.4</td>
<td>4.5</td>
<td>3.9</td>
<td>4.2</td>
<td>4.0</td>
</tr>
<tr>
<td>General wellbeing according to patient</td>
<td>6.4</td>
<td>5.7</td>
<td>5.3</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Pain score</td>
<td>6.5</td>
<td>6.8</td>
<td>6.2</td>
<td>5.7</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Significant changes compared with baseline (Wilcoxon’s signed ranks test), p<0.05;
**significant changes compared with 12 weeks (Wilcoxon’s signed rank test), p<0.05.

REFERENCES

Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis.

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ABSTRACT

Objective
To assess the efficacy and safety of leflunomide in active ankylosing spondylitis (AS) compared with placebo in a 24 week pilot study.

Methods
In a single centre randomised, double blind, placebo controlled study, 45 patients with active AS were randomised to either leflunomide 20 mg daily (n=30) or placebo (n=15). Active disease was defined as a score of at least 4 on the Bath ankylosing spondylitis disease activity index (0–10), and pain of at least 4 on a visual analogue scale (0–10). The primary efficacy variable at week 24 was the 20% response rate, as recommended by the Assessments in Ankylosing Spondylitis (ASAS) working group. Secondary outcome variables included general wellbeing, metrology index, swollen joint count, erythrocyte sedimentation rate, and C reactive protein.

Results
In all, 13 women and 32 men were studied. Demographic and disease indices were comparable between the two treatment groups at baseline. The rate of ASAS 20% responders was not significantly different: 27% in the leflunomide treated patients and 20% in the placebo group (95% confidence interval, −32% to 19%). No significant differences were found between the treatment groups in mean changes of the secondary outcome variables. Eleven patients were withdrawn prematurely from the study because of adverse events (7), lack of efficacy (3), and non-compliance (1). Most frequently adverse events were gastrointestinal side effects and skin disorders.

Conclusion
In this placebo controlled study, leflunomide treatment did not result in a significant improvement of the ASAS 20% response in active ankylosing spondylitis. No unexpected or severe adverse events occurred.

INTRODUCTION

Ankylosing spondylitis (AS) is an autoimmune disease characterised by chronic inflammation of the sacroiliac and spinal joints and entheses. The disease occurs mainly in young adults and can lead to stiffness and deformity of the vertebral column, with invalidating deformities. AS is often accompanied by extraspinal manifestations as arthritis of the peripheral joints, and involvement of the eye (acute anterior uveitis), heart, and lungs.

Treatment was, until recently, mainly based on non steroidal anti-inflammatory drugs (NSAIDs) and physical therapy [1]. The disease modifying anti-rheumatic drugs (DMARDs), for example sulfasalazine and methotrexate, seem to be less beneficial in AS than in other rheumatic diseases such as rheumatoid arthritis [2]. Recent studies have shown that the tumour necrosis factor α (TNFα) blocking agents infliximab and etanercept are very effective in a large proportion of patients with AS [3, 4]. These powerful drugs, however, are costly and are sometimes accompanied by severe adverse effects such as opportunistic infections. Moreover, these agents fail to reach efficacy in approximately 30% of the patients [5]. For these reasons we investigated the efficacy and safety of another DMARD, leflunomide: a drug proven to be effective in rheumatoid arthritis [6–9]. In addition, leflunomide shows beneficial effects in patients with psoriatic arthritis which, like AS, belongs to the group of spondyloarthritides [10–13]. In the present study the efficacy and safety of leflunomide was investigated in patients with active AS in a randomised, double blind, placebo controlled trial.

METHODS

Consecutive patients with AS were recruited from the outpatient rheumatology clinic of the Jan van Breemen Institute (referral centre) and the surrounding hospitals in Amsterdam. The study was carried out in the period from March 2002 to September 2003. The study group comprised 45 patients aged 18 to 70 years with active definite AS, diagnosed according to the modified New York criteria [14]. Active disease was defined as: at least a 4 point score on the Bath ankylosing spondylitis disease activity index (BASDAI; scale 0–10) and a pain score of at least 4 on a visual analogue scale (VAS; scale 0–10) at screening.

NSAIDs and corticosteroids up to a maximum daily dose of 15 mg prednisone were allowed on an unchanged regimen for at least 30 days before the study drug administration and throughout the study. The use of DMARDs (particularly sulfasalazine, methotrexate, and TNF blocking agents) during the study and within the 30 days before the study was not permitted.
Both men and women were required to practice contraception. In female patients of childbearing potential a urine pregnancy test was done at baseline and any pregnant women were excluded.

Other exclusion criteria were: impaired hepatic enzyme tests (alanine and aspartate transaminases more than twice the upper laboratory limit of normal), impaired renal function (serum creatinine >110 μmol/l), untreated hypertension, malignancy, diagnosis of other inflammatory joint diseases, impaired bone marrow function, recent serious infections, and any clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic diseases.

Design
Forty five eligible patients were randomised at baseline (within four weeks after screening) to receive either leflunomide (n=30) or matching placebo (n=15) for 24 weeks. The dosage schedule included a loading dose of 100 mg (given on day 1, 8, and 15) and leflunomide 20 mg on the other days during the first three weeks, followed by a maintenance dose of 20 mg daily. We often apply this slightly modified dosing schedule, as we have the impression that the rate of gastrointestinal complaints is less than with the standard schedule. Compliance was assessed by tablet counts of returned study preparations and was calculated on the basis of the number of days in the study.

Efficacy and safety indices (vital signs and adverse events) were assessed at baseline, week 4, week 12, and week 24. The following efficacy variables were used: BASDAI [15], pain assessed on a VAS (0–10), BASFI [16], Bath ankylosing spondylitis global score (BASG) [17], Bath ankylosing spondylitis metrology index (BASMI) [18], 44 swollen joint count (SJC), general wellbeing on a VAS (0–10) according to the physician, erythrocyte sedimentation rate (ESR), and C reactive protein.

Blood tests (haematology and blood chemistry) were monitored every two weeks during the first six weeks and at regular intervals later during the study period.

Statistics
Based on an assumed 50% response rate for leflunomide and 20% for placebo, adjusting for a non-evaluable rate of 25%, 61 patients per treatment would have been needed to reach a level of significance of 0.05 with a power of 80%. Underlining the explorative character of this trial, and because of obvious feasibility issues in this single centre study, it was decided to randomise 45 patients. Expecting a higher dropout rate in the leflunomide group, a randomisation ratio was defined with a 2:1 balance (30 leflunomide patients and 15 placebo patients) so as to ensure a minimum collection of efficacy and safety data in a new indication for leflunomide. Altogether, the power of the study was reduced to 65%, which reasonably can be said to show at most an effect trend.

The primary efficacy variable was the 20% response rate, as recommended by the Assessments in Ankylosing Spondylitis (ASAS) working Group [19]. Each patient was classified as a treatment responder or non-responder at the end point (week 24 or last available observation under treatment). The ASAS 20% response was defined as improvement of ≥20% and absolute improvement of ≥1 unit (on a scale of 0 to 10) in at least three of the following four domains and absence of deterioration (change for the worse of ≥20% and net worsening of ≥1 unit) in the remaining domain: patient global assessment, pain (VAS), BASFI, and inflammation (the mean of the two morning stiffness related BASDAI VAS scores).

The responder rates in the two treatment groups were compared using the binomial test for two samples, and the 95% confidence intervals were calculated. Subgroup analyses were done in patients with an ESR of >30 mm/h or a C reactive protein of >10 mg/l, or both, at baseline, and in patients with peripheral arthritis (SJC >1 at baseline).

The secondary efficacy variables at end point were compared with the assessments at baseline and 95% confidence intervals for the differences between leflunomide and placebo for the mean changes from baseline were calculated. Student’s t test was used for variables with a normal distribution and the Mann–Whitney U test for variables with a non-normal distribution. A two-sided p value of less than 0.05 was considered significant.

The primary and secondary efficacy analyses and safety analysis were carried out on an intention to treat basis.

The efficacy analysis was also done for the per-protocol (PP) population. We defined the PP population as all patients treated with a minimum drug exposure of eight weeks, and excluding one patient in whom the prednisone dose was increased. The PP population (36 patients) was identified before unblinding the treatment allocation. The study was approved by the local ethics review board, and written informed consent was obtained from all patients.

RESULTS

Baseline characteristics
The demographic data of the patients and disease characteristics at baseline are summarised in table 1. The variables were comparable and not statistically different between the two treatment groups. Fourteen patients had a history of uveitis (eight leflunomide and six placebo). Two patients in the leflunomide group and one in the placebo group had inactive inflammatory bowel disease and one patient in both
groups had psoriasis. NSAIDs were used by 93% of the leflunomide and 87% of the placebo treated patients. Corticosteroids were used by one patient. None of the patients had ever used a TNF blocking agent.

Table 1. Demographic and mean (or median) baseline characteristics (and ranges) of 45 patients with active ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=15)</th>
<th>Leflunomide (n=30)</th>
<th>95% CI*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>10 (67)</td>
<td>22 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% HLA-B27 positive</td>
<td>100 (14/14)</td>
<td>81 (21/26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 (25 to 58)</td>
<td>42 (22 to 66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median disease duration (years)</td>
<td>5.7 (0.3 to 14.1)</td>
<td>9.4 (0.3 to 38.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis (%)*</td>
<td>2 (13)</td>
<td>2 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASDAI (0–10)</td>
<td>5.9 (2.9 to 9.7)</td>
<td>6.4 (2.7 to 9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>18 (2 to 54)</td>
<td>22 (2 to 66)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of patients with at least one swollen joint.

BASDAI, Bath ankylosing spondylitis disease activity index; ESR, erythrocyte sedimentation rate.

Primary efficacy variable
The number of responders according to the ASAS 20% definition was 11: 8 (27%) in the leflunomide group and 3 (20%) in the placebo group (95% confidence interval (CI) for difference, −32% to 19%).

In the subgroup with an ESR of ≥30 mm/h, or a C reactive protein of ≥10 mg/l, or both, at baseline (n=26), the response rate was 32% and 29% for the leflunomide and the placebo group, respectively (−42% to 36%).

In the subgroup of patients with peripheral arthritis (SJS ≥1 at baseline), which included only four patients, the response rate was 50% in the leflunomide and 100% in the placebo group (−19% to 100%).

In the per-protocol population the response rate was 6/24 (25%) in the patients treated with leflunomide and 2/12 (17%) in the placebo treated patients (−36% to 19%).

Secondary efficacy variables
The mean secondary efficacy variables at baseline and the mean changes after 24 weeks did not show any significant differences of global disease activity (BASG), disease activity index (BASDAI), functional index (BASFI), pain, metrology index (BASMI), swollen joint count or C reactive protein between the treatment groups (table 2). The mean change in ESR was the only variable that differed significantly between the treatment groups in favour of the placebo group. This observation was the result of a skewed distribution of the ESR, because the differences between the median changes were much smaller.

Table 2. Mean efficacy variables at baseline and the mean change after 24 weeks with the 95% confidence interval for the difference in change between the treatment groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=15)</th>
<th>Leflunomide (n=30)</th>
<th>95% CI*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASG last week (0–10)</td>
<td>5.8 (−0.6 to 6.9)</td>
<td>6.9 (−1.3 to 1.3)</td>
<td>(−0.9 to 2.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>BASG last six months</td>
<td>6.7 (−1.5 to 7.4)</td>
<td>7.0 (−0.7 to 0.7)</td>
<td>(−2.2 to 0.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Pain (0–10)</td>
<td>6.2 (−0.5 to 6.8)</td>
<td>6.8 (−1.4 to 0.4)</td>
<td>(−0.9 to 2.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>BASFI (0–10)</td>
<td>5.4 (−0.4 to 5.2)</td>
<td>5.0 (0.0 to 1.0)</td>
<td>(−1.3 to 0.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>BASDAI (0–10)</td>
<td>5.9 (−0.3 to 6.4)</td>
<td>6.1 (−1.1 to 0.1)</td>
<td>(−0.5 to 2.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>BASMI (0–10)</td>
<td>3.3 (0.3 to 4.2)</td>
<td>3.0 (0.0 to 0.3)</td>
<td>(−0.1 to 0.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>SJC (0–44)</td>
<td>0.4 (−0.2 to 0.1)</td>
<td>0.2 (−0.0 to 0.2)</td>
<td>(−0.9 to 0.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Global physician (0–10)†</td>
<td>5.1 (−0.7 to 5.5)</td>
<td>5.5 (−0.5 to 1.5)</td>
<td>(−1.1 to 0.8)</td>
<td>0.70</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>18.1 (−1.9 to 22.1)</td>
<td>22.1 (8.4 to 23.5)</td>
<td>(−17.8 to −2.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>21.4 (−6.1 to 27.0)</td>
<td>26.5 (6.5 to 19.8)</td>
<td>(−30.9 to 5.8)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*95% confidence interval for difference of mean change between placebo and leflunomide.
†General wellbeing of the patient according to physician.

BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASG, Bath ankylosing spondylitis global score; BASMI, Bath ankylosing spondylitis metrology index; ESR, erythrocyte sedimentation rate; SJC, swollen joint count.

Adverse events and dropouts
Adverse events were seen in 24 leflunomide cases (80%) and 10 placebo cases (67%). The adverse events were classified as possibly drug related in 18 (60%) and six (40%) of the leflunomide and placebo treated patients, respectively. No serious adverse events were seen. Most frequent or clinically relevant adverse events were: gastrointestinal disorders (57% in the leflunomide and 33% in the placebo treated patients, respectively); upper respiratory tract infections (17% in the leflunomide and 27% in the placebo treated patients); dermatitis and prurigo (13% in both groups); fatigue (in 13% of the placebo treated patients); deep venous thrombosis (in one placebo patient). In the leflunomide group, a rise in liver enzymes to three times the upper normal limit was observed in one patient with borderline liver enzyme tests at
baseline. No clinically relevant changes were found in the other laboratory variables. No changes were seen in the mean blood pressures. Antihypertensive treatment had to be increased in one patient treated with leflunomide.

Eleven patients were withdrawn prematurely from the study (fig 1), for the following reasons: adverse events (five leflunomide patients, two placebo patients); lack of efficacy (three leflunomide patients); non-compliance (one placebo patient). Four of these dropouts were responders (three leflunomide patients and one placebo patient). Adverse events leading to withdrawal were gastrointestinal disorders (4), malaise (1), exacerbation of pain (1), headache (1), and erectile dysfunction (1).

![Trial profile](image)

**Figure 1.** Trial profile. Five screened patients are not included because they did not meet the criteria for disease activity, and two patients because they wanted to have a child. AE, adverse events.

Compliance
On the basis of the number of days in the study (leflunomide, mean 134 days; placebo, mean 142 days) and the number of returned tablets, the calculated compliance was 96% in the leflunomide group and 93% in the placebo group.

DISCUSSION
Leflunomide did not result in significant clinical improvement in active ankylosing spondylitis in this placebo controlled study. The number of AS patients who fulfilled the ASAS 20% response rate was higher in the leflunomide group than in the placebo group, but the difference did not reach statistical significance. The changes in the individual secondary disease outcome indices were comparable. Importantly, no serious or unexpected adverse events were encountered.

Only one other study has investigated the efficacy of leflunomide in AS; this was an open label non-comparative trial of 20 AS patients who were treated for 24 weeks [20]. Ten patients were prematurely withdrawn because of lack of efficacy, side effects, or non-compliance. In line with our results, leflunomide seemed to be ineffective. The only significant improvement observed was in a subgroup of 10 patients suffering from peripheral arthritis. In our study, only four patients had peripheral arthritis in at least one joint and therefore we could not draw any conclusions about the efficacy of leflunomide in this subgroup.

The efficacy of leflunomide in AS in our study appears disappointing but it is consistent with the experience with other DMARDs in AS. Most studies with DMARDs in AS, particularly sulfasalazine, show improvement of the peripheral arthritis and ESR, but no significant improvement in the axial complaints [2, 21]. Mesalazine, which is very effective in inflammatory bowel disease, was not shown to be effective in AS [22]. Limited data are available of methotrexate in AS, but a recent small placebo controlled trial (in which a lower dose was used than in most studies in rheumatoid arthritis) showed favourable results [23]. The large number of patients with peripheral arthritis in that study (65% of the 17 recruited patients) was striking.

In rheumatoid arthritis leflunomide reduces the numbers of macrophages and T cells infiltrating the synovium, and the expression of adhesion molecules, proinflammatory cytokines, and mediators of joint destruction such as matrix metalloproteinase (MMPs) [24]. Whereas the molecular pathways have been thoroughly analysed in rheumatoid arthritis, the mechanisms of joint inflammation and destruction are less well understood in AS. In sacroiliac biopsies from 32 patients with spondyloarthritis, T cells and macrophages were the predominant cells, suggesting an important role for these cell types in the pathogenesis [25]. Moreover, TNFα blocking treatment in AS downregulates both cytokines secreted by T cells and MMPs in the synovium in spondyloarthritis [26, 27]. Therefore an effect of leflunomide on AS could be expected. It is interesting that significantly higher serum MMP-3 concentrations are encountered in AS patients with peripheral joint disease than in those with only axial symptoms [27]. This latter finding could be the pathophysiological explanation for a possible effect of leflunomide in cases of AS with peripheral joint disease.

It is clear that leflunomide is not effective when compared with the very efficacious TNF-α blocking agents, although direct comparative trials have not been conducted. An interesting observation from a trial of anti-TNFα treatment in AS was that patients with a raised C reactive protein had greater benefit from the treatment than those with lower levels [3]. However, in our study no difference in responder rate between the treatment groups was seen in the subgroup with an ESR of ≥30 mm/hour or a C reactive protein of ≥10 mg/l, or both, at baseline.
Conclusion
This is the first double blind, placebo controlled study of leflunomide in active AS. Unfortunately, it was not possible to show that it had significantly better efficacy than placebo. Whether or not this drug is beneficial for AS patients with peripheral arthritis remains to be established, as in our study the number of such patients was too small to allow us to draw meaningful conclusions. This might be an interesting subject for future research.

REFERENCES


Leflunomide in AS

Chapter 4


CHAPTER 5

Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation.

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ABSTRACT

Objective
Correlation of serum trough infliximab levels and antibodies to infliximab (anti-infliximab) with clinical response in ankylosing spondylitis.

Methods
In accordance with the international ASsessment in Ankylosing Spondylitis (ASAS) consensus statement, patients were treated with infliximab (5 mg/kg) every 6 weeks after a starting regimen. Preinfusion sera were collected at baseline, 24 and 54 weeks. At every visit, the 20% improvement response (ASAS-20) was assessed and laboratory tests performed.

Results
24 of the 38 (63%) patients fulfilled ASAS-20 response criteria after 24 weeks of treatment and 21 (53%) after 54 weeks. After 54 weeks, 11 (29%) patients showed undetectable serum trough infliximab levels and detectable anti-infliximab; six of these patients developed an infusion reaction. Anti-infliximab was found significantly more often (p=0.04) in ASAS-20 non-responders compared with responders at week 54. Serum trough infliximab levels were significantly (p<0.0001) lower in patients with (mean 0.02 mg/l) than in those without (12.7 mg/l) anti-infliximab.

Conclusion
In ankylosing spondylitis, high levels of serum trough infliximab correlated with a good clinical response. Detection of anti-infliximab within 54 weeks is associated with undetectable serum trough infliximab levels, reduced response to treatment and increased risk of developing an infusion reaction.

