## New insights into anti-TNF treatment of ankylosing spondylitis

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## GENERAL DISCUSSION and SUMMARY

TNF blocking agents were introduced in 1998, after decades of limited possibilities for treatment of AS patients, such as exercises and NSAID's. The use of TNF blocking agents has diminished the disease burden of many AS patients dramatically. Patients who did not have any other treatment options before, received a treatment which made their lives almost back to normal again without pain and stiffness. The majority of AS patients (60%) respond very well, but many others, unfortunately, do not. There is no difference in response rate between the various TNF blocking agents: infliximab, adalimumab and etanercept(1-3). In primarily non responsive cases, this lack of response may be due to the fact that disease activity is monitored with a questionnaire, the BASDAI, which is a validated outcome parameter for AS, but which has the disadvantage of subjectivity without a direct relation with inflammatory parameters, such as acute phase reactants (ESR e.g.). A relatively high pain score, due to enthesitis or pain caused by structural deformities, for instance, may raise the BASDAI, even when there is little inflammation in the spine or sacroiliac joints.

On the other hand, patients who initially respond very well, might lose this responsiveness during continuous treatment with TNF blockers. Part of the mechanism behind this secondary non-response was unravelled by measurement of serum levels of anti-TNF and the detection of antibodies against these drugs, as described in **Section I**.

### Immunogenicity

In AS patients, inefficacy of infliximab or adalimumab correlated with the presence of low serum trough infliximab or adalimumab levels and the presence of antibodies against infliximab or adalimumab (**Chapter 2 and 3**), whereas

cases with good clinical responses showed the opposite (high serum trough levels and no antibodies against anti-TNF). Moreover, our data have demonstrated that development of anti-infliximab antibodies can precede an infusion reaction. The mechanism of the decrease in efficacy can be explained by lower serum trough infliximab or adalimumab levels, caused by neutralizing antibodies against the idiotype of infliximab and adalimumab, and enhanced clearance due to immune complex formation of antibodies against biologicals and the biologicals(4). Our hypothesis is that when drug levels decrease below a critical limit, the foreign protein might no longer be tolerated and might become immunogenic. The starting dose of infliximab (5 mg/kg) is higher than that of RA (3 mg/kg), which might suppress immunogenic reactions(5). Often, the infliximab dose is increased in AS when responsiveness subsides, but reasons for dose escalation in AS have not yet been well defined. More research is needed to assess whether anti-TNF levels can be used for to determine the optimum dose of anti-TNF in AS in daily clinical practice.

Another option for trying to prevent ineffectiveness caused by antibody formation is the concomitant administration of other immunosuppressive drugs. In contrast with treatment of RA, anti-TNF in AS is given without methotrexate. This may be an explanation for the higher incidence of anti-infliximab and anti-adalimumab formation in AS. In Crohn's disease and in RA, the concomitant use of immunosuppressive drugs or corticosteroids has proven to decrease antibody formation against infliximab(5;6). It has to be investigated whether coadministration of immunosuppressive drugs (such as methotrexate) inhibits antibody formation, because despite the use of immunosuppressive drugs in RA, anti-infliximab and anti-adalimumab formation occurs in around 17% of RA patients treated with adalimumab(7) compared with 31% of AS patients. Moreover, methotrexate has so far not proven to be effective on clinical symptoms in AS in contrast to RA, so the benefits of an additional drug

that might slow down or inhibit formation of anti-TNF antibodies should be weighed against the side effects of this drug.

Another TNF blocking agent, etanercept, does not seem to have high immunogenic properties. In **Chapter 4**, no correlation was found between etanercept levels, formation of antibodies against etanercept and clinical response. All patients had detectable serum levels of etanercept and no antibodies against etanercept were found during 6 months of treatment.

Interestingly, there seemed to be no difference in mean etanercept levels between responders and primary non-responders. These findings are in contrast with our previous studies with infliximab(8;9) and adalimumab in AS(8).

Therefore, this study seems to confirm the hypothesis that etanercept is less immunogenic than other TNF blocking agents, although the duration of this study was too short to exclude anti-etanercept formation after a longer period of therapy with etanercept.