INTRODUCTION

Large randomised clinical trials have shown that tumour necrosis factor blocking agents such as infliximab are very effective in ankylosing spondylitis [1]. It is unknown why >30% of patients with ankylosing spondylitis fail to respond, or why some initial responders lose responsiveness during treatment and in some cases even develop an infusion reaction.

The non-responsiveness to infliximab might be due to the development of antibodies against it, which has been described in patients with rheumatoid arthritis and Crohn’s disease [2–5]. In ankylosing spondylitis, we recently showed in a small group of patients that detection of anti-infliximab was associated with undetectable serum trough infliximab levels, a reduced response to treatment and a higher risk of infusion reactions [6].

The aim of this study was to evaluate these data in a larger group of patients with ankylosing spondylitis who were treated for a longer period of time and to specify the influence on infliximab levels.

METHODS

All consecutive patients with ankylosing spondylitis (according to the 1984 modified New York Criteria [7]) who received treatment with infliximab in our centre were included in this study.

Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [8] and the ASsessment in Ankylosing Spondylitis 20% response criteria (ASAS-20) [9]. Active disease was defined as a BASDAI score ≥4. Response to treatment with infliximab was defined as fulfilment of the ASAS-20 response criteria.

Patients with ankylosing spondylitis were treated with intravenous infliximab, 5 mg/kg bodyweight at baseline, weeks 2 and 6, and every 6 weeks thereafter. This treatment was initiated in accordance with the international ASAS consensus statement [9]. In case of decrease of clinical response, the dose of infliximab was increased to 7.5 mg/kg.

At each visit, the presence of infections, side-effects or infusion reactions, and the cause for discontinuation of therapy were recorded. Questionnaires and routine laboratory tests were obtained. Preinfusion sera were collected at baseline, weeks 24 and 54, before any dose escalation and at two consecutive visits after dose escalation. After 24 weeks of treatment, serum samples were collected from 15 patients to measure infliximab levels 2 weeks after the infliximab infusion.
Validated immunoassays (Sanquin Research, Amsterdam, the Netherlands) were used for detection of anti-infliximab and serum trough infliximab levels [5]. Trough serum infliximab levels were measured by ELISA, based on the principle that infliximab is captured through its ability to bind tumour necrosis factor-a. The assay, which was described previously, was modified recently. It currently uses specific polyclonal rabbit antibodies to infliximab for detection instead of the monoclonal anti human IgG that was previously used. The sensitivity of detection is 0.0003 mg/l.

A radioimmunoassay was used for anti-infliximab detection [5]. Arbitrary units per ml (AU/ml) were expressed as absolute amounts of infliximab-specific IgG (mg/l) (1 AU=12 ng of infliximab-specific IgG) [10]. The cut-off value for IgG anti-infliximab was determined by assaying in our anti-infliximab test 100 plasma samples from blood donors sent to Sanquin for IgG anti-tetanus toxoid testing. The average result (AU/ml) + 6 SD was 12 AU/ml (0.144 mg/l).

The clinical data and presence of HLA B27 were used to correlate disease activity with serum trough infliximab levels and anti-infliximab levels. Differences between groups were tested with the Mann–Whitney U test. Associations were calculated with logistic regression. The threshold for significance was set at p<0.05. The last observation was carried forward for patients who dropped out before week 54.

RESULTS

Demographic and clinical characteristics of the 38 patients included are shown in table 1. Four patients were lost to follow-up before week 54: one wanted to become pregnant, one preferred to be treated in a hospital nearby and two because of comorbidities.

There was a significant decrease in BASDAI, morning stiffness, global disease activity and C-reactive protein after 24 and 54 weeks of treatment (table 1) and all pre-treatment samples showed undetectable infliximab levels and no anti-infliximab. We did not detect anti-infliximab in the presence of infliximab.

After 24 weeks, 24 patients (63%) met ASAS-20 response criteria. Responders showed higher mean serum trough infliximab levels, and only two patients (8%) showed anti-infliximab, compared with 5 (36%) of the non-responders (p=0.08).

After 54 weeks of treatment, ASAS-20 response criteria were met by 21 patients (55%). The mean serum trough infliximab level for responders was significantly (p<0.01) higher that that of the non-responders (8.2 mg/l vs 6.3 mg/l; figure 1) and anti-infliximab was significantly (p<0.04) more often found in non-responders. Only 5% (1 of 21) of the responders showed anti-infliximab, compared with 59% (10 of 17) of the non-responders.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>26 (68)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 (10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HLA B27+ (%)</td>
<td>32 (84)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IBD (%)</td>
<td>6 (16)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of corticosteroids (%)</td>
<td>3 (8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of other immunosuppressives (%)</td>
<td>6 (16)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BASDAI</td>
<td>6.4 (1.2)</td>
<td>3.6 (2.6)†</td>
<td>4.1 (3.0)‡</td>
</tr>
<tr>
<td>Morning stiffness†</td>
<td>6.3 (2.2)</td>
<td>3.0 (2.5)†</td>
<td>3.5 (3.2)‡</td>
</tr>
<tr>
<td>GDA</td>
<td>6.8 (1.3)</td>
<td>4.3 (2.9)‡</td>
<td>4.9 (3.4)§</td>
</tr>
<tr>
<td>C-reactive protein (normal&lt;8.0 mg/l)</td>
<td>37 (34.2)</td>
<td>9.3 (10.7)‡</td>
<td>15.8 (21.1¶)</td>
</tr>
<tr>
<td>Detectable serum trough infliximab (%)</td>
<td>0</td>
<td>31 (82)</td>
<td>27 (71)</td>
</tr>
<tr>
<td>Anti-infliximab (%)</td>
<td>0</td>
<td>7 (18)</td>
<td>11 (29)</td>
</tr>
</tbody>
</table>

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (0–10 cm); GDA VAS, Global Disease Activity Visual Analogue Scale (0–10 cm); HLA B27, human lymphocyte antigen B27; IBD, inflammatory bowel disease. 
† Mean of item 5+6 of the BASDAI (0–10 cm).
¶ Compared with baseline: † p<0.001; ‡ p=0.005; § p=0.003.

In total, 9% (1 of 11) patients with detectable anti-infliximab was classified as a responder at week 54, compared with 74% (20 of 27) of patients without anti-infliximab (figure 2).

**Figure 1.** Serum trough infliximab level for responders (n=21; 8.2 mg/l) and non-responders (n=17; 6.3 mg/l) according to the ASAS-20 response criteria, at week 54 (p=0.018).
After correction for probable confounding variables such as gender and human leucocyte antigen B27 (HLA-B27), the absence of anti-infliximab remained a significant determinant for ASAS-20 response, with an odds ratio (OR) of 100 (95% CI 5.2 to 1000). Remarkably, the presence of anti-infliximab was significantly associated with the absence of HLA-B27 (OR=7.1; 95% CI 1.1 to 47.6; Pearson chi-squared test, p=0.03).

Two weeks after the infusion of week 24, significantly lower infliximab levels were measured (20 mg/l compared with 51 mg/l; p<0.01) in patients who developed anti-infliximab within 54 weeks of treatment.

In 12 patients, dose was increased within the 54 weeks, because of insufficient clinical response. Nine (75%) of these patients showed anti-infliximab antibodies. Increase in dose did not result in a significant increase of the serum trough infliximab level (p=0.33), or a significant decrease in the anti-infliximab level (p=0.90) and BASDAI (p=0.39). However, 2 of 12 patients reported longer duration of effect.

Infusion reactions occurred in six patients. Most reactions were mild, and all patients recovered after supportive therapy. Treatment with infliximab was stopped in each case. Every infusion reaction was preceded by development of anti-infliximab and consequently undetectable serum trough infliximab levels. All antibodies to infliximab consisted of IgG1 and IgG4 subtypes. Although these infusion reactions resemble a type 1 allergic reaction, no IgE was detected. One patient’s pre-infusion serum contained an anti-infliximab level of 6.4 g/l, indicating that approximately half of his total serum IgG consisted of infliximab-specific antibodies.

**DISCUSSION**

A good clinical response of ankylosing spondylitis to treatment with infliximab was correlated with the presence of high serum trough infliximab levels and the absence of anti-infliximab antibodies, and inefficacy with the reverse. Moreover, these data demonstrate that anti-infliximab antibodies precede an infusion reaction.

The mechanism of the decrease in efficacy can be explained by the lower serum trough infliximab levels, probably caused by enhanced clearance due to immune complex formation of anti-infliximab antibodies and infliximab. A recent study in RA showed an enhanced clearance as a consequence of this process and an accumulation in the macrophage–phagocyte system (liver and spleen) [11]. Indeed, in those patients with ankylosing spondylitis who developed detectable anti-infliximab within 54 weeks of treatment with infliximab, a significantly lower infliximab level was found 2 weeks after infusion compared with patients who did not develop anti-infliximab.

Often, the infliximab dose is increased in ankylosing spondylitis when responsiveness decreases, but reasons for dose escalation in ankylosing spondylitis are not yet well defined. In our small sample, no clear increase in serum trough infliximab level after dose escalation was shown.

Another option is to try to prevent anti-infliximab formation with the concomitant administration of other immunosuppressive drugs such as methotrexate; however, this medication is not efficacious in ankylosing spondylitis [12].

Remarkably, absence of HLA B27 shows significant correlation with anti-infliximab formation. Further genetic evaluation will be performed to unravel this interesting observation.

It also has to be investigated whether coadministration of immunosuppressive drugs inhibits anti-infliximab formation, and whether infliximab levels can be used for determination of the optimum dose of infliximab in ankylosing spondylitis.

In accordance with our previous report, the efficacy of infliximab in ankylosing spondylitis is clearly related to infliximab levels and the formation of anti-infliximab antibodies. Detection of anti-infliximab antibodies within 54 weeks is associated with undetectable serum trough infliximab levels, reduced response to treatment and increased risk of development of an infusion reaction.
REFERENCES


Elevated liver enzymes in patients with ankylosing spondylitis treated with etanercept.

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**ABSTRACT**

**Objective**
TNF-alpha blocking agents are very effective in patients with ankylosing spondylitis (AS), but several cases of liver problems have been published. We systematically studied the frequency of this potential side effect in our AS patients treated with etanercept.

**Methods**
Consecutive AS patients treated with etanercept for at least 3 months were included. Liver disease was defined as elevated liver enzymes more than 1.5 times the upper normal limit (UNL) and was categorised as probably, possibly, probably not or not related to etanercept treatment. Patients with and without raised liver enzymes were compared for prognostic factors.

**Results**
A total of 105 patients were included. Fifteen patients had elevated liver enzymes more than once. In nine cases, the liver disease was probably (five) or possibly (four) related to etanercept treatment. The liver enzyme elevations were serious (≥3x UNL) in six cases and resulted in permanent cessation of etanercept in two cases. The nine patients with liver disease were compared with patients without elevated liver enzymes. No differences were found in age or use of alcohol; however, in patients with liver disease, a higher body mass index and a trend for a higher atherogenic index were observed. Hepatic steatosis was observed in five of six patients with elevated liver enzymes.

**Conclusion**
Elevated serum aminotransferases, probably or possibly related to etanercept treatment, were observed in 9% of the AS patients. An increased risk for the elevation of liver enzymes was found in patients with a higher body mass index. We recommend regular testing of liver enzymes in patients treated with etanercept.

**INTRODUCTION**

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial skeleton and entheses. Until recently, therapeutic options were limited to physiotherapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and in case of peripheral arthritis, sulfasalazine [1].

Since 2002, TNF-alpha blocking agents proved to be very effective in patients with spondyloarthropathy [1]. Well-known and most frequent adverse events are infections, allergic reactions, pruritus, injection site reactions and fever [2].

In placebo-controlled trials, serious liver problems were seldom seen [3]. And thus far, a few case reports of liver disease during treatment with a TNF-alpha blocking agent have been published [4-7].

Unexpectedly, we observed in our clinical practice several AS patients with liver enzyme elevations during treatment with etanercept. This prompted us to study systematically the frequency of this potential side effect in our AS patients treated with etanercept and to identify prognostic factors.

**METHODS**

From 2004 onwards, all AS patients treated with etanercept are prospectively followed in the outpatients clinic of Reade (formerly Jan van Breemen Institute) in Amsterdam. All patients fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for treatment with a TNF-alpha blocker: AS was diagnosed according the modified New York criteria and disease activity index (BASDAI) ≥ 4 despite the use of at least two NSAIDs during at least 3 months [8].

In these patients, laboratory tests were done at screening, baseline, week 4, week 12 and thereafter every 3 months. The tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase. At screening, the following parameters are determined: gender, age, HLA-B27 status, body mass index (BMI), atherogenic index (i.e. total cholesterol/HDL-cholesterol ratio), co-morbidity as diabetes mellitus, use of alcohol, all co-medication as NSAIDs, disease-modifying antirheumatic drugs (DMARDs) and isoniazide (as isoniazide is nowadays more frequently used in biologic treated patients).

For the present study, AS patients treated with etanercept 50 mg weekly for at least 3 months were included. Liver disease was defined as elevation of at least one of the liver enzymes more than 1.5 times the upper normal limit (UNL) at least at two time points. Liver enzyme elevation of ≥3 times UNL was defined as serious.
A total of 155 patients were included (mean age 43 years, 74% male). Fifteen patients (10%) had elevated liver enzymes (ALT or AST >1.5 UNL) during treatment. The majority (13 patients) had elevated liver enzymes due to isoniazide. One of the 15 patients had diabetes mellitus.

In all but one case, the increase in ALT was higher than in AST. Levels of alkaline phosphatase were normal. One of the 15 patients had diabetes mellitus.

In table 1, details of the patients with elevated liver enzymes are shown. In all but one case, the increase in ALT was higher than in AST. Levels of alkaline phosphatase were normal. One of the 15 patients had diabetes mellitus.

**RESULTS**

**Statistical analysis.** Patients with raised liver enzymes were divided into two groups: those with a strong temporal relation and those without. The groups were compared using Chi-square tests. Dichotomous variables are presented as number (percentage). The Mann-Whitney test was used to compare continuous variables. A p-value of <0.05 was considered statistically significant.

**Table 1. Clinical details of the 15 ankylosing spondylitis patients with elevated liver enzymes (ALT or AST >1.5 UNL) during treatment with etanercept.**

<table>
<thead>
<tr>
<th>nr</th>
<th>sex</th>
<th>age (yr)</th>
<th>raised ALT history</th>
<th>time after start ETN (months)</th>
<th>max. ALT (U/l)</th>
<th>virus test</th>
<th>ANA</th>
<th>ultrasounds</th>
<th>scan</th>
<th>stop ETN</th>
<th>comments</th>
<th>relation etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>43</td>
<td>no</td>
<td>0</td>
<td>240</td>
<td>n.a.</td>
<td>dub</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Recovery stop MTX.</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>52</td>
<td>yes</td>
<td>1</td>
<td>82</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Improvement stop ETN.</td>
<td>probably no in history ALT 110.</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>58</td>
<td>no</td>
<td>1</td>
<td>87</td>
<td>n.a.</td>
<td>neg</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Recovery stop meloxicam and paroxetine.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>49</td>
<td>yes</td>
<td>10</td>
<td>97</td>
<td>n.a.</td>
<td>neg</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Spontaneous fluctuation.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>36</td>
<td>yes</td>
<td>2</td>
<td>120</td>
<td>gGT (466)</td>
<td>neg</td>
<td>steatosis</td>
<td>no</td>
<td>no</td>
<td>Improvement after stop diclofenac and alcohol.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>36</td>
<td>yes</td>
<td>2</td>
<td>170</td>
<td>n.a.</td>
<td>neg</td>
<td>n.a.</td>
<td>temp.</td>
<td>no</td>
<td>Improvement after temporary stop for other reason.</td>
<td>possibly</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>26</td>
<td>yes</td>
<td>1</td>
<td>43</td>
<td>n.a.</td>
<td>pos</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Same as patient 7.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>f</td>
<td>57</td>
<td>yes</td>
<td>3</td>
<td>75</td>
<td>n.a.</td>
<td>neg</td>
<td>n.a.</td>
<td>n.a.</td>
<td>no</td>
<td>Temp. rel. Improvement after stop flurbiprofen.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>50</td>
<td>no</td>
<td>1</td>
<td>107</td>
<td>neg</td>
<td>neg</td>
<td>steatosis</td>
<td>no</td>
<td>steatosis</td>
<td>Pos. rechallenge. Also influence of diclofenac / INH</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>40</td>
<td>no</td>
<td>6</td>
<td>166</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>temp.</td>
<td>temp.</td>
<td>Pos. rechallenge. Also influence of diclofenac / INH</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>37</td>
<td>no</td>
<td>1</td>
<td>124</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>temp.</td>
<td>temp.</td>
<td>Strong temp. relation and pos. rechallenge.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>m</td>
<td>35</td>
<td>no</td>
<td>3</td>
<td>146</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>no</td>
<td>no</td>
<td>Strong temp. relation.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>f</td>
<td>63</td>
<td>no</td>
<td>1</td>
<td>162</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>def.</td>
<td>no</td>
<td>Strong temp. relation.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>m</td>
<td>34</td>
<td>no</td>
<td>2</td>
<td>179</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>def.</td>
<td>no</td>
<td>Strong temp. relation and pos. rechallenge.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>m</td>
<td>27</td>
<td>no</td>
<td>1</td>
<td>187</td>
<td>n.a.</td>
<td>neg</td>
<td>steatosis</td>
<td>no</td>
<td>no</td>
<td>Strong temp. relation.</td>
<td></td>
</tr>
</tbody>
</table>

**Raised ALT history:** ALT or AST >1.5 UNL in past. **Time after start ETN:** time of event in months after start etanercept. **Max. ALT:** maximal level of ALT (U/l). **gGT:** gamma glutamyl transferase (U/l). **Virus test:** antibody tests for viral hepatitis. N.a.: not applicable. Neg: negative. Dub: dubious. Pos: positive. ANA: antinuclear antibody. Steatosis: hepatic steatosis. CT: computer tomography. **Stop ETN:** cessation of treatment with etanercept because of increased liver enzymes. **Temp:** temporary. Def: definitively. MTX: methotrexate. INH: isoniazide. Pos. rechall.: positive re-challenge. Temp. relation: temporal relation.
phosphatase were (nearly) normal and gamma glutamyl transferase was elevated in one patient. In the 2 years before start of etanercept, at least one to three results of liver enzyme tests were known of most patients. In the five cases with "liver disease probably related to etanercept," the liver enzymes were normal before the start of etanercept. In three of the four cases with "liver disease possibly related to etanercept," liver enzymes were abnormal at the start of etanercept and two had elevated ALT >1.5 ULN in the past. However, in these cases, the enzymes clearly increased after start of the medication and etanercept seemed to aggravate a pre-existing liver problem. DMARDs (3x sulfasalazin, 1x methotrexate) were stopped because of the elevated enzymes, resulting in recovery in only one case. Thirteen of the 15 patients used a NSAID, which was stopped to assess the possible effect on the liver enzymes. In some cases, the liver disease appeared to be related to the combination of medication, as liver enzymes were raised during the use of the combination of etanercept and other medication and were normal during the use of the individual drugs. Increase of liver enzymes was observed 1-3 months after the start of etanercept, but in one case after 6 months.

Hepatic steatosis, diagnosed by ultrasonography and in one case by computer tomography (CT), was observed in most patients (seven out of eight) with elevated liver enzymes. Ultrasonography was only performed when the treating physician considered this as necessary and therefore was not done in all patients with liver disease and in none of the patients without liver abnormality. No liver biopsy was done.

Serious liver enzyme elevations (≥3 times UNL) were observed in six cases and resulted in definitive cessation of etanercept in two cases with decreasing enzymes during the follow-up period. In the other cases, the liver enzymes decreased after temporary cessation or after stopping other medication or the enzymes fluctuated in ranges that were considered acceptable by the treating rheumatologist.

The nine patients with liver disease probably or possibly related to etanercept were compared with the patients without elevated enzymes (table 2). No differences were found with respect to age, sex or alcohol use. However, in patients with liver disease, a higher BMI (p=0.000) and a trend for a higher atherogenic index (i.e. total cholesterol/HDL-cholesterol ratio) were observed. (p=0.15)

Table 2. Median baseline values of patients with liver disease probably or possibly related to the use of etanercept compared to patients using etanercept without raised liver enzymes.

<table>
<thead>
<tr>
<th></th>
<th>normal ALT/AST (n=90)</th>
<th>elevated ALT/AST (n=9)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), med (IQR)</td>
<td>43 (37-51)</td>
<td>38 (36-51)</td>
<td>0.679</td>
</tr>
<tr>
<td>Male, no (%)</td>
<td>64 (72)</td>
<td>7 (78)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI, med (IQR)</td>
<td>25 (23-28)</td>
<td>31 (29-34)</td>
<td>0.000</td>
</tr>
<tr>
<td>Atherogenic index, med (IQR)</td>
<td>3.6 (2.9-4.5)</td>
<td>4.3 (3.7-4.6)</td>
<td>0.151</td>
</tr>
<tr>
<td>Alcohol (units/wk), med (IQR)</td>
<td>1.0 (0.0-7.0)</td>
<td>2.0 (0.0-9.0)</td>
<td>0.885</td>
</tr>
</tbody>
</table>


Figure 1 depicts the levels of ALT and AST, in relation to the medication, in a representative HLA-B27 positive male patient aged 34 years with elevated liver enzymes probably related to etanercept (patient 14 in table 1). He used naproxen for several years. After starting etanercept 25 mg twice weekly, ALT and, to a lesser extent, AST raised in 3 months from near normal levels to 157 U/L (normal <45) and 80 U/L (normal <35), respectively. Alkaline phosphatase and gamma glutamyl transferase were normal. IgM antibodies to Epstein-Barr, cytomegalovirus and hepatitis A were negative as well as HBsAg, anti-HBs, hepatitis C antibodies and the antinuclear antibody (ANA) test. Baseline total cholesterol was 3.7 mmol/l, the atherogenic index was 4.6 and he was overweight (BMI 39 kg/m²). CT scan revealed hepatic steatosis. Due to the presence of obesity, a liver biopsy was not performed. There was no alcohol abuse and no co-morbidity such as diabetes mellitus. Stopping naproxen did not change the level of the liver enzymes. After stopping etanercept, ALT dropped to 88 U/L in 2 months. Another 2 months later, etanercept was restarted and ALT rose again, from 75 U/L to 179 U/L in one month. After again stopping the etanercept, ALT dropped to 122 U/L in a few weeks and after 3 months ALT was 66 U/L. The figure also shows that liver enzymes raised again after the start of adalimumab, another TNF-alpha blocking agent.
Elevated liver enzymes

Chapter 6

DISCUSSION

Increased liver enzymes were found in 15 of 105 (14%) AS patients who were treated with etanercept for at least 3 months. In nine of these cases (60%), a relation of liver enzyme abnormality with the use of etanercept was classified as probable or possible.

As raised liver enzymes are observed in studies of the normal population, comparison with a placebo group would be preferable [10]. However, we compared the data of the patients with the levels of liver enzymes in the 2 years before the start of etanercept. In several placebo-controlled trials with TNF blockers, liver enzyme abnormalities were seen sporadically, but here, only the more severe abnormalities were mentioned [3, 11, 12]. Two studies however, which are summarized below, reported less severe abnormalities as well [13, 14].

The first study was a double-blind trial comparing adalimumab with placebo for 24 weeks in patients with AS. Mean increases in ALT, AST and total bilirubin concentrations were statistically significant different between the two groups. Six patients taking adalimumab and one taking placebo had a post-baseline ALT concentration ≥3x UNL. The ALT concentration returned to normal during continued adalimumab treatment in four of the six patients. An AST concentration ≥3x UNL was less frequently observed.

The second study was a placebo-controlled trial of golimumab in AS. Increased (>UNL) ALT and AST levels were seen in 2.6 and 1.3% of the patients in the placebo group and 6.0 and 5.3% in the golimumab-treated patients. Marked abnormal post-baseline ALT or AST values were observed in one placebo-treated patient and in eight golimumab-treated patients. In three patients (all in the 100 mg group), the study drug was discontinued for this reason.

In summary, in these placebo-controlled trials, liver enzyme increases of >3x UNL are seen occasionally and more frequent in the patients using the TNF blocker. Also, the mean increase of liver enzymes is higher compared to the placebo-treated patients.

In our study, the frequency of elevation of liver enzymes in patients treated with etanercept was investigated. However, these elevations have been seen in all TNF blocking agents, as was described in the above-mentioned placebo-controlled trials and in several published case histories [4, 5]. It is unknown if the frequency of this adverse event differs between the several TNF-blocking agents in AS. In a study in patients with rheumatoid arthritis, liver enzyme elevations were most consistently associated with infliximab, less commonly observed with adalimumab and not observed with etanercept compared with comparator DMARDs [15]. Unlike our case shown in the figure, it has been reported that a successful switch to another TNF blocker is possible without relapse [6, 18]. Perhaps the frequency of elevation of liver enzymes during treatment with a TNF blocker is higher in AS than in other rheumatic diseases [17]. Obviously, this cannot be explained by the use of hepatotoxic co-medication like methotrexate, which is used more often in rheumatoid arthritis and seldom in AS. A role of other co-medications as NSAIDs and prednisone is unlikely, but cannot be completely excluded.

When elevation of liver enzymes is observed during treatment with medication, other causes like alcohol and other toxic agents, viral infections, co-medication and co-morbidity have to be excluded. When another aetiology is unlikely and the event recurs on re-challenge, a relation with the drug is probable. Several pathogenetic mechanisms could play a role.

One possibility is reactivation of viral hepatitis which was described in patients receiving etanercept [18]. However, in other case series of patients with viral hepatitis, etanercept appeared to be safe [19-23]. Another option is that toxic hepatitis occurs due to etanercept like the reported case of liver biopsy-confirmed toxic hepatitis attributable to infliximab [6]. Another publication described a liver biopsy which revealed a granulomatous hepatitis associated with etanercept [5]. This case is interesting because more cases of sarcoid-like granulomatosis were reported in patients treated with TNF blockers [24]. Theoretically, this is related to the

Figure 1. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (U/l) and use medication in a male with ankylosing spondylitis. X-axis time in months.
type of TNF blocker and seen more often in the soluble receptor blocker compared to the monoclonal antibodies. This might be caused by differences in the action on T cells and differences in the ability to induce apoptosis [25]. This different effect on granuloma formation is also reflected in the higher risk of tuberculosis with monoclonal antibody therapy [25].

TNF blockers can also induce autoimmune disease by triggering development of auto-antibodies and following infliximab therapy autoimmune hepatitis has been diagnosed based on liver biopsy and positive ANA and double-stranded DNA antibody test results [4]. These authors suggested the possibility that this adverse event could be more frequent in AS than in rheumatoid arthritis, as in AS immunosuppressive co-medication is used much less frequent. In case of autoimmune hepatitis, therapy with steroids can be successful. As in our study, in the published cases and in the above-mentioned placebo-controlled trials, laboratory tests in TNF blockers suggest hepatocellular injury. However, in rare cases cholestatic liver disease is described [5, 26].

In our study, an increase of liver enzymes was associated with a significantly higher body mass index and a higher atherogenic index. Serum ALT activity is found to be independently related to body mass index and to laboratory indicators of abnormal lipid or carbohydrate metabolism [27]. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes in the developed countries [28]. Most NAFLD patients will develop impaired glucose tolerance and progression of liver fibrosis is associated with more pronounced insulin resistance and more significant weight gain. Several cytokines play a role in these processes. An increased expression of inflammatory enzymes like TNF-alpha is found in alcoholic and non-alcoholic fatty liver disease [29]. TNF blockers may also have a favourable effect on the lipid profile in patients with rheumatic diseases [30]. Therefore, blocking TNF-alpha could have a favourable effect in fatty liver disease. But our study suggests that etanercept can aggravate a pre-existing liver problem, possibly because hepatocytes in livers with fatty changes are more vulnerable to the effects of TNF blockers.

In most patients, a small increase of liver enzymes has no clinical relevance. However, in several of our patients, we had to stop co-medication, had to start another TNF blocker and in some cases anti-TNF therapy had to be stopped permanently. In the literature, several cases of severe hepatic toxicity have been reported including jaundice, hepatic failure, liver transplantation and death [4]. Therefore, we recommend regular testing of liver enzymes, especially ALT and AST, in all patients treated with TNF blockers, particularly in those patients that seem to be more at risk, i.e. patients with a high body mass index and high atherogenic index.

In conclusion, elevated serum aminotransferases, probably or possibly related to etanercept treatment, were observed in 9% of the AS patients. An increased risk for elevation of liver enzymes was found in patients with a high body mass index and high atherogenic index.

REFERENCES

Elevated liver enzymes


What do we miss? ASAS non-responders on anti-TNF therapy show improvement in performance-based physical function.

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ABSTRACT

Objective
A prospective study was conducted in order to establish whether AS patients, who are defined as non-responders after 3 months of anti-TNF therapy, show improvement on performance-based tests of physical functioning.

Methods
At baseline and 3 months after the start of anti-TNF therapy, AS patients completed seven performance-based tests of physical functioning, questionnaires on self-reported physical functioning (BASFI) and disease activity (BASDAI), and a pain and a global patient assessment. The concordance between ≥20% intra-individual improvement on the performance-based test of physical functioning and (i) response to anti-TNF therapy (Assessment of SpondyloArthritis international Society 20% (ASAS20) response) and (ii) ≥20% intra-individual improvement on self-reported physical functioning (BASFI) was assessed.

Results
One hundred AS patients were included, of which 82 patients completed all tests at both time points. After 3 months of anti-TNF therapy, 27 (32.9%) patients were categorized as non-responders according to the ASAS20 response criteria. Improvement in performance-based physical functioning was seen in 13 of the 27 non-responders (48.1%) (i.e. n = 13/82 = 15.9% of the total group). Furthermore, 30 (36.6%) patients showed no improvement on self-reported physical functioning (BASFI). However, 17 of the 30 (56.7%) patients did improve on the performance-based tests of physical functioning (i.e. n = 17/82 = 20.7% of the total group).

Conclusion
After 3 months of anti-TNF therapy, performance-based tests of physical functioning showed improvement in 48.1% of the ASAS20 non-responders. With these performance-based tests, new information on outcome after anti-TNF therapy can be generated. Using performance-based tests alongside the BASFI could have additional value in the evaluation of outcomes for patients receiving anti-TNF therapy.

INTRODUCTION

AS is characterized by limitations in physical functioning due to pain, stiffness and fusion of the spine. Anti-TNF therapy has been shown to improve physical functioning [1]. For evaluation of the disease course and the effectiveness of anti-TNF therapy, physical functioning is an important outcome measure.

Physical functioning in AS is most commonly assessed with the BASFI [2, 3], a self-reported, disease-specific, valid and reliable outcome measure [4–6]. In the absence of a true gold standard, the BASFI is considered the best option to assess physical functioning. However, it is a self-reported outcome measure and therefore is susceptible to subjective interpretation (under- or overestimation) due to confounding effects of perceived physical functioning, personality traits, pain, language or depression [7–10].

Performance-based tests are a more objective outcome measure to evaluate physical functioning. Performance-based tests of physical functioning based on the BASFI have been developed and have shown adequate to excellent reliability [11]. The association between the performance-based tests and the BASFI is only moderate [11, 12]. Furthermore, a previous study showed that alongside actual performance, AS patients seem to incorporate exertion and pain in their assessment of perceived physical functioning on the BASFI [12]. This suggests that performance and self-reported measures do not measure the same aspects of physical functioning. Consequently performance-based tests could provide an objective outcome measurement for the evaluation of physical functioning and give additional information on changes in physical functioning in addition to the BASFI. This would provide an argument for the use of performance-based tests alongside the BASFI in the evaluation of treatment modalities like anti-TNF therapy.

This prospective study therefore aimed to establish whether AS patients showed improvement on performance-based tests of physical function after 3 months of anti-TNF therapy (etanercept or adalimumab). We investigated whether patients, defined as non-responders according to the Assessment of SpondyloArthritis International Society 20% response (ASAS20) [13, 14], showed improvement in performance-based physical functioning. Furthermore, we investigated the differences between improvement in performance-based and self-reported (BASFI) physical functioning after 3 months of anti-TNF therapy.
PATIENTS AND METHODS

Patients were recruited from a large outpatient centre for rheumatology and rehabilitation (Reade) in Amsterdam. Enrolment took place from May 2006 to June 2010. The following inclusion criteria were applied: diagnosis of AS according to the modified New York criteria [15], ≥18 years of age, eligible for treatment with anti-TNF and sufficient command of the Dutch language. Patients were excluded if they had pulmonary, cardiovascular or neurological comorbidity affecting the patient’s ability to perform daily activities. The study was approved by the medical ethics committee of Reade. All patients gave written informed consent according to the Declaration of Helsinki.

Measures

At baseline and after 3 months of anti-TNF treatment (etanercept or adalimumab), patients completed seven performance-based tests of physical functioning, questionnaires on self-reported physical functioning (BASFI) and disease activity (BASDAI) [16], and a pain and patient global assessment. At both time points, spinal and hip mobility was also assessed, using the BASMI [17, 18].

Before each test the patient was uniformly instructed as to how to execute the test. The tests were carried out in the following order. The outcome of the performance tests was the time needed to complete the task, measured in seconds. A detailed description of the performance-based test was given in an earlier publication [11]. The performance tests were based on items of the BASFI and consisted of seven items representing one domain: physical functioning [12].

(i) Climbing stairs: patients faced a flight of 12 steps and were instructed to climb the stairs without using the handrail or a walking aid.
(ii) Bending: patients were instructed to bend forward from the waist and pick up six pens from the floor without an aid and place them on a shelf one by one.
(iii) Reaching: patients faced two shelves placed below each other. Six pens were placed on the lower shelf. Patients were instructed to reach up and place the pens on the highest shelf without help or aids.
(iv) Putting on socks: patients stood barefooted with a pair of socks in one hand and were instructed to put on the socks without help or aids.
(v) Reclining and declining from a chair: patients were instructed to stand up and sit down three times in a row from the chair without using their hands or any other assistance.
(vi) Getting up from the floor: patients began the test lying supine on the mat and were instructed to get up without help.
(vii) Physically demanding activities: two pylons were placed 10 m apart. Patients were provided with a heart rate monitoring device and were instructed to perform the shuttle walk test. The test was stopped if the patient’s heart frequency (HF) exceeded 80% of the HF maximum, if the patient could not keep up with the pace as instructed by the assessor or if the patient wanted to stop.

Statistical analyses

Descriptive statistics were computed by calculating mean and s.d. for all continuous data and percentages for categorical data. Paired samples t-tests were used to assess improvement on performance-based tests and self-reported physical functioning (BASFI), disease activity (BASDAI) and spinal and hip mobility (BASMI).

A score for performance-based physical functioning was computed by calculating the mean of the seven performance-based tests [12]. Although the unit of measurement for all tests was the same (i.e. seconds), a standardization procedure was necessary because the distributions between the tests varied (i.e. different mean and s.d.). Therefore raw performance scores were transformed into z-scores. In this way, all tests contributed evenly to the mean performance score.

The ASAS20 response [13, 14] was used to categorize patients as responders or non-responders to anti-TNF therapy. Analogous to the ASAS criteria, an individual improvement of ≥20% was used to classify patients as improvers or non-improvers on performance-based tests of physical functioning. On self-reported physical functioning, patients were defined as improved if they showed an individual improvement of ≥20% and ≥1 unit on the BASFI. This is the same extent of improvement as described for the BASFI in the ASAS20 improvement criteria [13, 14].

Subsequently, cross-tabulations were produced to establish the concordance between improvers on performance-based physical functioning (number and percentage) in (i) (non-) responders on the ASAS20 criteria and (ii) (non-) improvers on self-reported physical functioning (BASFI). All analyses were performed using SPSS for Windows 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

The study population consisted of 100 patients with a confirmed diagnosis of AS, fulfilling the modified New York criteria. Data for 18 patients were incomplete after follow-up; 7 patients (7%) did not start treatment, 4 stopped treatment within 3 months (4%) and 7 (7%) were not reassessed due to other reasons. No patients were excluded for having pulmonary, cardiovascular or neurological comorbidity affecting the patient’s ability to perform daily activities. Accordingly, 82 patients (67.5% men,
n = 56) with a mean age (± s.d.) of 43.9 ±11.3) years were reassessed and included in
the analyses. Medication at baseline was used by 89% of the study population and consisted mainly of NSAIDs. Table 1 displays the characteristics of the study population.

According to the ASAS20 criteria, 27 (32.9%) patients were categorized as non-responders. After 3 months of anti-TNF therapy, patients experienced a significant decline in self-reported limitations in physical functioning and disease activity, as shown by lower BASFI and BASDAI scores (P < 0.0001). Furthermore, an improvement in spinal mobility (BASMI) (P < 0.01) and performance-based physical functioning were observed (P < 0.0001).

**Table 1.** Characteristics of 82 AS patients.

<table>
<thead>
<tr>
<th></th>
<th>Before anti-TNF therapy</th>
<th>After 3 months of anti-TNF therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, % [n]</td>
<td>67.5 (56)</td>
<td>65.0 (47)</td>
</tr>
<tr>
<td>Age [a], years</td>
<td>43.9 (11.3)</td>
<td>43.9 (11.3)</td>
</tr>
<tr>
<td>Symptom duration [a], years</td>
<td>21.3 (11.1)</td>
<td>21.3 (11.1)</td>
</tr>
<tr>
<td>Disease duration [a], years</td>
<td>13.4 (9.4)</td>
<td>13.4 (9.4)</td>
</tr>
<tr>
<td>Medication, % [n]</td>
<td>9.6 (8)</td>
<td>9.6 (8)</td>
</tr>
<tr>
<td>None</td>
<td>9.6 (8)</td>
<td>9.6 (8)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>77.1 (64)</td>
<td>77.1 (64)</td>
</tr>
<tr>
<td>DMARDs [b]</td>
<td>12.0 (10)</td>
<td>12.0 (10)</td>
</tr>
<tr>
<td>HLA-B27+, % [n]</td>
<td>79.5 (66)</td>
<td>79.5 (66)</td>
</tr>
<tr>
<td>ESR [c], mm/h</td>
<td>22.8 (19.0)</td>
<td>22.8 (19.0)</td>
</tr>
<tr>
<td>Extra-spinal symptoms</td>
<td>39.8 (33)</td>
<td>39.8 (33)</td>
</tr>
<tr>
<td>Arthritis, % [n]</td>
<td>6.0 (5)</td>
<td>6.0 (5)</td>
</tr>
<tr>
<td>Psoriasis, % [n]</td>
<td>7.2 (6)</td>
<td>7.2 (6)</td>
</tr>
<tr>
<td>ASAS20 response, % [n]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>67 (55)</td>
<td>67 (55)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>33 (27)</td>
<td>33 (27)</td>
</tr>
<tr>
<td>BASFI [c], score 0–10</td>
<td>5.4 (2.1)</td>
<td>3.3 (2.4)</td>
</tr>
<tr>
<td>BASDAI [c], score 0–10</td>
<td>6.0 (1.7)</td>
<td>3.1 (2.1)</td>
</tr>
<tr>
<td>BASMI [c], score 0–10</td>
<td>4.1 (1.9)</td>
<td>3.7 (1.9)</td>
</tr>
<tr>
<td>Performance-based tests [c]</td>
<td>1.03 (0.84)</td>
<td>0.72 (0.60)</td>
</tr>
</tbody>
</table>

*a Values are presented as mean (s.d.), unless indicated otherwise. bDMARDs: SSZ, MTX. cReported score is mean z-score.