Several arguments are in favour of the hypothesis that etanercept shows less immunogenicity than other TNF-inhibitors. Firstly, etanercept has a less immunogenic structure compared with other TNF blocking agents. Etanercept is a dimeric fusion protein consisting of two TNF receptors, linked to the Fc portion of an immunoglobin (Ig)G1. Only the fusion part of the molecule may contain immunogenic epitopes. Infliximab is a chimerical monoclonal IgG1 antibody against TNF, partly consisting of murine protein. Adalimumab is a fully human monoclonal antibody against TNF. These monoclonal antibodies have more epitopes within the variable region of the antibody to which an immune response can be directed. Secondly, major fluctuations in serum levels may precipitate an immune response and the development of antibodies against the TNF blocking agent. This is mainly the case in treatment with infliximab, which is administered once every six to eight weeks. Treatment with etanercept, however, produces stable levels between two injections and it is dosed more

frequently (once a week). Thirdly, there may be different mechanisms for non-response, for example caused by inadequate blocking of TNF. This can be caused by enhanced clearance or as a result of inadequate dosing. A dose-response relation of etanercept in AS has not been investigated systematically. We are very interested to learn to what extent new TNF blocking agents such as golimumab and certolizumab pegol will prove to be immunogenic. Golimumab is a fully human monoclonal IgG1 against TNF, which is administered once a month, whereas certolizumab has a totally different structure, containing a Fab' fragment of monoclonal IgG1 anti-TNF antibody linked to polyethylene glycol which is dosed every other week.

As discussed in **Section I** there is some doubt about whether validated patient questionnaires, such as the BASDAI, are the most optimal outcome parameters to measure disease activity in AS. Therefore some studies were performed to explore other biomarkers (**Section II** ) of disease activity.

Inflammation in AS does not only cause symptoms such as pain and stiffness, but also increases comorbidity due to cardiovascular disease by accelerating the process of atherosclerosis. Next to biomarkers of disease activity, studies were performed to examine biomarkers of cardiovascular disease in AS. The second chapter in **Section II** contains a review on Andersson lesions and its prevalence in our AS cohort. It is important to consider the presence of such a lesion, as specifically AS patients with an ankylosed spine, who have had a (minor) trauma, have an increased risk at an AL.

**Biomarkers of disease activity: inflammatory markers**

The study in **Chapter 5.1,** in our large prospective cohort of AS patients, has demonstrated that a combination of elevated baseline levels of CRP and SAA can be a valuable tool in the selection of AS patients who are likely to respond to treatment with anti-TNF. Moreover, inflammatory markers, CRP and SAA in

particular, seem to be useful in monitoring the level of inflammation in patients with AS who are treated with etanercept or infliximab.

Most AS patients showed a significant decrease of several inflammatory markers upon treatment with anti-TNF. In some cases, a secondary increase of these inflammatory markers was seen, which may have been caused by a concurrent infection or inadequate therapeutic levels. Although about 68% of the AS patients in this study had elevated inflammatory markers before the start of anti-TNF therapy, it is known that normal inflammatory markers do not necessarily indicate a low disease activity in AS(10). That is why inflammatory markers were, until recently, not implemented for assessment of disease activity or response to treatment, which is in contrast to RA. This study supports the previous data that raised inflammatory markers are indicative of active disease in AS. It seems useful to add decrease of inflammatory markers to response criteria for continuation of anti-TNF treatment in AS patients showing elevated inflammatory markers at baseline. In 2009, a new ASAS endorsed disease activity score for AS was developed, the ASDAS(11). This tool for assessment of disease activity in AS was derived in analogy with the DAS used in RA. The ASDAS includes the domains of back pain, duration of morning stiffness, patient's global assessment, peripheral pain or swelling and CRP or ESR. This score promises to improve comparison of individual patients' disease activity, and the individual score gives a more reliable reflection of the disease activity at that particular moment.

Despite the fact that ESR showed the strongest association with the BASDAI over time, we consider ESR the least suitable parameter for inclusion in the ASDAS, because in our study, it had no additional value and the half-life of this inflammatory marker was too long for early detection of changes.

Since anti-TNF therapy is very expensive and not without risks, it is of great importance to identify patients who are likely to respond to this type of drug. At

this moment, we believe that inflammatory markers can be very useful predictors for a good response, but a raise of inflammatory markers should not be mandatory for allowing AS patients to be treated with anti-TNF, because patients with normal baseline levels of CRP and SAA may respond to anti-TNF therapy as well.

Additionally, in **Chapter 5.2**, we investigated whether CRP levels, the important acute phase reactant, are influenced by common single-nucleotide polymorphisms (SNPs) and haplotypes in the *CRP* gene. We saw that genotypes and the haplotype tagged by allele A of rs3091244 associated with high CRP levels, independent of BASDAI and other confounders. Therefore, the carrying of distinct genetic variants might explain the lack of elevated CRP levels despite high disease activity in some AS patients. This observation can be important for interpreting disease activity scores that incorporate CRP levels, such as ASDAS.