**Improvement in performance-based tests vs ASAS20 response after anti-TNF therapy**

Table 2 shows the cross-tabulation between (non-)improvers on the performance-based tests and (non-)responders on the ASAS20 response. Improvement in performance-based physical functioning was seen in 70.9% (n = 39/55) of the responders (i.e. n = 39/82 = 47.6% of the total group). However, 48.1% (n = 13/27) of the ASAS20 non-responders showed a ≥20% improvement in performance-based physical functioning (i.e. n = 13/82 = 15.9% of the total group).

**Table 2.** (Non-)improvers (performance-based functioning) vs (non-)responders (ASAS20) and (non-)improvers (self-reported functioning) after 3 months anti-TNF therapy (n = 82)*

<table>
<thead>
<tr>
<th></th>
<th>No (%)</th>
<th>Yes (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responder to anti-TNF therapy</strong> (ASAS20 response)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (17.1)</td>
<td>13 (15.9)</td>
<td>27 (32.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (19.5)</td>
<td>39 (47.6)</td>
<td>55 (67.1)</td>
</tr>
<tr>
<td><strong>Improvement in self-reported physical functioning</strong> (BASFI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (15.9)</td>
<td>17 (20.7)</td>
<td>30 (36.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (20.7)</td>
<td>35 (42.7)</td>
<td>52 (63.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30 (36.6)</td>
<td>52 (63.4)</td>
<td>82 (100)</td>
</tr>
</tbody>
</table>

*Percentages of the total group are given. Improvement defined as ≥20% intra-individual change on performance-based tests. Responder defined according to ASAS20 response criteria: improvement of ≥20% and ≥1 unit in at least three of four self-reported domains, and no worsening of ≥20% and ≥1 unit in the remaining domain on an NRS of 0–10. Improvement defined as ≥20% and ≥1 unit intra-individual change on the BASFI questionnaire.

**Improvement in performance-based vs self-reported physical functioning after anti-TNF therapy**

The cross-tabulation between (non-)improvers on the performance-based tests and (non-)improvers on self-reported physical functioning (BASFI) is also shown in Table 2. Thirty patients (36.6%) did not improve in physical functioning according to the BASFI after 3 months of anti-TNF therapy. However, 17 of the 30 patients (56.7%) showed an improved performance-based physical functioning (i.e. n = 17/82 = 20.7% of the total group).

Of the total group (n = 82), 57 patients were treated with etanercept and 25 patients were treated with adalimumab. Analyses were repeated and performed separately for etanercept and adalimumab. Analyses yielded similar results to the total group.
DISCUSSION

This prospective study focused on the improvement in performance-based physical functioning after 3 months of anti-TNF therapy. Our results showed that 48.1% of the AS patients, who were defined as non-responders on the ASAS20 criteria, displayed at least 20% improvement in performance-based physical functioning (i.e. 15.9% of the total group). Furthermore, 56.7% of the patients who did not improve in self-reported physical functioning (BASFI) did improve on the performance-based tests (i.e. 20.7% of the total group).

Until now, outcome after anti-TNF therapy had only been measured with self-reported outcomes like the BASFI, BASDAI 50% response [19] or a combination of self-reported outcomes such as the ASAS20 response (which contains the BASFI). Our results suggest that using both self-reported and performance-based outcome measures could have additional value in evaluating outcome after interventions in AS patients.

We showed that 48.1% of the non-responders to anti-TNF therapy (ASAS20) improved in performance-based physical functioning. This suggests that patients improve due to the effects of anti-TNF therapy objectively (e.g. they can get up from the floor more quickly), however, they do not feel better in a subjective way (i.e. they still experience pain, stiffness and/or fatigue). We also would like to point out that 29.1% (n = 16/55) of the patients who showed a response according to ASAS criteria did not improve on the performance-based tests. This suggests that patients experience a decline in pain, stiffness or fatigue and/or improvement in self-reported physical functioning after anti-TNF therapy, while the actual level of physical functioning may not have changed at all. Both observations are in line with previous findings that self-reported levels of functioning are strongly related to pain and exertion and less to the time required to complete a task [10, 12]. Also, the contrast between improvement in self-reported (BASFI) and performance-based physical functioning underlines that perceived and actual physical function are two related but distinct entities.

In conclusion, after 3 months of anti-TNF therapy, improvement in performance-based physical functioning was seen in 48.1% of the ASAS20 non-responders. Performance-based tests provide the opportunity to generate new information in the evaluation of outcome after anti-TNF therapy. In the future, using performance-based tests alongside the BASFI could provide additional value in evaluating outcome for AS patients receiving anti-TNF therapy.
REFERENCES


Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with ankylosing spondylitis.

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ABSTRACT

Objective
To investigate whether use of adalimumab decreases the frequency of attacks of anterior uveitis (AU) in patients with ankylosing spondylitis (AS).

Methods
Consecutive patients with AS, visiting an outpatient clinic and treated for at least 12 weeks with adalimumab, were enrolled. The number of attacks of AU in the year before start and during treatment were assessed by patient history and ophthalmological controls.

Results
In the 77 patients a total of 52 AU attacks occurred in the year before baseline (68 attacks per 100 patient-yrs), whereas during adalimumab treatment 19 attacks were seen (14 per 100 patient-yrs; reduction rate 80%). Twenty-six patients with AU in the year before start of adalimumab treatment had recurrent attacks, with a median number of 2.0 AU attacks per year [interquartile range (IQR) 1.00–3.00], whereas during treatment this decreased to 10 patients with a median number of 0.56 attacks per year (IQR 0.30–0.75). Hence, the number of attacks per year decreased by 72% (p = 0.000).

Conclusion
In patients with AS, a significant reduction in the number of AU attacks, as well as in the number of attacks per patient, was observed during adalimumab treatment.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that starts at a young age and causes inflammatory back pain, stiffness, and bone deformation of the sacroiliac joints and vertebral spine. Recently, treatment with tumor necrosis factor (TNF)-blocking agents, such as infliximab, etanercept, adalimumab, and golimumab, has proven to be very effective in treatment of spinal inflammation in AS [1-4].

In AS, in addition to the spine, other organs can be affected, like the eye (anterior uveitis), gut (inflammatory bowel disease), and skin (psoriasis).

Anterior uveitis (AU) is strongly associated with the HLA-B27 antigen. The occurrence of AU is increased in the HLA-B27-positive population, with a lifetime cumulative incidence of 1% compared with 0.2% in the general population [5]. Up to 47% of patients with AU are positive for the HLA-B27 antigen [6]. The mean prevalence of AU in AS was 33% in a systematic literature review, and increased with disease duration [7]. More importantly, AU can be the first presenting symptom of AS [8-10]. The attacks of uveitis are usually unilateral and recurrent and cause sudden ocular pain, with redness and photophobia. These attacks might lead to inflammatory debris accumulating in the anterior chamber, which may cause pupillary and lens dysfunction and blurring of vision. Most of the time the uveitis subsides in several weeks, but in some cases glaucoma and severe visual impairment may occur if adequate treatment is delayed [11]. Acute attacks call for urgent treatment by the ophthalmologist with topical (or in some cases even systemic) corticosteroids.

In refractory uveitis (often panuveitis, idiopathic or secondary to an autoimmune disease), infliximab proved to be beneficial, but overall the degree of efficacy of the different TNF-blocking agents for extraspinal manifestations in AS, such as acute AU, varies [12-15]. Data available at the start of the current study showed a different pattern for infliximab compared with etanercept: etanercept was associated with a smaller reduction in the recurrence rate of the attacks in comparison to infliximab [16-19]. However, the majority of these studies in AS were based on retrospective analyses of clinical trials or open-label studies. Moreover, registrations of the attacks were reported by the patients and ophthalmologic controls were not systematically performed.

Therefore, our objective was to examine whether the use of adalimumab decreases the frequency of attacks of AU in patients with AS, who received this treatment for their spinal disease activity. This prospective follow-up study was carried out in close collaboration with an ophthalmologist who evaluated the patients at several times during the investigation.
Chapter 8

MATERIALS AND METHODS

Consecutive patients with AS (who fulfilled the modified New York criteria, attended the outpatient clinic of the Jan van Breemen Institute Reade, and fulfilled the Assessment in SpondyloArthritis international Society (ASAS) criteria for treatment with a TNF-blocking agent were enrolled [20, 21]. They were treated for at least 12 weeks with 40 mg adalimumab every other week, while other medication was continued. The number of attacks of AU in the year before start and during adenalmumab treatment was assessed by patient history and ophthalmological controls at baseline and yearly thereafter. The study started August 2006 and follow-up ended January 1, 2012, or upon discontinuation of adenalmumab treatment for any reason. All patients gave written informed consent prior to enrolment, and the local medical ethical committee gave its approval for this study.

Historical data were collected by patient questions on the occurrence of uveitis in the past, and confirmative answers were verified with the medical records of the treating ophthalmologist. Additionally, an examination by our ophthalmologist was performed at baseline and every 12 months during the first 2 years of treatment. In case of a uveitis attack the patient was treated by his or her own ophthalmologist, who was always contacted by our study ophthalmologist afterwards. The number of attacks of uveitis during treatment with adenalmumab was compared with the number of attacks in the year before therapy. According to the Standardization of Uveitis Nomenclature (SUN) working group a relapse in < 3 months after discontinuing treatment was defined as chronic uveitis; therefore a maximum of 3 flares per year were counted as separate episodes [22]. Patients with insufficient data (no previous uveitis data or follow-up data available, or less than 12 weeks follow-up) were excluded from the analysis.

The patients were assessed by a physician and research nurse at regular intervals. The following measurements and questionnaire data were collected: swollen joint count, spinal measurements (Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global score (BASG), and ASQOL (AS Quality of Life questionnaire), and the occurrence of extraspinal manifestations (like colitis, psoriasis, and uveitis) [23-26]. In addition, laboratory tests were performed, e.g., erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Visits took place at screening, baseline (within 2 weeks after screening), after 1, 3, 6, 9, and 12 months during the first year, and every 6 months thereafter.

The primary outcome measure was the occurrence of attacks of AU in the year before baseline and during treatment with adenalmumab. The secondary outcome measures were the changes in disease variables and the efficacy of adenalmumab on disease activity of AS measured with the ASAS 20%, ASAS 40%, and BASDAI 50% responses during treatment [27].

Statistical analysis

The distribution of continuous variables was tested for normality. Data are represented as mean ± standard deviation (SD), median, and interquartile range (IQR) or percentages. A paired t-test, or when appropriate the Wilcoxon signed-ranks test, was used to determine significant changes from baseline; missing values were excluded in listwise fashion. Binary variables (such as occurrence of uveitis) were analyzed with the McNemar test. P values < 0.05 were considered statistically significant. All analyses were performed using SPSS version 17.0.

RESULTS

A total of 100 consecutive patients with AS were screened for study, of whom 90 were included and 10 were not: 5 patients never started with adenalmumab therapy for several reasons, 4 declined to participate in the study and 1 declined due to pregnancy. Out of these 90 patients, 13 were excluded: 2 withdrew consent and 11 patients had incomplete follow-up (Figure 1). The remaining 77 patients were included in the final analyses. Demographic and disease characteristics at baseline are shown in Table 1. Disease-modifying antirheumatic drugs were used at baseline by 27% of patients (e.g., sulfasalazine or methotrexate) and 21% did not respond to prior anti-TNF treatment (etanercept and in 1 case infliximab; Table 1). The patients were predominantly male (61%) with a median disease duration of 7 years. The prevalence of HLA-B27 antigen was 76%, and 33 patients (43%) had experienced at least 1 attack of uveitis.

Comparison between patients with and those without uveitis showed that among patients who had experienced at least 1 attack of uveitis, the prevalence of the HLA-B27 antigen was significantly higher: 29/33 (94%), compared with those who never had uveitis: 28/44 (64%) (p = 0.003). The median BASMI was lower in the patients with uveitis-ever (score 3.0; IQR 1.5–5.0) compared to the rest of the patients (score 3.0; IQR 1.5–5.0) (p = 0.007). The median disease duration of patients with uveitis-ever (12.0 yrs; IQR 2.8–19.8) was longer than that in patients who never had uveitis (7.0 yrs; IQR 1.5–12.5), but this difference was not significant (p = 0.069). No other significant differences were seen between patients with and those without uveitis-ever in other patient or disease characteristics (data not shown).
Table 1. Demographic and disease characteristics of patients with ankylosing spondylitis (AS) at baseline (n = 77) and during follow-up with adalimumab treatment. Mean values (standard deviation) or median (interquartile range, IQR) are shown, as appropriate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>47 (61)</td>
<td></td>
<td></td>
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<tr>
<td>Age, yrs, mean (SD)</td>
<td>45 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>53 (75)</td>
<td></td>
<td></td>
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<tr>
<td>Duration of inflammatory back pain, median yrs (IQR)</td>
<td>17 (10–25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (diagnosis), median yrs (IQR)</td>
<td>7 (2–15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since first uveitis, median (IQR)</td>
<td>11 (4–23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior uveitis ever, n (%)</td>
<td>33 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior uveitis last year, n (%)</td>
<td>26 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B27 present, n (%) (n = 75)</td>
<td>57 (76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis, n (%)</td>
<td>5 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease, n (%)</td>
<td>9 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of NSAID at baseline, n (%)</td>
<td>65 (84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of DMARD at baseline, n (%)**</td>
<td>21 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of prednisone, n (%)</td>
<td>4 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous use of other anti-TNF therapy***</td>
<td>16 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASDAI, mean (SD)</td>
<td>5.5 (2.1)</td>
<td>3.8 (2.5)*</td>
<td>3.7 (2.4)*</td>
</tr>
<tr>
<td>BASFI, median (IQR)</td>
<td>4.7 (2.7–6.6)</td>
<td>3.6 (1.1–5.4)*</td>
<td>2.9 (0.9–5.6)*</td>
</tr>
<tr>
<td>BASG, mean (SD)</td>
<td>6.6 (2.1)</td>
<td>4.9 (2.4)*</td>
<td>4.0 (2.5)*</td>
</tr>
<tr>
<td>BASMI, median (IQR)</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>ASQOL, median (IQR)</td>
<td>9.0 (5.8–13.0)</td>
<td>6.5 (2.0–10.0)*</td>
<td>4.0 (2.0–9.0)*</td>
</tr>
<tr>
<td>No. patients with at least 1 swollen joint (SJC-JC-72) (%)</td>
<td>18 (25)</td>
<td>6 (9)*</td>
<td>3 (6)*</td>
</tr>
<tr>
<td>ESR, median mm/h (IQR)</td>
<td>14 (7–31)</td>
<td>6 (3–15)*</td>
<td>6 (2–14)*</td>
</tr>
<tr>
<td>CRP, median mg/l (IQR)</td>
<td>4 (2–13)</td>
<td>1 (1–4)*</td>
<td>1 (1–3)*</td>
</tr>
<tr>
<td>No. ASAS-20% responders (%)</td>
<td>25 (56)</td>
<td>20 (53)</td>
<td></td>
</tr>
<tr>
<td>No. ASAS-40% responders (%)</td>
<td>1 (2)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>No. BASDAI-50% responders (%)</td>
<td>31 (55)</td>
<td>19 (41)</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 followup towards baseline. ** DMARD: In most cases sulfasalazine (n = 10) or methotrexate (n = 8). *** Previous use of other anti-TNF agent: etanercept (n = 15), infliximab (n = 1). NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying drug; BASDAI: Bath AS Disease Activity Index (0–10); BASFI: Bath AS Functional Index (0–10); BAS-G, Bath AS Global Score (0–10); BASMI, Bath AS Metrology Index (0–10); ASQOL, AS Quality of Life (0–18); SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASAS: Assessment of Spondyloarthritis International Society; TNF: tumor necrosis factor.

In total, 67 of the 77 patients (87%) were seen by the ophthalmologist at baseline and 44 (57%) during follow-up; the other data were retrieved from hospital charts and protocol visits to the research physician. The median follow-up period (i.e., duration of treatment) was 1.74 years (IQR 0.83–2.84), with a total of 139 patient-years. Three subjects had symptomatic uveitis at baseline. Ophthalmological examinations in patients without symptoms did not reveal any uveitis.

Out of the 77 patients at baseline, 51 (66%) had no attacks of uveitis in the year before treatment, nor during treatment. No patient developed uveitis for the first time during adalimumab treatment. Seven patients (9%) were classified as having chronic uveitis, but during adalimumab treatment chronic uveitis did not occur.

In all patients, the total number of uveitis attacks was 52 in the year before baseline (i.e., 68 attacks per 100 patient-yrs), whereas during adalimumab treatment 19 attacks were seen (14 per 100 patient-yrs; reduction rate 80%). Uveitis attacks were treated with topical steroids.
Among the 26 (34%) patients with uveitis in the year before treatment, 10 had flares of uveitis during treatment and 16 had no uveitis (Figure 2). This indicates a 62% decrease in the number of patients with uveitis attacks \( (p < 0.0001) \). The patients with chronic uveitis responded as well as the other uveitis patients: 27% of the patients with uveitis in the year before baseline had chronic uveitis and 2 of these had uveitis after start of adalimumab (20% of all patients with uveitis during therapy).

The 26 patients with uveitis in the year before start of adalimumab experienced recurrent attacks, with a median number of 2.0 uveitis attacks per year (IQR 1.00–3.00), whereas during treatment this dropped to 10 patients, with a median number of 0.56 attacks per year (IQR 0.30–0.75). Hence, the number of attacks per year dropped by 72% \( (p < 0.0001) \).

The 26 patients with uveitis in the year before therapy had 200 flares per 100 patient-years before therapy and during adalimumab had 19 flares in 61 patient-years (31 flares per 100 patient-years; reduction rate 84%; Table 2).

Disease measures at follow-up are shown in Table 1. In general, improvement was seen in measures for disease activity, functionality, and quality of life. These improvements were statistically significant, except for the BASMI. The percentages of patients with ASAS 20% and BASDAI 50% response were 56 and 55, respectively, at Week 12 and 53 and 41, respectively, at Week 52. At Week 52 complete datasets were available for 47 patients.