**Discovertebral lesions in AS**

Apart from reversible inflammatory signs of the pelvis and spine, visible on MRI, chronic structural lesions can occur in AS, such as the development of localised vertebral or discovertebral lesions of the spine, first described by Andersson in 1937(16) (**Chapter 6**). We conducted an extensive review of literature in order to align communication on aetiology, diagnosis and management between treating physicians. In an attempt to structure the broad spectrum of Andersson lesions (ALs) complicating AS, a provisory division in localised and extensive lesions can be used. Localised lesions are limited to certain parts of the intervertebral disk and they always have an inflammatory origin. Extensive lesions affect the whole disk or vertebral body and may be caused by both mechanical and inflammatory factors. Aetiologies range from spinal (stress-) fractures to a local delay in the ankylosing process compared to

adjacent levels, resulting in the last mobile segment. There is no evidence for an infectious origin. Regardless of the exact aetiology, mechanical factors in the ankylosed spine will prevent the healing of extensive lesions and promote the formation of pseudarthrosis. The diagnosis of AL is established with conventional radiography, but computed tomography and magnetic resonance imaging will both provide additional information. Surgical instrumentation and fusion with the correction of a kyphotic deformity, when present, is considered to be the principle treatment of a symptomatic AL that does not respond to conservative treatment(17;18). The eponym Andersson lesion should be preserved to extensive lesions, which is actually a spinal pseudarthrosis and the final common pathway of several different aetiologies.

In our AS patients, with a high disease activity, only one lesion resembling an AL of the thoracic spine was detected with MRI before start of the therapy, but this lesion lacked a fracture line on conventional radiograph. The low prevalence of ALs was unexpected because this group of AS patients had a relatively high rate of ankylosis of the spine and signs of active inflammation. The percentage of ALs, as described in literature in this subset of severe AS patients, varies between 1–28%(19-25). The low prevalence of ALs in our study was probably caused by the relatively short disease duration and small sample size. This could be due to a selection bias mainly for young patients with an active disease were referred for treatment with TNF blocking agents, whereas the efficacy of TNF blockers in older and more severe cases of AS with complete ankylosis of the spine was still doubtful at the time of this study.

Despite the absence of ALs in our study we would like to increase the awareness of this complication in AS. In case of a minor spine trauma an MRI should be combined with conventional spine radiographs in order to detect this lesion in the stiff and vulnerable spine, which is often osteoporotic as well(26;27). In previous studies, there has been no sequential MRI study of the

spine in patients with AS that visualizes the evolution from an early discovertebral lesion - as described in our patient - into a severe destructive discovertebral lesion, by some authors also known as AL. Thus it remains unclear whether and how often an abnormality in the discovertebral junction develops into an AL. More research with a long term follow up of discovertebral lesions is necessary to clarify the evolution of these lesions.

**Biomarkers of cardiovascular risk: lipid profile**

Patients with AS have approximately a twofold increased mortality rate compared to general population. This is predominantly caused by an increased cardiovascular (CV) risk(12). Inflammation has shown to deteriorate the lipid profile, which is the main risk factor for atherosclerosis. In **Chapter 7**, we noted favourable changes in lipid profile and HDL composition upon TNF blockade. This was reflected by increased HDL-c and Apo A-I levels and an improved Apo B:Apo A-I ratio. Anti-TNF treatment also led to favourable alterations in HDL composition, by diminishing the SAA concentration within the HDL particles, which rendered the lipid profile more atheroprotective.

SAA is an acute-phase reactant, which is synthesized mainly in the liver in response to pro-inflammatory cytokines such as interleukin-1, interleukin-6, and TNF(13), and elevated levels of SAA are associated with increased CV risk(14). Moreover, SAA-rich HDL particles are rapidly cleared from plasma, and thus the increase in SAA during inflammation could also contribute to the decrease of total HDL-c concentrations(15). However, other mechanisms may also play a role in decreased HDL-c levels during inflammation as well. It has been suggested that remodelling HDL through activation of secretory phospholipase $A_2$ may be an alternate explanation for reduced HDL-c levels during the acute-phase response. In addition, inflammation may convert HDL de novo into a more proatherogenic form by coordinate but inverse transcriptional regulation

of SAA and Apo A-I in the liver(13). This may explain the observed inverse correlation between plasma levels of SAA and Apo A-I, but not between plasma levels of SAA and levels of HDL-c, at baseline. Changes in total cholesterol, HDL-c and Apo A-I levels were significantly inversely associated with changes in levels of disease activity parameters over time, confirming the role of inflammatory activity in lipid profile changes.