Table 2. Number of anterior uveitis (AU) attacks/100 patient-years and reduction during anti-tumor necrosis factor (anti-TNF) therapy compared to placebo, i.e., year before therapy in this study compared with other studies. Duration of followup in patient-years and mean patient-years/patient.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. AU Attacks/100 Patient-yrs During Placebo</th>
<th>No. AU Attacks/100 Patient-yrs During Anti-TNF</th>
<th>Reduction, %</th>
<th>Followup, Patient-yrs (No. patients)</th>
<th>Mean Patient-yrs/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun, 2005 [1]*</td>
<td>16</td>
<td>ETN 8</td>
<td>49</td>
<td>430 (297)</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFX 3</td>
<td>78</td>
<td>146 (90)</td>
<td>1.6</td>
</tr>
<tr>
<td>Sieper, 2010 [28]*</td>
<td>19</td>
<td>ETN 12</td>
<td>38</td>
<td>1137 (1074)</td>
<td>1.1</td>
</tr>
<tr>
<td>Before anti-TNF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rudwaleit, 2009 [30]</td>
<td>15</td>
<td>ADA 7</td>
<td>51</td>
<td>363 (1250)</td>
<td>0.3</td>
</tr>
<tr>
<td>Current study</td>
<td>68</td>
<td>ADA 14</td>
<td>80</td>
<td>139 (77)</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*A randomized controlled trial (RCT) + open-label (OL) phase; ETN: etanercept; IFX: infliximab; ADA: adalimumab.

Discontinuation of therapy and adverse events

Twenty-eight (36%) of the patients stopped adalimumab therapy, usually because of inefficacy (17 patients, 61% of dropouts) or adverse events (3 patients, 11%). Other reasons for dropping out were as follows: moving out of area (2), withdrawal of informed consent (1), and other reasons (5). No patient discontinued because of an AU episode. The median follow-up period of the dropouts was 0.82 years (IQR 0.37–1.48).

A total of 268 adverse events (AE), mostly mild, were observed among 67 (87%) patients, of whom 43 (64%) were still on drug and 24 (36%) had stopped. Infection was the most common AE observed (69 times). One patient was hospitalized (due to local skin infection), and in 13 cases antibiotics were given. No patient died during adalimumab treatment.

**DISCUSSION**

The number of attacks of uveitis in patients with AS before and during adalimumab treatment revealed a significant decrease in the number of patients with uveitis (82%) during treatment, as well as a decrease in the number of attacks per patient (72%), even in patients with chronic uveitis. No patient developed uveitis for the first time during adalimumab treatment. The majority (87%) of patients remained free of uveitis attacks for the entire follow-up period. A significant improvement of disease activity (ASAS 20% response in 56% of patients) was seen as well, which is similar to the results of placebo-controlled trials with anti-TNF agents [3, 4].
Patient characteristics of those who experienced uveitis and those who did not have any attack did not differ, except for the prevalence of HLA-B27 antigen, which was significantly higher among the patients who had experienced at least 1 attack of uveitis. This observation is in accord with previous studies, which show a strong association between uveitis and HLA-B27 [5, 28]. The lower median BASMI in the patients with uveitis-ever is probably due to chance, as all other disease measures were not different. A longer disease duration in patients who had ever had uveitis could be expected, but this difference did not reach statistical significance in our patients [7].

In contrast with other studies in AS, information about uveitis in our study was obtained at visits to the ophthalmologist at baseline and during follow-up. Because the visit to the ophthalmologist could not be combined with the other protocol visits, not all patients were seen by the ophthalmologist. However, it is not likely that this had a significant influence on our results as (1) this was particularly the case in those who never had eye problems, and (2) in case of an attack of uveitis, patients were always seen by their attending ophthalmologist and this was verified by our (study) ophthalmologist.

The rates of uveitis per 100 patient-years in our study are compared with other studies that investigated this topic in Table 2. In 2 studies the incidence of uveitis during placebo and during anti-TNF therapy was determined from several clinical trials of etanercept and infliximab, including open-label extension studies [28, 29]. In an open-label uncontrolled study the rate of uveitis during adalimumab treatment was compared with the incidence reported during the year before treatment [30]. In all studies the rate of uveitis during anti-TNF treatment was lower compared to that of the placebo period or the year before therapy. The 80% reduction in recurrence rates of uveitis during adalimumab treatment in our study was higher in comparison with the other studies, which varied from 78% for infliximab, to 38%–49% with etanercept, and 68% with adalimumab (Table 2).

Differences in reduction of uveitis between these studies could be explained by differences in duration of follow-up. In our study the mean number of patient-years per patient was 1.8 years versus 0.3 years in the study of Rudwaleit, et al [30]. In some patients the efficacy of the anti-TNF treatment could last some months, an observation that might be overlooked in studies with shorter follow-up period.

Another difference is that a high percentage of our patients (n = 33, 43%) had experienced uveitis at some time before treatment, whereas in most AS studies the prevalence of AU ranged between 25% and 40% among patients [11]. Comparing the rates of uveitis flares/100 patient-years (Table 2) also shows a higher number (n = 68) in our study compared with the lower rates before treatment or during placebo in patients of other studies (which described 15 to 19 flares/100 patient-yrs). Obviously, the absolute numbers of patients with uveitis during therapy cannot be compared with other studies, but the rates of reduction can. We observed a high rate of reduction of uveitis, even in our patients with a high incidence of uveitis or chronic uveitis.

In addition, we cannot exclude that the high percentage of uveitis at baseline in our study might be due to a selection bias, because of preferential prescription of adalimumab in cases of a history of uveitis during the period of our study. On the other hand, comparing the frequency of earlier treatment with another anti-TNF therapy in this study (21%) with that of another study (26%), the study populations appear to be comparable [30].

The prevalence of uveitis in AS increases with longer disease duration [7]. However, the high prevalence of uveitis recorded in our study cannot be explained by longer disease duration compared to other studies. In contrast, the median disease duration in our study was 7 years (IQR 2–15), compared to a mean duration of 9.5–11 years in other studies [28, 30].

Interestingly, in our study no patient developed AU for the first time during adalimumab treatment, but other studies have described that a first attack of uveitis may occur during therapy with several TNF-blocking agents [30-32].

We observed a significant and substantial reduction of the rate of recurrence of attacks of acute anterior uveitis during adalimumab treatment in patients with AS, even in patients with chronic uveitis. The majority (87%) of patients remained completely free of uveitis attacks for the entire follow-up period.
REFERENCES


Etanercept increases bone mineral density in ankylosing spondylitis, but does not prevent vertebral fractures.

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W F Lems\textsuperscript{1,2}  
MT Nurmohamed\textsuperscript{1,2}  
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I E van der Horst-Bruinsma\textsuperscript{1,2}

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ABSTRACT

Objective
Ankylosing spondylitis (AS) is characterized by chronic inflammation leading to ankylosis, but also to low bone mineral density (BMD) and vertebral fractures (VF). Treatment with TNF blockers decreases inflammation and has shown to be effective in increasing BMD. We studied the effects of etanercept on BMD and VF in AS patients after 2 years treatment. Furthermore we studied changes in bone-markers (CTXI, CTXII, RANKL, OPG, Osteocalcin) and radiological damage.

Methods
Patients with active AS, treated with etanercept for 2 years, were included. BMD lumbar spine and hips was measured at baseline and after 2 years, as well as the radiological damage (mSASSS, including thoracic spine), VF (Genant method) and change in bone-markers.

Results
Forty-nine AS patients were included. After 2 years of etanercept, BMD hip raised with 2.2% (p=0.014) and BMD lumbar spine with 7.0% (p<0.001). The BASDAI decreased significantly (p<0.001) as well as CRP and ESR (p<0.001). Despite etanercept therapy, the number of patients with VF more than doubled (from 6 to 15 patients, p=0.004). Also the radiological damage increased significantly over time (from 12.1 to 18.5, p<0.001), however no significant change in bone-markers was found.

Conclusion
This prospective longitudinal observational cohort study showed that after 2 years etanercept, BMD of hip and spine increased significantly, but the number of patients with VF and the severity of VF increased as well. Besides that, radiological progression, including the thoracic spine, increased significantly. Thus, the favourable bone preserving effect is accompanied by unfavourable outcomes on VF and radiological damage.

INTRODUCTION

Ankylosing spondylitis (AS) is characterized by chronic inflammation leading to ankylosis of the spine and sacroiliac joints. Bone loss is a well known complication of AS [1, 2], which is highly prevalent after long disease duration, but starts already at an early stage [3, 4]. Bone loss and inflammation are probably responsible for the occurrence of vertebral fractures (VF) in this patient group [5-7]. The pathogenesis of the decrease in bone mineral density (BMD) is complex. Persistent inflammation (by inflammatory cytokines like TNF-α) might be an important etiologic factor [8, 9].

A way to decrease inflammation is treatment with TNF-α blockers. In rheumatoid arthritis, several studies showed an increase of BMD, additionally to the positive effects on disease activity and radiographic progression [10-12]. In AS, many studies showed positive effects of TNF-α blockers on inflammation and disease activity, although effects on decreasing radiographic progression are disappointing [13, 14]. Considering effects of TNF-α blockers on BMD, patients treated with infliximab showed significant increases in BMD scores over 2 years [15]. A very small study (n=10) of Marzo-Ortega et al. showed that etanercept increased BMD in a short follow-up study of 6 months [16]. Arendts et al. also showed an increase in BMD and, in addition, an effect in favour of bone formation by measuring bone-markers in patients treated with different types of TNF-α blockers [17], but whether there were differences between the effects of TNF-α blockers did become clear. Furthermore, clinically relevant outcome measures like VF, radiographic progression and disease activity combined in one study were not performed.

Therefore, the aim of this study was to measure the effects of 2 years of etanercept on bone quality by measuring change of BMD and the incidence of VF. Further, we assessed changes in bone-markers and the effects on radiographic damage.

PATIENTS AND METHODS

Study population
AS patients, who fulfilled the modified New York criteria for AS and were eligible for treatment with anti-TNF-α (etanercept) according to the ASAS guidelines, were recruited from the Jan van Breemen Research Institute/Reade, a large outpatient rheumatology center in Amsterdam [18]. The data for this open prospective follow-up study were collected systematically every 3 months during the first year and twice yearly thereafter.

AS patients were treated during 2 years with etanercept as decided by their physician with etanercept (25 mg twice a week or 50 mg once a week) if they had previously failed on at least two nonsteroidal anti-inflammatory drugs (NSAIDs)
and if they had active disease (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4).

Demographic data, such as HLA-B27 status, extra-articular manifestations, current use of medication, including anti-osteoporotic drugs, as well as data on known risk factors for osteoporosis, such as age, sex, race, smoking and disease duration [19, 20], were collected at baseline.

The protocol was approved by the local Medical Ethics Committee and all patients provided written informed consent.

**Outcome measures**

**Bone mineral density**

First, the change in BMD of the lumbar spine (L2-L4) and left proximal femur after 2 years of etanercept was investigated. Each patient was measured by dual energy X-ray absorptiometry (DEXA) using Lunar (Lunar expert DPX-IQ, Oldeift). Results were presented as BMD (g/cm2), T-scores and Z-scores. The T-score corresponds to the number of standard deviations (SD) from the normal mean obtained from young healthy adults and the Z-score is the T-score with a correction for age. Osteopenia and osteoporosis are defined according to the World Health Organization (WHO): 1) osteoporosis (T-score ≤ -2.5 in spine and/or hip), 2) osteopenia (-2.5 < T-score < -1.0 in spine and/or hip, without osteoporosis) [21].

**Vertebral fractures**

Further, we investigated the occurrence of VF. Radiographs of thoracic and lumbar spine were made at baseline and after 24 months. The lateral radiographs were evaluated chronologically for VF by two experienced investigators (WL and BD), who were blinded for medication the patients received. Vertebral deformities were determined by grading each vertebral body (T4-L5) according to the Genant criteria for fractures [22]. In Genant's semiquantitative assessment, the vertebrae receive a severity grade based on the visually apparent degree of vertebral height loss. The reduction in height is divided in grades on a scale of 0-3: grade 0 (normal) represents a reduction in anterior, middle, and/or posterior vertebral heights of less than 20%, grade 1 (mild) represents a reduction of 20-25%, grade 2 (moderate) reduction of 25-40% and grade 3 (severe) more than 40% reduction. VF were defined as a reduction of ≥ 20% of the vertebral body height [22].

**Markers of bone turnover**

Different bone-markers, CTX-I, CTX-II, RANKL, OPG and osteocalcin were obtained at 0, 3, 6 and 12 months. Non-fasting serum and urine were collected and stored at -20°C until analyses. Bone resorption was measured by CTX-I and CTX-II. CTX-I was determined by β-isomerised carboxy terminal telopeptide of type 1 collagen (β-CTx) in serum using commercial assays according to the instructions of the manufacturer (Roche Diagnostics, Mannheim, Germany). CTX-II was determined using a urine Cartilaps ELISA (from Immunodiagnostic Systems; IDS) for the quantification of degradation products of C-terminal telopeptides of type II collagen in human urine. Levels of osteoclast-regulating proteins, including total RANKL and OPG, were determined in serum using an ELISA (from Immunodiagnostic AG, Bensheim, Germany). Bone formation was measured by osteocalcin, using commercial assays according to the instructions of the manufacturer (Roche Diagnostics, Mannheim, Germany). All assays on the analyzer had an intra-assay and inter-assay coefficient of variation of ≤ 5%. The ELISAs had an intra-assay and inter-assay coefficient of variation of ≤ 10%.

**Radiographic progression**

The degree of radiological damage of the spine, before and after treatment with etanercept, was also investigated. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was used as the index of radiological damage of the cervical and lumbar spine [23]. The lateral radiographs of the spine of each patient, at baseline and after 24 months, were examined by two experienced investigators (CvD and IvdH). Additionally, the radiographs of the thoracic spine were assessed as well (T9-T12), although they are not implemented in the official scoring method of the mSASSS. However, since the low thoracic spine might have an additive effect on the sensitivity to change [24] and is a predilection place for VF, the thoracic X-rays were included in the measurement.

**Disease activity**

Disease activity measures included the disease activity score BASDAI [25], whereby the functional capacity scores BASFI (Bath Ankylosing Spondylitis Functional Index) [26] and BASMI (Bath Ankylosing Spondylitis Metrology Index) [27] measured the physical function. The ASAS criteria for response were applied to define response [28] as a 60% improvement or as an absolute improvement of 2 points of the BASDAI (0-10 scale) and an expert opinion in favour of continuation of treatment after 3 months.

**Statistical analysis**

Categorical variables were calculated as frequencies and percentages. Continuous variables were reported as mean and SD, or when skewed, as median and IQR. To examine the longitudinal changes in BMD (and T- and Z-scores), BMD was first tested for normality (with the Shapiro-Wilk test), and subsequently the paired t-test or Wilcoxon's signed rank test was used. Differences in VF was tested with the McNemar test. Bone-markers were tested for a linear trend with regression analyses. To detect differences between different time moments the Friedman test was used. Radiological damage was analysed first by testing for normality and
subsequently the change over time was tested with the non-parametric Wilcoxon’s signed rank test. Disease activity changes in BASDAI, CRP and ESR were also analysed with the non-parametric Wilcoxon’s signed rank test because of the skewed distribution.

Statistical analyses were performed with SPSS statistical software, version 20.0 (SPSS, Chicago, IL). P-values less than 0.05 were considered as significant.

RESULTS

Patient characteristics
In total, 49 patients with AS were enrolled and monitored after starting with etanercept. The mean follow-up duration of these patients was 2.3 years. The baseline demographics and clinical features are shown in Table 1.

Most patients were male (82%), the mean age was 42 years and the mean disease duration was 12.2 years. Three patients had a total hip replacement at inclusion. There was a high disease activity before start of therapy and the majority responded well.

Table 1. Baseline characteristics AS-etanercept cohort (N=49).

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>40 (81.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.8 (9.2)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>38 (77.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease related variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>12.2 (9.1)</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td>15.8 (9.9-23.4)</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>2.3 (0.7)</td>
</tr>
<tr>
<td>HLA-B27 positivity</td>
<td>43 (87.8)</td>
</tr>
<tr>
<td>ESR (mm/hr), &lt;20</td>
<td>20.0 (6.0-39.0)</td>
</tr>
<tr>
<td>CRP (mg/l), &lt;10</td>
<td>14.0 (3.0-39.0)</td>
</tr>
<tr>
<td>BASDAI (0-10)</td>
<td>5.7 (1.6)</td>
</tr>
<tr>
<td>BASFI (0-10)</td>
<td>5.7 (2.1)</td>
</tr>
<tr>
<td>BASMI (0-10)</td>
<td>4.4 (2.3)</td>
</tr>
<tr>
<td>Uveitis (history of)</td>
<td>17 (34.7)</td>
</tr>
<tr>
<td>Psoriasis (history of)</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>Inflammatory bowel disease (history of)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Peripheral arthritis (history of)</td>
<td>16 (32.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiographic damage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mSASSS (0-72)</td>
<td>10.0 (3.8-35.5)</td>
</tr>
<tr>
<td>Total mSASSS+ThSpine (0-90)</td>
<td>12.1 (6.8-42.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMD related variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (3.4)</td>
</tr>
<tr>
<td>Post-menopausal status</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>One or more prevalent vertebral fractures</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>24 (49.0)</td>
</tr>
</tbody>
</table>

Bone mineral density
All 49 patients had two DEXA scans of the spine and 46 patients had a DEXA of the hip (three patients had a total hip replacement). At baseline, 12% of the patients had osteoporosis, 45% osteopenia and 43% had a normal BMD. After 2 years of etanercept this changed to 4% osteoporosis, 41% osteopenia and 55% normal BMD (Table 2).

After 2 years of treatment, BMD hip raised significantly with 2.2% (5.7; p=0.014) and BMD lumbar spine raised significantly with 7.0% (9.5; p<0.001). The mean T- and Z-scores showed the same significant increase of the hip (p=0.037 vs p=0.002) and lumbar spine (both p<0.001).

Table 2. Bone mineral density of femur and spine.

<table>
<thead>
<tr>
<th>t = 0 year, before etanercept</th>
<th>t = 2 years, after etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip*</td>
<td>Spine</td>
</tr>
<tr>
<td>Normal BMD</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>19 (38.8)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4 (8.2)</td>
</tr>
</tbody>
</table>

Normal BMD= T-score ≥ -1.0, Osteopenia= -2.5 < T-score < -1.0, Osteoporosis= T-score ≤ -2.5.
Vertebral fractures
At baseline six patients (12.2%) already had at least one VF. After 2 years of etanercept, the number of patients with one or more VF was more than doubled to 15 patients (30.6%) (p=0.004). Most VF were localised in the (mid)thoracic spine. Not only the number of patients with VF increased significantly over 2 years, but also the severity (grade) of the VF; from 4 fractures (out of 8) graded 2 or more to 13 fractures (out of 21) graded at least 2 (Table 3). Analyses for risk factors for the development of VF did not show any parameter to be associated with these incident VF (such as age, BMD, disease activity, radiological damage; data not shown).

Table 3. Vertebral fractures before and after etanercept in AS (N=49).

<table>
<thead>
<tr>
<th>Vertebral fractures</th>
<th>t=0 year, before etanercept</th>
<th>t=2 years, after etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N patients</td>
<td>Number of VF</td>
</tr>
<tr>
<td>0 Vertebral fracture*</td>
<td>43 (87.8)</td>
<td>34 (69.4)</td>
</tr>
<tr>
<td>1 Vertebral fracture*</td>
<td>4 (8.2)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Grade I</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Grade II</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 Vertebral fractures*</td>
<td>2 (4.1)</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>Grade I</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Grade II</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total number of VF</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Total patients with VF*</td>
<td>6 (12.2)</td>
<td>15 (30.6)</td>
</tr>
</tbody>
</table>

*number of patients(%) VF= Vertebral Fracture, Grade I= reduction of vertebral height 20-25%, Grade II= reduction of vertebral height 25-40%, Grade III= reduction of vertebral height >40%.