Our results highlight the importance of understanding the role of functional characteristics of HDL cholesterol in CV diseases related to chronic inflammatory conditions, such as AS.

We were also interested in studying extraspinal manifestations, such as IBD and conduction disturbances in the heart, as described in **Section III**.

**Extraspinal manifestations: Pathophysiological link between AS and IBD**

The study in **Chapter 8** reports on the prevalence of serological markers associated with IBD (pANCA, ASCA and OmpC antibodies) in AS patients. For a proper evaluation, three groups of patients with chronic inflammatory diseases were included in this study: one with AS, one with IBD, and one with patients with concurrently AS and IBD.

All determined serological markers were frequently observed in AS patients: pANCA, ASCA IgA, and ASCA IgG antibodies in 21%, 19% and 8% of 52 AS patients, respectively. Furthermore, we demonstrated for the first time that OmpC antibodies are highly prevalent in AS patients (19%). These markers, notably ASCA and OmpC antibodies, rarely occur in healthy controls(28). pANCA was statistically significantly more often present in AS patients with concurrent UC than in AS alone with an OR of 8.2 (95%CI 1.2-55.6). Thus, pANCA might be a valuable tool to screen AS patients with abdominal complaints: if pANCA is present an endoscopy is indicated.

The involvement of the gastrointestinal tract in AS can be interpreted in three different ways: as an aberrant immune response following gastrointestinal infection, as part of an inflammatory disease sharing a common genetic background(29;30) or as a result of intestinal leakage due to treatment with NSAIDs(31).

We have demonstrated that the presence of IBD-associated markers in AS patients is indicative that AS and IBD share a similar pathophysiological origin. These findings apply to AS patients with and without proven IBD since serum markers were also found in AS patients without (symptoms of) IBD. Prospective follow-up of AS patients with positive IBD serology markers in comparison with seronegative patients might shed new light on this discussion and might contribute to the decision whether or not to perform ileocolonoscopy in symptomatic patients and which TNF blocking agents might be most effective, as some (e.g. etanercept) seem to be ineffective in colitis.

**Extraspinal manifestations: Conduction disturbances in the heart**

Previous literature has revealed that AS patients have an increased risk of conduction disturbances (CD) which is mainly associated with HLA-B27 antigen(32). These studies were mainly based on hospitalized AS patients with a long disease duration and therefore a prospective study was started in our out-patients population of 131 cases (**Chapter 9**). A first-degree AV-block was found in 6 of our AS patients. One patient suffered from a complete right bundle branch block and 1 patient had a left anterior hemiblock. A prolonged QRS-interval (pQRS >100ms) was observed in 38 patients, including those with a complete or incomplete bundle branch block. Age, disease duration and body mass index were significantly associated with PR-interval, and male gender, disease duration, and BASMI with QRS-interval. In the multivariate analyses,

disease duration remained independently associated with both the PR- and QRS-interval.

To conclude, intraventricular CD are highly prevalent in AS, particularly in patients with longstanding disease. Further research is needed to determine whether intraventricular CD may contribute to increased CV risks and long-term cardiovascular mortality in AS.

**Future goals**

Our main goal is to detect and treat AS, and its complications, at an early stage in order to prevent damage. One of the trials that should be performed is to test the efficacy of very early treatment with anti-TNF, even before abnormalities of AS are visible on radiographs. The goals of such a trial would be to prevent damage and to stop progression of the disease. At this moment we have started such a placebo-controlled trial with etanercept (PREVAS study) at VUmc. Concerning extraspinal manifestations, it is interesting to see whether AS patients with serological markers of IBD will develop manifest IBD in time or not. Particularly AS patients with pANCA and gastrointestinal complaints probably have a higher risk of developing ulcerative colitis. Cardiovascular risks, such as conduction disorders and increased risk of atherosclerosis, can be determined by performing an electrocardiogram and assessment of lipid profile in daily practice, and cardiovascular risk management should be considered. Lowering inflammatory activity by optimum use of TNF blocking agents can be supported by development of reliable biomarkers of disease activity and damage. Further research is needed whether serum trough levels of anti-TNF can be used for clinical decision making and adjustment of the anti-TNF dose. It is possible that non-responsive AS patients require a higher dose, but it is also possible that a lower dose suffices in responsive AS patients. This would lead to a considerable cost reduction in the future. New research has to be done to see

whether concomitant immunosuppressive medication can prevent antibody formation against anti-TNF, which is a significant problem in AS. To conclude, with the introduction of anti-TNF, future perspectives of AS patients have improved dramatically and future studies should aim on refinement of this treatment for individual patients.

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