Markers of bone metabolism
Boxplots of the distribution of bone-markers over time, as well as the change in disease activity (BASDAI) and inflammation (CRP) are shown in Figure 1. Bone-markers were tested for linear trend with regression analyses, but there was no significant trend over time for the bone ‘resorption’ markers, the ‘osteoclast-regulation’ markers, nor for the bone ‘formation’ marker. To detect differences between different time moments, the Friedman test was used. No significant changes in bone-markers were detected over time, except for OPG (which showed a decreasing trend). However the RANKL/OPG ratio did not change significantly over time.

Radiological progression
The median radiological damage (total mSASS-score) at baseline was 10.0 (3.8-35.5) and increased after 2 years to 15.5 (5.5-42.5). The total mSASS+ThSpine had a median at baseline of 12.1 (6.8-42.7) and progressed to 18.5 (8.7-52.0). There was a significant difference between the radiological damage at baseline and after 2 years.
Bone mineral density and vertebral fractures

Chapter 9

Disease activity
Disease activity measured by BASDAI decreased from 5.8 (5.1-6.8) at baseline to 2.1 (1.0-4.1) after 12 months and to 2.8 (1.0-4.4) after 24 months (p<0.001 at all time points compared with baseline). According to the ASAS clinical response criteria, 85% of the patients responded to etanercept at 3 months, 69% at 12 months and 63% at 24 months.

Disease activity measured by inflammation markers like CRP and ESR also decreased significantly (p<0.001 at all time points compared with baseline). CRP decreased from 14.0 (3.0-39.0) at baseline to 2.0 (1.0-6.0) at 12 months. ESR decreased from 20.0 (6.0-39.5) at baseline to 5.0 (2.0-9.0) at 12 months. ESR and CRP changes were strongly correlated (p<0.001).

There was a significant relation between the change in BMD hip and spine and the change in inflammation markers (i.e. ESR and CRP) over 12 months. Both the decrease in ESR and CRP was significantly associated with increase in BMD hip and spine (ΔBMD hip: p=0.040 vs p=0.005 and ΔBMD spine: p=0.012 vs p<0.001).

DISCUSSION
This prospective observational cohort study in patients with active AS demonstrated that after 2 years of TNF-α blocking therapy with etanercept, BMD of the hip as well as BMD of the spine increased significantly, whereas the number and severity of VF and radiographic damage increased. This observation suggests that despite the decrease in inflammation and increase in the amount of bone, the anticipated increase in bone quality stays behind. In addition, the ongoing bony proliferation is also unfavourable, which emphasizes that despite TNF-α blockers bone-(patho)physiology is still not optimal.

Since persistent inflammation might be an etiologic factor of bone loss in AS, anti-TNF-α therapy has been proposed as treatment that controls inflammation with subsequent prevention of osteoporosis and associated VF [28, 30]. This study shows that after 2 years of etanercept, the BMD increased significantly in lumbar spine as well as in the hips. This finding is in concordance with other studies that also showed an increasing trend in BMD after treatment with TNF blockers [15, 17, 31, 32].

Strikingly, this is the first study that describes the rapid progression of the number and severity of VF over two years, despite lowering disease activity and inflammation through etanercept therapy and despite the increase of BMD. The interpretation of VF in AS is a challenge, since the method of Genant does not differentiate between AS-related deformities, degenerative changes or osteoporotic fractures. The presence of low BMD and the localization of the VF suggest that these fractures are ‘real’ osteoporotic fractures. We have documented earlier in a cohort of early Spondylarthropathy patients a high number of patients (15%) with VF in especially the thoracic spine [7]. Unfortunately, VF in AS are often missed in clinical routine procedures, however diagnosing these fractures is important because the knowledge of existing fractures is necessary for optimal assessment of risk for future fractures and treatment [6, 33]. However, until now there are no clear guidelines for how we should treat these patients. In this study the treatment of the osteopenic/osteoporotic patients was performed by the treating rheumatologist. Most patients were treated with calcium/vitD, no bisphosphonate treatment was started in the period of the study.

The increased prevalence of VF despite the increase of BMD suggests that it is more likely that despite the increase in ‘quantity’ of bone mass, the problem in AS is more due to a decrease in ‘bone quality’. A specific definition of the quality of bone is difficult to be given, because multiple factors contribute to the structural integrity of bone: not only the total bone mass, but also bone geometry and properties of constituent tissue [34]. As BMD has been shown to be a limited predictor of fracture risk [35], now more clinical interest is needed for complementary measures of bone quality that could improve fracture risk prediction [36]. One of these measures could have been bone-markers, but unfortunately we did not find a linear trend of bone ‘resorption’ markers (CTX-I, CTX-II), ‘osteoclast-regulating’ markers (RANKL, OPG), or of the bone ‘formation’ marker (osteocalcin) over time during etanercept treatment, whereas the inflammatory parameters (CRP and ESR) and disease activity responded well. A decrease in bone-resorption markers and osteoclast-regulating markers was therefore expected alongside an increase in the bone-formation marker [12, 15, 17]. Still, our results were in line with the study of Allali et al. who also found in 29 AS patients an increase in BMD during treatment with TNF-α blockers and no change in biochemical markers (osteocalcin and total deoxypyridinoline) [31]. However, an early increase after 2-12 weeks in markers of bone formation (bone alkaline phosphatase) was found in other studies [15, 37], but no change in levels of CTX, OPG and RANKL [37]. Arens et al. however, showed an increase in BALP (bone formation marker), but also a decrease of serum collagen-telopeptide (bone resorption marker) [17]. It is not fully clear why we did not find changes in the investigated bone-markers. It could be related to methodological errors (samples were not taken in a fasting state), type of TNF-α blocker or type of the measured bone-markers. However until now, the result are conflicting and the value of bone markers is still not fully elucidated, especially in clinical practice [38]. Interestingly, despite etanercept the radiological damage increased significantly.
over time (p<0.001). This is confirmed by other studies with TNF blockers, including etanercept, which show no delay in radiological progression in AS [13, 39]. Kang et al. recently wrote about the ‘paradoxical effects’ of TNF inhibitors on BMD and radiographic progression in AS, since they also found an increase in BMD in combination with radiographic progression of the spine, like we did [40]. Although they didn’t study VF in combination with radiological progression. Maksymowych et al. hypothesized that early inflammatory lesions resolve after treatment with TNF blockers before the induction of reparative changes, whereas in more mature inflammatory lesions (visible on MRI as focal fat infiltration which reflects post-inflammatory tissue) new bone will be formed. New bone will be formed once the signalling pathways have been activated (through down regulation of dickkopf-1 which upregulates the Wnt pathway). Our study population consisted of patients with highly active disease and a long disease duration. It could be that the resolution of inflammation in these more mature lesions following etanercept treatment may have caused the ongoing process of new bone formation [40-42].

The fact that there are no studies at this moment that investigated the effects of etanercept on both BMD, the occurrence of VF and radiological progression in combination with bone-markers, makes this study unique. As such this is a very clinically relevant combination of outcome measures. However, there are some potential limitations to be mentioned, such as the limited size of the cohort (n=49). Nevertheless, this number is higher compared to other studies [16, 31, 40] and the results are clear enough to show the challenges we are facing on this topic. Further, the duration of the study is limited by 2 years and the measurements of the bone-markers are performed within a maximum treatment duration of 1 year. However, it was to be expected that changes in biomarkers would have occurred the first year of etanercept treatment, since it is known to have a strong and early effect on disease activity and subsequently, also on bone-markers as has been shown in rheumatoid arthritis [12]. Finally, three patients used bisphosphonates. In our opinion this has not influenced the outcomes of this study, because they used it already for more than 3 years and the results including these patients were not significantly different from when excluding them (results not shown).

This prospective cohort study shows that after 2 years of TNF-α blocking therapy with etanercept, BMD of the hip and spine increases, also both the number and severity of VF. Besides that, the radiological damage, including the thoracic spine, increased significantly. With this study we showed that with increasing the BMD, bone quality is not necessarily increased. The favourable bone preserving effect is accompanied by unfavourable outcomes on VF and radiological damage, suggesting both a lack of increase in bone strength and also a further ankylosis of the spine. More attention and research is needed to investigate the aspects of quality of bone in AS patients and the thoracic spine may not be overlooked as important place for VF.

REFERENCES

Bone mineral density and vertebral fractures

Chapter 9


Die heißen (46°) hochradioaktiven Thermen von
Bad Teplitz-Schönau (Böhmen)
erzielen seit Jahrtausenden die hervorragendsten Heilwirkungen bei
Gicht, Rheuma, Neuralgien
(Ischias)

Bad Teplitz-Schönau ist ein abhängiges Rheinbad, das älteste Bad der Tschechoslowakischen Republik.
Die hochradioaktiven Thermen (nach Dr. Běhounek 120 Mache-Einheit, bei 46° Temperatur) werden verwendet:
1. Als Theralbäder
2. In Form von Quellidunst-Bädern (Emanations-Kummen nach Prof. Dr. Püller, Dresden)
3. Zu Moorbaden (natürlichef Therme Wasser mit hochverwittertem Teplitzer Mineralmoor verrührt)
4. Zur Trinkkur
Die hervorragende Heilwirkung der Teplitzer Kurmittel wurde längst durch heimische Versuche dargetan.
Die Kurstadt bietet neben ihren hervorragenden Kurmitteln alle Annehmlichkeiten eines bedeutenden Kurzentrums (Theater, Kurorchester u. v. a.)

SAISON GANZJÄHRRIG

Hochmoderne Kuranstalten mit allem Komfort:
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Auskünfte und Druckschriften durch die
Städt. Kurdirektion, Bad Teplitz-Schönau
Telephon 507
1. GENERAL DISCUSSION AND SUMMARY

Evolving treatment of Ankylosing Spondylitis.
The therapy of ankylosing spondylitis (AS) consisted for a long time of patient education, exercise therapy and non-steroidal anti-inflammatory drugs (NSAIDs) and nowadays these are still the cornerstone of treatment. Traditionally, NSAIDs are anti-inflammatory drugs that mainly affect symptoms. In contrary, the role of disease modifying antirheumatic drugs (DMARDs), which are characterized by changing the course of the disease and delaying structural damage, was always limited in AS. Over ten years now, the tumour necrosis factor (TNF)-blockers have dramatically changed the therapeutic options in AS and spondyloarthritis (SpA).

However, the traditional distinction between NSAIDs and DMARDs is not always clear in AS. There is some evidence that NSAIDs do not only modify symptoms, but also seem to delay radiographic progression. On the other hand the effect of DMARDs was often primarily measured as effect on symptoms and inflammation and it was doubted if TNF-blockers would have effect on radiographic progression. In addition, the clinical relevance of the growth of some syndesmophytes is debatable in patients who experience impressive relief of symptoms, following TNF-blocking therapy [1]. However, for clarity, in this chapter the traditional denomination of NSAIDs and DMARDs, as used in rheumatoid arthritis (RA), was followed.

The first part of this thesis consists of studies performed just before the TNF-blockers became available and the second part concerns several aspects of anti-TNF therapy itself. The TNF-blockers seem to have solved many of the problems in AS patients, but still many questions about drug therapy in AS remain outstanding: Do NSAIDs really have disease modifying effects? What is the role of DMARDs in AS? How do we assess the efficacy of medication? What is the effect of medication on extra-articular manifestations, especially anterior uveitis, and what is the effect on bone and cardiovascular disease? What is the effect of TNF-blockers and what are the main adverse events? What can we say about non-responders and do we know enough about long-term therapy? Is there still an unmet need for new drugs to treat AS?

These various aspects of drug therapy in AS are discussed in this chapter. Summaries of the previous chapters of this thesis and conclusions are shown in cursive script.

NSAIDs.
Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2-selective inhibitors (coxibs), are recommended as first-line therapy for inflammatory back pain and stiffness in patients with AS [2]. Evidence that NSAIDs not only give symptomatic relief but also have anti-inflammatory properties is supported by the decrease of acute phase reactants (erythrocyte sedimentation rate (ESR)) and a small effect on axial MRI bone lesions during treatment with etoricoxib in an open-label study [3]. Continuous use of a NSAID, in contrast to on-demand use, proofed to retard radiographic ossification of the lumbar spine, especially in patients with elevated acute phase reactants [4-6]. Hence, in addition to analgetic and antiflogistic effects, NSAIDs might have disease modifying properties. Inhibition of bone formation was seen also in the prevention of heterotopic ossification by coxibs and effect on bone mineral density [8]. Considering the continuous use of a NSAID, the likelihood of radiographic progression in an individual patient has to be taken into account and weighted against potential (gastrointestinal and cardiovascular) adverse events [9]. The best predictor of structural progression is the presence of syndesmophytes at baseline [10]. In contrast, high levels of functional dickkopf-1 predicts protection from syndesmophyte formation [11].

In summary NSAIDs are still the cornerstone of the treatment of AS. Continuous use is recommended in patients with elevated acute phase reactants and progressive disease.

DMARDs: sulfasalazine and mesalazine.
Sulfasalazine is not effective in AS with only spinal symptoms, but several studies showed some efficacy of sulfasalazine in active AS/SpA with peripheral arthritis (weighted mean difference in ESR -4.79 and morning stiffness VAS -100mm -13.89 compared to placebo) [12-15]. Presently, sulfasalazine is still the initial treatment option for AS patients with peripheral involvement [2, 16].

Sulfasalazine is split in the large intestine in sulfapyridine and mesalazine (5-aminosalicylic acid), having antibacterial and antiflogistic properties, respectively. Mesalazine is the active drug in the treatment of inflammatory bowel disease. The effect of mesalazine was investigated in 20 patients with active AS in an open study for 24 weeks (chapter 2). There was a high rate of premature discontinuation because of intolerance. Except for a small significant decrease in erythrocyte sedimentation rate, treatment with mesalazine did not show improvement in other disease variables.

The mode of action of sulfasalazine in AS is unknown. However in 1985, a high rate of incidence of inflammation in the intestine was found in patients with HLA-B27 related arthritis [17]. In more recent studies, these numbers of intestinal involvement were confirmed in axial SpA patients [18, 19], which might explain the beneficial effects of sulfasalazine. Moreover the bacterial flora of the gut seems to be an important factor in the role of HLA-B27 in the pathogenesis of AS [20]. When the role
of the bowel and its flora is more elucidated in AS, the intestines and the enteral microbes could again be important as targets for treatment.

In AS patients with peripheral arthritis sulfasalazine is recommended. There is no evidence for use of only mesalazine in these cases.

Statins as antirheumatic drugs.
Statins have anti-inflammatory properties, as demonstrated by lowering C-reactive protein and disease activity in rheumatoid arthritis [21]. The effect of the statin rosuvastatin in AS was investigated in 15 consecutive patients with active disease in an open study during 12 weeks, followed by an observational period of 12 weeks (Chapter 3). Treatment with rosuvastatin resulted in significant decreases of C-reactive protein and erythrocyte sedimentation rate after 12 weeks and a trend of improvement in several clinical variables. A randomised, placebo controlled trial is required to prove the anti-inflammatory and disease modifying properties of statins in AS. As could be expected, total and LDL-cholesterol levels were significantly reduced during treatment in this study.

The improvement of the lipid profile is a favourable effect of statin therapy in AS, particularly in view of the increased cardiovascular risk in AS patients [22, 23]. Concerning this increased cardiovascular risk in AS patients, attention is also needed for cardio-respiratory fitness and other traditional risk factors for cardiovascular disease, as smoking, high blood pressure, diabetes and overweight [24, 25]. Moreover, effective treatment of inflammation has favourable effects on the cardiovascular risk in AS [26-28].

In addition to treatment of inflammation, in AS patients attention is recommended for traditional risk factors for cardiovascular disease. Further studies on antirheumatic properties of statins are needed.

DMARDs: leflunomide.
Leflunomide is proven to be effective in rheumatoid arthritis and psoriatic arthritis, but studies in AS were lacking so far [29, 30].

The effect of leflunomide in AS was studied in a double blind, randomised, placebo controlled trial in 45 patients with active disease (Chapter 4). The number of responders according to the Assessment of SpondyloArthritis international Society (ASAS) 20% definition was higher in the leflunomide group than in the placebo group, but the difference did not reach statistical significance. Although the study was underpowered, the differences between the treatment groups were small and therefore striking differences in a trial with higher numbers of patients are not likely. These data were confirmed by another small and open label study. In this study axial symptoms did not improve, but in patients suffering from peripheral arthritis the number of inflamed joints was reduced with leflunomide treatment [31]. The number of patients with peripheral arthritis in our trial was too small to draw any conclusion about the efficacy of leflunomide in this subgroup. If a difference in efficacy between these subgroups would exist, this might be explained by differences in pathophysiology. Significant higher MMP-3 concentrations, for example, are found in AS patients with peripheral disease compared to those with only axial disease [32].

In general, there is no place for leflunomide in the treatment of AS, but leflunomide might be considered in patients with peripheral arthritis resistant to other therapies.

Other DMARDs.
Corticosteroids are effective when used intra-articular in peripheral or sacroiliac joints [33]. Oral corticosteroids were seldom studied in AS. A recent study showed short-term efficacy of a high dose prednisone when given for two weeks [34]. A 50% improvement of the Bath AS Disease Activity Index (BASDAI) was seen in 33% of the patients treated with 50 mg prednisone every day, versus 8% on placebo. More studies are needed to establish the role of corticosteroids. An option could be that corticosteroids are used in AS as bridging therapy, like in RA, awaiting the efficacy of another treatment.

Methotrexate (MTX) was studied in a few randomized controlled AS trials, but in low numbers of patients and only in low doses (7.5-10 mg/week). Thus far, insufficient evidence was found to support benefit of MTX in the treatment of AS [35]. Studies with higher doses of MTX are needed, also in the light of the possible role of MTX in reducing immunogenicity, as is discussed below.

A short course of therapy with corticosteroids could be considered in AS, but more studies are needed to investigate long-term treatment with corticosteroids and high doses of methotrexate.

TNF-blockers
From the beginning of this century tumour necrosis factor alpha (TNF) blockers were used in AS and proofed to be very effective on both a short-term and long-term basis. During treatment with TNF-blockers, improvement was seen in symptoms, including spinal pain, morning stiffness, functioning, spinal mobility, arthritis, enthesitis, extra-articular manifestations, sleep, quality of life and also in acute phase response, hemoglobin levels and inflammatory MRI lesions [1, 36-38]. Currently, five TNF-blockers are available for treatment of AS: infliximab, etanercept, adalimumab, golimumab and certolizumab [39-43]. In a meta-analysis the odds ratio
for being in ASAS40 response was 4.7 (95% CI 3.8 - 6.0) for patients taking a TNF-blocker compared with placebo [44].

The ASAS has published international recommendations for the use of TNF-blockers in patients with axial spondyloarthritis [45]. Treatment with TNF-blockers is considered the standard of care for AS patients with active disease, who fail to respond adequately to conventional treatment. Active disease is defined as at least four weeks active disease, according to a Bath AS Disease Activity Index (BASDAI) score of at least 4 (0-10) and positive expert opinion. Conventional therapy is defined as treatment with at least two NSAIDs over a 4-week period in total, at maximum recommended or tolerated anti-inflammatory dose unless contraindicated. Moreover, patients with symptomatic peripheral arthritis must have had at least one local steroid injection and should normally have had a therapeutic trial of a DMARD, preferably sulfasalazine. Patients with peripheral enthesitis must have failed appropriate local treatment. The effect of treatment with a TNF-blocker is evaluated after at least 12 weeks. The response criteria are a 50% relative change or absolute change of 2 (0-10 scale) in BASDAI score and expert opinion in favour of continuation.

In a questionnaire among AS patients, recruited from a secondary care clinic, 64% reported a BASDAI score of at least 4 (scale 0-10). The authors concluded that there is a large unmet need for TNF-blocking therapy in AS, although an expert opinion was not available in most of these patients [46]. In a representative group of Belgian rheumatology offices about 40% of the AS patients were supposed to be eligible for anti-TNF therapy, for the most part according to the international recommendations [47].

A main disadvantage of this successful treatment are the high costs. In 2011 two TNF-blockers were on the first and second place of the top ten of expenses for drugs delivered by the public pharmacies in the Netherlands [48]. The expenses for the two drugs together were more than 350 million euros (total drug expenses 5001 million euros). Next to the registered TNF-blockers, so-called biosimilars have been developed, which may be more cost-effective. The first studies with a biosimilar of infliximab in AS showed equivalent efficacy compared to the original TNF-blocker [49].

TNF-blockers are often effective for most of the signs and symptoms of AS and have dramatically broadened the therapeutic arsenal in AS.

Immunogenicity of TNF-blockers.

In RA it has been shown that several TNF-blockers can induce an immune response and the formation of antidrug antibodies. The antibodies were associated with low serum drug levels and reduced response to treatment [50].

Serum drug levels and antidrug antibodies were studied in 38 AS patients treated with infliximab for 54 weeks (chapter 5). At the end 53% of the patients met the 20% ASAS response criteria. The mean serum trough infliximab level for responders was significantly higher compared to the non-responders (8.2 mg/l versus 6.3 mg/l). In addition, anti-infliximab was significantly more often found in non-responders (59% versus 5%). As shown in other studies, antibodies against the TNF-blocker were in our study associated with increased risk of infusion reactions [51].

Antidrug antibodies, associated with reduced treatment response, were also shown in 31% of 35 AS patients treated with adalimumab for six months [52]. In RA, co-administration of methotrexate (MTX) reduces the immunogenicity of the TNF-blocker in a dose-dependent manner. The overall Odds Ratio was 0.20 (95% CI 0.12-0.34) to develop antibodies against adalimumab in RA patients using MTX compared with patients without MTX [53]. In AS, the same effect was suggested in a small open label controlled study in which infliximab in combination with MTX seemed to be more efficacious than infliximab alone [54].

Despite the fact that evidence for effect of MTX on AS disease activity is lacking, it might be interesting to conduct studies on the effect of MTX and other immunosuppressive drugs on antibody formation against TNF-blockers and the influence on the response rate in AS.

In case of insufficient response or adverse events during TNF-blocking treatment, switching to another TNF-blocker can be effective. Overall the response rates among switchers are lower, but about half of them achieve treatment response [55-57]. Information about drug serum levels or antidrug antibodies could be helpful in these situations.

Antidrug antibodies, associated with reduced treatment response, are found in 29-31% of AS patients treated with infliximab or adalimumab. Further studies are needed to determine the effect of immunosuppressive drugs on antibody formation and to define the role of antibody determination in clinical decision making.

Adverse events of TNF-blockers.

In placebo controlled trials, the most frequent adverse events of TNF-blockers were injection site reactions (or infusion reactions) and mild infections [39-43]. In this paragraph the risks of serious infections, malignancy and liver problems are discussed in more detail.

In assessing the risk of serious infections one has to keep in mind that patients with immune mediated inflammatory disorders have an increased risk of infections not only due to medication, but also because of the disease itself. In a meta-analysis, RA patients on TNF-blockers had an increased risk of serious infections (adjusted hazard
ratios (aHR) between 1.1 and 1.8) and tuberculosis (aHR 12.5) versus patients on conventional DMARDs [58]. In AS, the incidence rate of serious infections was found to be lower compared to RA and Crohn's disease [59]. Perhaps this is related to the lower use of immunosuppressive drugs in AS. In a systematic literature review in AS, the absolute risk of serious infections in patients not exposed to TNF-blockers was low. The risk of serious infections in patients receiving TNF-blockers was higher, but the difference was not significant, possibly due to a lack of power [60].

Next to the role of TNF in host defence, it plays an important role in the pathobiology of cancer [61]. Therefore, malignancy has been considered as a possible adverse event of TNF-blockers. Regarding the risk of malignancy during TNF-blocking therapy, the possibility of a higher risk for certain malignancies by the inflammatory disease itself has to be taken into account. Patients with RA appear to be at higher risk of lymphoma and lung cancer compared with the general population, but overall the malignancy risk is almost similar [62]. Data on a possible increased risk of malignancy during treatment with TNF-blockers are conflicting, but in a Swedish register TNF-blockers were not associated with a further increase of the risk for lymphoma in RA [63]. In another study TNF-blocking therapy in RA was associated with an increased risk for non-melanoma skin cancer [64].

Less is known about the incidence of malignancy in AS patients, with and without TNF-blocking therapy. In a Belgian cohort, a tendency towards a higher incidence of malignancy in SpA patients treated with a TNF-blocker was seen, compared to the general population. However, the numbers were too small to draw definite conclusions [61]. In a Taiwanese cohort with matched controls, an increased risk of cancer, particularly lung or head and neck cancer, (aHR 1.38) was found in TNF-blocker naïve AS patients [65]. The risk of malignant lymphoma in AS was not elevated in a national register and not affected by the use of TNF-blockers [66].

The overall malignancy rates for adalimumab-treated patients with AS or other inflammatory disorders was as expected for the general population in a meta-analysis of clinical trials [59].

Serious liver problems were rarely seen in trials with TNF-blockers [40, 43]. [Gorman, 2002; Landewé, 2014] In clinical practice, however, we observed several AS patient with liver enzyme elevations during treatment with etanercept. This prompted us to study this systematically (chapter 6). Of 105 consecutive AS patients treated with etanercept for at least three months, 15 patients had significant elevation of liver enzymes (defined as more than 1.5 times the upper normal limit) more than once. In nine cases the elevation was probably or possibly related to treatment with the TNF-blocker. An increased risk of elevation of liver enzymes was found in patients with a higher body mass index (BMI). This observation might be explained by an increased vulnerability of a liver with steatosis, whereas on the other hand a favourable effect of TNF-blockers on fatty liver disease is expected [67].

The definite risk of hepatic disturbance during treatment of TNF-blockers can only be determined by comparison with a control group. In some placebo controlled trials of several TNF-blockers, increases of liver enzymes were seen 2-3 times more frequent in patients using the TNF-blocker than those using placebo [41, 42, 68]. Also the mean increase of liver enzymes was higher compared to the placebo-treated patients and therefore it is likely to be ascribed to TNF-blockers.

The most important adverse event of TNF-blockers is an increased risk of infections. This risk seems to be lower in AS patients than in RA. To assess the risk of malignancy in AS patients, treated with a TNF-blocker, more studies in large cohorts are required.

Increase of liver enzymes in TNF-blocker treated AS patients was seen in 9% of the patients. Therefore, regular testing of liver enzymes in these patients is recommended (for example every three months in the first year of therapy). Patients with higher BMI appear to be more prone to this side effect.

Measuring physical function and TNF-blocking. The efficacy of TNF-blockers in AS is determined by the improvement in several disease parameters during treatment. The most important outcome parameters in AS are disease activity, function, spinal mobility and quality of life [1]. These parameters are interrelated and are assessed for a great part by self-reported, disease-specific, visual analogue scale (VAS) based questionnaires and physical functioning is commonly assessed with the Bath AS Functional Index (BASFI) questionnaire [69, 70]. However self-reported outcome measures are susceptible to under- or overestimation [71].

Previous studies suggested that performance-based tests of functioning and the BASFI questionnaire are only moderately associated, indicating that these methods measure different aspects of physical functioning [72]. Further evaluating this subject, the improvement of performance-based assessment of physical function was established in 82 patients treated with a TNF-blocker for three months (chapter 7). Improvement of performance-based physical function tests was seen in 48% of the patients that were categorized as non-responders according to the ASAS20 response criteria and in 56% of the patients showing no improvement in self-reported physical functioning. Therefore the discrepancy between a performance-based and a questionnaire-based assessment of response was confirmed.

Additional studies are needed to show the clinical relevance and the underlying mechanisms of these differences. In knee-osteoarthritis it was observed that self-
reported physical function was more influenced by pain than by performance-based function [73]. In AS, the influence of cardiovascular fitness on perceived disease activity was seen and, in AS patients with peripheral joint impairment, two questionnaires of functioning performed differently [74, 75]. Another study showed worse BASFI scores in AS patients compared with control subjects, but they reported and objectively performed the same amount of physical activity [76]. It is proposed to use a combination of measurements in evaluating different aspects of functioning of AS patient, keeping in mind feasibility. Similarly, a lack of correlation is sometimes seen between spinal inflammation and reported level of disease activity [77]. Therefore, disease activity in AS is preferably assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS), which includes an objective measure of inflammation (ESR or CRP) in contrast to the BASDAI questionnaire [78].

Disease parameters in AS show correlations as well as discrepancies between self-reported and performance-based tests. Performance-based tests should be further developed. For good understanding of the cause and degree of the problems of the patient several tests have to be used, including performance-based tests.

Extra-articular manifestations and TNF-blockers.

In AS extra-spinal and extra-articular manifestations regularly occur, in particular psoriasis, inflammatory bowel disease and anterior uveitis. One or more extra-articular manifestations were seen in 42% of AS patients in a Belgian study [47]. Other studies found even higher incidences and extra-articular manifestations can also affect the bone, heart, lung and kidney [79]. The mean prevalence of anterior uveitis was 33% in a systemic review [80]. The anterior uveitis in AS is usually acute, unilateral and often recurrent. Inadequately treated the sequels for the eye can be vision-threatening. The primary therapy of anterior uveitis is treatment by the ophthalmologist with topical corticosteroids in combination with pupil dilating eye drops.

The effect of the TNF-blocker adalimumab on the occurrence of anterior uveitis was studied in 77 consecutive AS patients with active axial disease treated for at least 12 weeks (chapter 8). Compared to the year before treatment, the number of attacks per 100 patient years was 80% reduced and the number of uveitis attacks per year decreased with 72%.

TNF-blockers appear to differ in the degree of their effect on extra-articular manifestations, especially uveitis and inflammatory bowel disease [81]. Part of this difference could be explained by the observation that the soluble receptor blocker etanercept has less effect on granulomas than the other TNF-blockers, which are monoclonal antibodies. This might explain why etanercept is not effective in inflammatory bowel disease. On the other hand this difference is favourable for the soluble receptor blocker with respect to the risk of tuberculosis during therapy with TNF-blockers [82]. Despite the positive effect of TNF-blockers in general on extra-articular manifestations, an apparent paradoxical effect can sometimes be seen when uveitis, psoriasis or inflammatory bowel disease occur during treatment with TNF-blockers [83-85].

TNF-blockers have favorable effects on several extra-articular manifestations of AS, but in this respect the several TNF-blockers differ in efficacy.

Bone and TNF-blockers.

Interestingly, AS is characterized by the paradox of new bone formation (syndesmophytes and ankylosis) on the one hand and bone loss and increased risk of fractures on the other hand [8].

The influence of a TNF-blocker on bone was studied in 49 AS patients treated with etanercept (chapter 9). After two years of treatment the bone mineral density (BMD) of hip and spine was increased significantly (2.2%, resp. 70%). However, an increase was also seen in vertebral fractures (from 6 to 15 patients) and new bone formation (radiological score from 12.1 to 18.5). No significant changes were found in several markers of bone turnover.

In AS a decreased BMD is seen, although measurement of BMD of the spine with dual-energy X-ray absorptiometry (DEXA), in contrast to the hip, can be overestimated in case of new bone formation along the spine. A decreased BMD in AS is probably related to inflammatory factors. The expected positive effect of strong anti-inflammatory drugs, like TNF-blockers, on BMD was also demonstrated in other studies [86, 87]. It is unknown what the influence of TNF-blockers is on the ultimate outcome, namely fractures (without or with symptoms). In our study the number of vertebral fractures increased during treatment with the TNF-blocker, but a control group was lacking. In addition, there is lack of knowledge about the effect of anti-osteoporotic drugs like bisphosphonates on BMD and fractures in AS. The effect of bisphosphonates is also interesting because of the claimed anti-inflammatory activity in AS [88-90].

TNF-blockers reduce MRI-detected spinal inflammation [38]. Previously, it was demonstrated that inflammatory MRI lesions predict the development of new syndesmophytes, although other studies show a less clear association [91, 92]. Despite the anti-inflammatory effects of TNF-blockers, new bone formation during treatment was seen in comparison with the progression in TNF-blocker naïve historical cohorts [93-95]. These somewhat disappointing results raise questions about the mechanism of (un)coupling of inflammation and bone formation [87]. It
is hypothesized that, although TNF-blockers can decrease inflammation, they do not directly inhibit the formation of new bone. Bone formation might be the result of a repair mechanism, driven by mesenchymal tissue responses which are triggered by the resolution of inflammation and perhaps also triggered by mechanical stress [96]. Recent long-term studies however, demonstrated that finally less pathological bone formation occurs in AS patients treated with TNF-blockers, probably because of the reduction of new inflammatory lesions [97-99]. More studies are needed to unravel the effect of early treatment on radiographic progression before irreversible changes have occurred. Moreover, it would be interesting to study the effect of continuous use of NSAIDs or other therapies on the progression of new bone formation during (the first years of) treatment with TNF-blockers. This should be done by controlled and long-term studies, because of the slow rate of radiographic progression in AS [100].

During treatment with TNF-blockers bone mineral density increases in AS, but so far there is no evidence that TNF-blockers reduce the number of new vertebral fractures. Radiographic progression in AS is probably retarded by TNF-blockers on the long-term.

Early treatment with TNF-blockers?

TNF-blocking has shown to be effective in patients with early axial SpA in comparison with placebo or NSAID, although in many of these studies a considerable amount of the patients already meet the radiographic criteria of AS [43, 101-104]. In case of high disease activity, AS can be treated with TNF-blockers in the early (pre-radiographic) phase of the disease and possibly radiographic progression can best be retarded by early treatment. The classification criteria of axial spondyloarthritis (SpA) can be helpful to diagnose and treat the disease early [45]. Another argument to treat non-radiographic axial SpA and AS in the same way, is their similar burden of disease, defined as disease activity, functional impairment and quality of life [105, 106].

On the other hand little is known about the long term prognosis of the whole group of axial SpA [107]. Not all cases of non-radiographic axial SpA finally evolve to definite AS and partially non-radiographic axial SpA has features of a distinct disease entity [108, 109]. When considering therapy in axial SpA patients, it has to be taken in account that a higher response rate is seen in patients with radiographic features and in patients with objective signs of inflammation, reflected in MRI lesions or acute phase response [102, 104, 106, 110].

Patients with (early) non-radiographic axial SpA can be treated with TNF-blockers, especially when objective signs of inflammation are present as MRI lesions or raised acute phase response.

Duration of treatment with TNF-blockers?

Several studies show persistent favourable clinical results in AS patients treated with TNF-blockers for many years [111, 112]. Early remission is the best predictor for long-term remission through 5 years of treatment [113]. What is known about the necessary duration of therapy with a TNF-blocker? Discontinuation of the TNF-blocker in a patient with a favourable response seems to lead to a relapse in many cases [114, 115]. However, in part of the patients (32-47 %) it is presumably possible to maintain low disease activity with TNF-blockers in reduced doses [116, 117]. Dose reduction might be possible in case of high serum drug levels. Predictive characteristics for successful discontinuation or dose reduction are not yet known; disease duration, age or duration of remission could be such factors.

Another question is whether non-radiographic axial SpA patients are less prone to develop a flare after stopping TNF-blocking therapy than patients with definite AS. After two years follow-up only 8 % of patients with early axial SpA reached permanent drug-free remission after treatment with etanercept for one year [118]. In 24 patients with non-radiographic axial SpA and good response after treatment with adalimumab for 1 year, only 17% experienced no disease flare during 2 years after withdrawal of the drug [119]. However, in another study about 43% of the axial SpA patients remained in remission during 6 months in those patients who reached partial remission after treatment for 28 weeks with either infliximab plus naproxen or naproxen alone in the preceding period [120]. An attempt to discontinue treatment in good responders seems justified, because the response to retreatment with the TNF-blocker seems well in AS and non-radiographic axial SpA [119, 121].

Relapse of the disease is seen in many AS/SpA patients after discontinuation of successful therapy with a TNF-blocker. However, dose reduction and discontinuation should be attempted and studied further.

Other biologicals?

Overall, about 30% of the AS patients do not respond to treatment with TNF-blockers. This might be explained in several ways. One reason could be that the patient has no active inflammation and the symptoms are caused by other mechanisms. This is not always clear, because objective signs of inflammation are often absent in AS. In many patients blood inflammatory markers are low and MRI is not always conclusive. Another explanation might be that the inflammation is TNF-driven, but the TNF-blocker is not tolerated or TNF is not adequately blocked, for example because of antibodies against the drug. Also, the role of TNF in the inflammation could be limited. Therefore, there is need for disease modifying drugs which modulate other pathways of inflammation than TNF-blockade.
Open label trials failed to demonstrate efficacy of anakinra (IL-1 antagonist) and abatacept (T cell inhibition) in AS [122, 123]. The B cell inhibitor rituximab was not effective in an open trial, although effect was seen in the subgroup of TNF-blocker naïve patients [124]. Placebo-controlled trials failed to show efficacy of tocilizumab in AS [125]. Another interleukin (IL)-6 inhibitor, sarilumab, neither showed efficacy in a placebo-controlled study in AS [126]. Apremilast, an oral inhibitor phosphodiesterase 4, showed some improvement compared to placebo in a pilot study, but further testing is needed [127].

Ustekinumab, a monoclonal antibody that inhibits IL-12 and IL-23, proofed to be efficacious in treating psoriatic arthritis [128]. In AS ustekinumab reduced signs and symptoms in an open-label study [129]. Presently, the most promising results in AS patients are found in blocking of IL-17. In animal models intestinal interleukin-23 and subsequent stimulation of IL-17/22 was found to be involved in development of spondyloarthritis syndrome [130]. TNF-independent increase in IL-17-expressing mast cells may contribute to synovial inflammation in peripheral SpA [131]. The anti-IL-17a antibody secukinumab was superior to placebo in reducing signs of AS in a small, randomized, double-blind study [132].

**Because not all AS patients respond to therapy with a TNF-blocker, there is still need for other therapies. Most promising are results of agents blocking interleukin 23/17, but larger controlled studies are needed for further evaluation of these new therapeutic options.**

**Some future research suggestions.**

NSAIDs are still the cornerstone of the drug treatment of AS. Prospective long-term studies are needed comparing continuous use with on demand use. The rate of radiographic progression in these groups can be compared, as well as the adverse events. This can be done in patients without TNF-blocking therapy, as well as in patients using TNF-blockers, because after the start of TNF-blocking treatment new bone formation is still going on.

Sulfasalazine is used in AS patients with peripheral arthritis. Furthermore, the role of the traditional DMARDs in AS is limited. There is an unmet need for controlled studies with higher doses of methotrexate, eventually in combination with a pulse dose of corticosteroids, to determine the effect on disease activity and also the effect on antibody formation against TNF-blockers.

The antirheumatic properties of statins have to be studied in a controlled trial, as well as the effect of cardiovascular risk screening and management in AS.

The effects of bisphosphonates in AS on bone mineral density, as well as on disease activity and radiographic progression have to be studied in placebo controlled trials.

TNF-blockers are an important advancement in the treatment of AS. Accurate (nationwide) registration of efficacy, extra-articular manifestations and adverse events of the different TNF-blockers and biosimilars would be very informative.

The role of antibodies against TNF-blockers has to be elucidated and especially their role in predicting successful dose reduction, stopping and switching of therapy. Performance-based tests should be further developed and incorporated in the current outcome parameters of efficacy of therapies.

Long-term follow-up is needed of patients with axial SpA, especially those without radiographic signs, because the long term outcome of non-radiographic SpA is largely unknown.

It would be very interesting to investigate the characteristics of patients not responding to treatment with a TNF-blocker. For part of these non-responders studies for other (biological) therapies are needed. Undoubtedly ongoing pathophysiologic research is needed in the search for new therapies.
REFERENCES CHAPTER 10.1


Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis


Chapter 10

General discussion and summary


General discussion and summary

Chapter 10


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2. NEDERLANDSE SAMENVATTING

Inleiding
Het onderwerp van dit proefschrift is de medicamenteuze behandeling van de aandoening ankyloserende spondylitis (AS). In Nederland wordt AS nog vaak "de ziekte van Bechterew" genoemd. Bij patiënten met AS is er sprake van een chronische reumatische ontsteking in gewrichten, vooral in het bekken en de wervelkolom. De oorzaak van de ontsteking is niet precies bekend, maar bij het ontstaan van de ziekte spelen erfelijke aanleg, bacteriën in de darm en waarschijnlijk andere factoren van buiten een belangrijke rol. De ontsteking veroorzaakt rugpijn, met name aan het eind van de nacht, ochtendstijfheid, moeheid en beperkingen in het dagelijkse functioneren. Kenmerkend voor AS is de aangroei van bot die kan optreden als gevolg van de ontstekingen. Hierdoor kunnen blijvende veranderingen van de wervelkolom ontstaan en in een ver gevorderd stadium de kenmerkende voorovergebogen houding.

Historie
In de inleiding van het proefschrift wordt beschreven dat er kenmerken van AS zijn gevonden in oude skeletten, zelfs al in die van Egyptische farao's. Toch werd lange tijd AS niet als een aparte ziekte gezien, maar als een vorm van acuut reuma of gewrichtsreuma. In de loop van de negentiende eeuw werden wel diverse ziektegevallen gepubliceerd die passen bij AS. Aan het eind van die eeuw begon men AS als een aparte aandoening te beschouwen na publicaties van onder andere de Russische neuroloog W. Bechterew. Toch duurde het nog meer dan een halve eeuw tot de ziekte in de hele wereld als zodanig werd erkend. Ontwikkelingen die hier ook aan hebben bijgedragen, waren röntgen – en bloedonderzoek (met name bepaling van erfelijke factor HLA-B27).

In 1963 zijn internationale criteria voor classificatie van AS opgesteld die in 1984 zijn gewijzigd en nog steeds worden gebruikt. De belangrijkste criteria zijn: rugpijn passend bij ontsteking, bewegingsbeperking van rug en borstkas en een röntgenfoto met kenmerken van ontsteking. Men zag al jaren dat er bij AS overeenkomsten en ook overlap was met andere reumatische ontstekingen, zoals bij de huidziekte psoriasis, bij chronische darmontstekingen en reactieve gewrichtsontsteking na bepaalde infecties. De overkoepelende term voor deze ziektebeelden werd spondylarthropathie en later (axiale) spondyloartritis (SpA). Recent zijn hiervoor nieuwe criteria opgesteld met inbegrip van het vroege stadium van AS waarin röntgenfoto's nog niet afwijkend zijn.

Therapie
Patiënten met AS worden reeds lang effectief behandeld met fysiotherapie en in de afgelopen tien jaar is het nut van oefentherapie in onderzoeken bevestigd. Sinds de ontdekking van aspirine in de negentiende eeuw zijn ontstekingsremmende middelen de belangrijkste therapie voor AS. Met name de niet-steroid anti-inflammatoire medicijnen (NSAIDs) zijn nog steeds de hoeksteen van de behandeling. Traditioneel wordt verondersteld dat deze middelen vooral de symptomen onderdrukken.

Daarnaast spreekt men in de reumatologie van ziekte modificerende medicijnen (DMARDs) die geacht worden het beloop van de ziekte te beïnvloeden. Besproken wordt dat dit onderscheid echter niet altijd zo zwart-wit is. Dit proefschrift bevat in de eerste hoofdstukken studies waarin het effect van DMARDs bij AS is onderzocht.

Sedert circa 2002 zijn andere type medicijnen in gebruik bij AS: de zogenaamde biologicals. Deze bestaan uit eiwitten die een onderdrukking bewerkstelligen van specifieke signaaleiwitten die een rol spelen bij ontstekingen. Deze zogenaamde TNF-alpha blokkers kunnen alleen per injectie of infuus worden toegediend en blijken een heel gunstig effect op de symptomen van AS te kunnen hebben. De laatste hoofdstukken van dit proefschrift betreffen studies waarin diverse aspecten van behandeling met TNF-blokkers zijn onderzocht.

Aan het eind van het proefschrift wordt een overzicht gegeven van de medicamenteuze mogelijkheden bij AS zoals die zich in de afgelopen vijftien jaar hebben ontwikkeld. Hieronder volgt daarvan de samenvatting.

Niet-steroid anti-inflammatoire medicijnen (NSAIDs)
NSAIDs zijn nog steeds de geneesmiddelen van eerste keus bij de behandeling van AS vanwege hun gunstige werking op pijn en stijfheid. Voor de meeste patiënten is andere medicamenteuze behandeling niet noodzakelijk. Uiteraard moeten de voordelen van behandeling altijd worden afgewogen tegen de mogelijke bijwerkingen. Hoewel het risico op maagzweren bij nieuwe soorten NSAIDs lager is, kunnen deze middelen nadelig werken op bloeddruk, hart, nieren en de bloedstolling.

NSAIDs lijken echter meer te doen dan alleen bestrijding van de symptomen. Jaren geleden werd in een Nederlandse studie al gevonden dat continu gebruik van een NSAID ook de overmatige aangroei van bot bij AS afremt. Recentere studies hebben deze bevinding bevestigd, met name bij patiënten met verhoogde ontstekingswaarden in het bloed. Dit leidt tot de aanbeveling om patiënten met progressieve ziekte en verhoogde ontstekingswaarden chronisch te behandelen met een NSAID.
Ziekte modificerende medicijnen (DMARDs)

Sulfasalazine heeft gunstige effecten op de ziekte AS indien er niet uitsluitend ontstekingen in de rug zijn, maar tevens gewrichtsontstekingen in gewrichten buiten de rug (perifeer). Sulfasalazine wordt in de darm gesplitst in het antibacteriële sulfapyridine en het ontstekingsremmende mesalazine. Mesalazine is het werkzame bestanddeel bij de behandeling van chronische darmontstekingen. Het effect van mesalazine op AS werd in een open studie gedurende 24 weken onderzocht bij 20 patiënten met actieve ziekte (hoofdstuk 2). Veel patiënten moesten voortijdig stoppen met de behandeling vanwege bijwerkingen. Hoewel de gemiddelde ontstekingswaarde in het bloed significant daalde, veranderden andere ziekteparameters niet gedurende de behandeling met mesalazine.

Cholesterol verlagende medicijnen hebben ook een ontstekingsremmende werking. Het effect van de cholesterolverlager rosuvastatine werd daarom onderzocht bij 15 patiënten met AS in een open studie gedurende 12 weken met een observatie periode van totaal 24 weken (hoofdstuk 3). Ook hier werd een significante daling van de gemiddelde ontstekingswaarde in het bloed gevonden, maar toonden klinische parameters alleen een trend tot verbetering. De waarden van het cholesterol in het bloed verbeterden. Hetgeen gunstig is, omdat het risico op hart- en vaatziekten door een reumatische ontsteking op zich ook al verhoogd is.

Leflunomide is een DMARD met bewezen effect bij andere reumatische ziekten. Het effect van leflunomide werd onderzocht in een dubbelblinde gerandomiseerde studie bij 45 patiënten met actieve AS (hoofdstuk 4). De resultaten van de patiënten behandeld met leflunomide en die met een placebo verschilden niet significant. In een Duitse studie werden aanwijzingen gevonden dat het middel wel een gunstig effect had bij patiënten met perifere gewrichtsontsteking. Dit konden wij niet onderzoeken, omdat perifere gewrichtsontsteking bij onze patiënten bijna niet voorkwam.

Andere DMARDs, zoals we die kennen bij gewrichtsreuma, zijn bij AS relatief weinig onderzocht. Recent is een studie gepubliceerd waarin een korte termijn effect werd gezien van een kortdurende behandeling met een hoge dosis prednison. Het effect van methotrexaat is enkele keren onderzocht met negatief resultaat, maar steeds in lagere doseringen dan we gewend zijn te gebruiken bij gewrichtsreuma.

Concluderend is de rol van traditionele DMARDs bij de behandeling van AS nog steeds beperkt. Er is een rol voor sulfasalazine en misschien voor leflunomide bij AS met perifere gewrichtsontsteking. Er is geen rol voor mesalazine. De rol van cholesterolverlagers, methotrexaat in hogere doseringen en ook prednison zou verder onderzocht kunnen worden in placebo gecontroleerde studies.

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wel beter functioneerden tijdens de uitvoering van fysieke functietesten. Hieruit bleek dat de verschillende testen deels andere aspecten van het functioneren meten. Aanbevolen wordt het effect van medicatie op meerdere manieren te meten en de verschillen en overlap tussen deze methoden verder te onderzoeken.

Bij AS komen niet alleen ontstekingen voor in rug en perifere gewrichten, maar ook van de huid, darm of oog, de zogenoemde extra-articulaire verschijnselen. Ontsteking van het regenboogvlies (uveitis anterior) komt het meeste voor; bij circa 33% van de AS patiënten treedt deze oogontsteking minimaal eenmaal op. Het effect van de TNF-blokker adalimumab op het voorkomen van deze uveitis werd onderzocht bij 77 patiënten die gedurende minstens 12 weken waren behandeld vanwege actieve AS in de rug (hoofdstuk 8). Ten opzichte van het jaar voor de behandeling nam het aantal aanvallen van uveitis significant af. Mede op grond van andere onderzoeken kan geconcludeerd worden dat TNF-blokkers een gunstige werking hebben op extra-articulaire verschijnselen, maar dat er tussen de TNF-blokkers wat dat betreft wel onderlinge verschillen zijn.

Bij AS bestaat de bijzondere combinatie van enerzijds plaatselijke overmatige botvorming en anderzijds een afname van de algehele botmassa (osteoporose) met verhoogde kans op botbreuken (onder andere wervelinzakkingen). De invloed op bot van behandeling met de TNF-blokker etanercept werd onderzocht bij 49 patiënten met AS (hoofdstuk 9). Het bleek dat de botmassa tijdens behandeling was toegenomen. Aangezien een onbehandelde groep ontbrak, kan niet worden uitgesloten dat een TNF-blokker op deze laatste fenomenen toch een remmend effect heeft. Andere medicijnen, die algemeen gebruikt worden bij osteoporose, zijn nog nauwelijks onderzocht bij AS. Bij verder onderzoek is niet alleen het effect op de botmassa, maar vooral op het optreden van botbreuken van belang.

Wat betreft de voor AS kenmerkende plaatselijke overmatige botvorming, waren ook de resultaten van andere onderzoekers, die de toename van botvorming vergeleken met historische groepen, teleurstellend. Het leek alsof de TNF-blokkers, ondanks zeer gunstige effecten op ontstekingen, deze botvorming niet afremden en in die zin dus geen zichtbare modificerende werking hadden. Recente onderzoeken suggereren echter dat weliswaar na het tot rust komen van ontstekingen plaatselijke botaanleg optreedt, maar dat op termijn van vele jaren tijdens behandeling met een TNF-blokker deze botaanleg niet minder optreedt.

Tenslotte worden een aantal actuele thema’s betreffende de behandeling met TNF-blokkers besproken.

Zo is er de vraag of patiënten in een zo vroeg mogelijk stadium met TNF-blokkers moeten worden behandeld. Meerdere TNF-blokkers zijn nu ook geregistreerd voor axiale spondylarthritis wanneer er (nog) geen afwijkingen op de röntgenfoto zichtbaar zijn. In deze gevallen moet alleen behandeling met een TNF-blokker overwogen worden als er wel kenmerken zijn van ontsteking in het bloed of op afbeeldingen van een MRI scan. Daarover is internationaal consensus.

Verder is niet bekend hoe lang behandeling met een TNF-blokker moet worden voortgezet. Waarschijnlijk valt de ziekte bij een groot deel van de AS patiënten op na stoppen van de behandeling. Anderzijds kan bij een flink aantal van de behandelingen de dosis van het medicijn worden verminderd zonder verlies van effectiviteit. Ook blijkt hervatten van de behandeling na staken over het algemeen weer succesvol.

Ondanks het succes van TNF-blokkers in het algemeen bij AS, blijft er een grote groep AS patiënten bestaan waarbij TNF-blokkers niet werkzaam zijn of waarbij de behandeling gestopt moet worden vanwege bijwerkingen. Er blijft dus behoefte aan nieuwe medicijnen. Diverse geneesmiddelen, die werkzaam zijn bij gewrichtsreuma, blijken niet werkzaam te zijn bij AS. Maar de eerste resultaten met een eiwit, dat in plaats van TNF-alpha een andere ontstekingfactor (interleukine-17) remt, zijn veelbelovend.

Diverse suggesties voor verder onderzoek zijn beschreven aan het eind van de discussie.

Concluderende opmerking
Er is in de afgelopen 15 jaar een enorme positieve ontwikkeling op gang gekomen in de medicamenteuze behandeling van AS. Verder onderzoek is echter nodig om te kunnen blijven werken aan het uiteindelijke doel: verbetering van het welzijn en de ziekte-uitkomst van patiënten met de ziekte van Bechterew.
3. DANKWOORD

Alle personen die op enige wijze hebben bijgedragen aan de totstandkoming van dit proefschrift wil ik hierbij heel hartelijk bedanken.

De dankbaarheid is groot, maar ik houd het graag bij een simpele opsomming van de mensen die hebben geholpen.

Zij die inmiddels niet meer onder ons zijn: Betty Dekker-Saeys, Marcel van der Paardt en Rob van de Stadt.
Hans Bijlsma, mijn promotor.
Irene en Mike, mijn vasthoudende copromotoren.
Ben Dijkmans, de initiator.
De promotiecommissie.
Mijn paronymfen.
De mede-onderzoekers, met name Mike Peters, Mirjam de Vries, Salima van Weely, Maria Suttorp-Schulten, Ingrid Visman en Mignon van der Weijden.

4. CURRICULUM VITAE


25 jaar nadat in 1964 de eerste paal was geslagen van het Jan van Breemen Instituut (JBI) aan de Dr Jan van Breemenstraat te Amsterdam, begon hij daar zijn werk als reumatoloog en inmiddels is hij daar 25 jaar werkzaam. Namens het JBI werkt hij twee dagen per week in het Waterlandziekenhuis te Purmerend. Reade is de nieuwe naam van de organisatie sinds de fusie in 2010 van het JBI met het revalidatiecentrum Amsterdam aan de Overtoom. In 2014 is het reuma onderzoek van AMC, Reade en VUmc gebundeld in het Amsterdam Rheumatology & Immunology Center (ARC).
5. List of Publications


6. LIST OF ABBREVIATIONS AND ILLUSTRATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADA</td>
<td>adalimumab</td>
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<tr>
<td>AE</td>
<td>adverse events</td>
</tr>
<tr>
<td>aHR</td>
<td>adjusted hazard ratio</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
</tr>
<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
</tr>
<tr>
<td>ASQOL</td>
<td>ankylosing spondylitis quality of life</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AU</td>
<td>anterior uveitis</td>
</tr>
<tr>
<td>BASDAI</td>
<td>Bath ankylosing spondylitis disease activity index</td>
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<tr>
<td>BASFI</td>
<td>Bath ankylosing spondylitis functional index</td>
</tr>
<tr>
<td>BasmG</td>
<td>Bath ankylosing spondylitis global score</td>
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<tr>
<td>BASMI</td>
<td>Bath ankylosing spondylitis metrology index</td>
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<tr>
<td>BC</td>
<td>before Christ</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>COXIB</td>
<td>cyclooxygenase-2 selective inhibitor</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>CTX-I,II</td>
<td>carboxy terminal crosslinking telopeptide type I,II collagen</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual-energy X-ray absorptiometry</td>
</tr>
<tr>
<td>DISH</td>
<td>diffuse idiopathic skeletal hyperostosis (Forestier's disease)</td>
</tr>
<tr>
<td>DMARD</td>
<td>disease modifying antirheumatic drug</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>ESR</td>
<td>erythrocyte sedimentation</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ETN</td>
<td>etanercept</td>
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<tr>
<td>GDA</td>
<td>global disease activity</td>
</tr>
<tr>
<td>GWB D/P</td>
<td>general wellbeing according to doctor / patient</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
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<tr>
<td>HF</td>
<td>heart frequency</td>
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<td>HLA</td>
<td>human leukocyte antigen</td>
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IBD inflammatory bowel disease
ICC intraclass correlation coefficient
IFX infliximab
IQR interquartile range
IL interleukin
INH isoniazide
LDL low density lipoprotein
MRI magnetic resonance imaging
MMP matrix metalloproteinase
mSASSS modified Stoke ankylosing spondylitis spine score
MTX methotrexate
NAFLD non-alcoholic fatty liver disease
NSAID nonsteroidal anti-inflammatory drug
OL open-label
OPG osteoprotegerin
PCR polymerase chain reaction
PP per-protocol
RA rheumatoid arthritis
RANKL receptor activator of nuclear factor kappa-B ligand
RCT randomized controlled trial
SD standard deviation
SJS / SJC swollen joint score / count
SpA spondyloarthropathy / spondyloarthritis
SSZ sulfasalazine
TJS tender joint score
TNF tumour necrosis factor-alpha
UNL upper normal limit
VAS visual analogue scale
VF vertebral fractures
X-rays röntgen radiation

Verantwoording illustraties
Omslag: Sassenpoort Zwolle, gebouwd in 1406-09 (foto auteur).
Introductie:
Figuur 1: Slide collection 7-C-3, American College of Rheumatology.
Figuur 2: D O’Connell. Ankylosing spondylitis: the literature up to the close of the
Figuur 4, 5: A Goldscheider und P Jacob: Handbuch der physikalischen Therapie.
Verlag von George Thieme, Leipzig, 1902.
Figuur 11: RKW Kuipers. De orthopaedische behandeling van spondylarthritis