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General introduction and aim of the thesis

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Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is the prototype of a systemic autoimmune disorder. The severity of the disease is variable, ranging from mild to very severe and life-threatening. The course of SLE is unpredictable and is, in general, characterized by alternate phases of remission and exacerbation of disease activity. The disease process is considered to have an autoimmune nature and may involve every organ system of the body. The skin, synovial joints, kidneys, pericardium, pleura and blood vessels are frequently affected by the inflammatory process, which may subsequently lead to the destruction and failure of organ functions. The treatment of patients with SLE is directed at the suppression of disease activity and the prevention of irreversible organ damage. From the patient's perspective, maintaining functional ability and quality of life is a major aim.

Impact of systemic lupus erythematosus

SLE predominantly affects young and middle-aged persons, especially females, and has a large impact on their physical, social and emotional functioning^{1,2} and contributes to the burden of socio-economic costs of the rheumatic diseases.³

The prevalence of SLE ranges worldwide between 15 and 200 per 100.000 and varies among ethnic groups, with higher prevalence rates reported from the Asian and the Afro-Caribbean population.^{4,5} Incidence rates of SLE between 1.5 and 7.6 per 100.000 have been reported.⁵

The survival of patients with SLE has improved over the last 4 decades from a 5-year survival of 50%-75% in 1950-1976⁶⁻⁸ to a 90-95% 5-year survival in 1990-2004.⁹⁻¹¹ The improved survival of patients with SLE has been attributed to earlier and better diagnostic methods and improved immunosuppressive treatment strategies. However, the prolonged survival of patients with SLE is also associated with considerable morbidity due to long-term disease complications. It has been proposed that the assessment of patients with SLE should comprise three domains: disease activity, quality of life, and accumulated damage.¹² However, the side effects of therapies used and comorbidity also influence the outcome in patients with SLE. Therefore, the assessment of lupus patients should include not only disease activity, quality of life and disease damage, but also comorbid conditions and drug side-effects.¹³

Complications c.q. organ damage in systemic lupus erythematosus

The assessment of complications and their causal factors in patients with SLE is a challenge. With respect to this subject, the terminology used in the literature is somewhat confusing, since complications in SLE are not synonymous with organ damage. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI) has been developed for the assessment of organ damage in patients with SLE.¹⁴ The SDI measures accumulated organ damage that has occurred since the onset of SLE, resulting from either active lupus disease itself, therapy, comorbid disease or any combination of these. Damage in patients with SLE is a predictor of further damage¹⁵ and high SDI scores are associated with mortality in the majority of studies.¹⁶ In addition, organ damage is associated with functional limitations and a reduced quality of life.¹⁷ However, the SDI does not comprise some important adverse events often occurring in patients with SLE, like infections. In the present thesis, we describe the results of the investigations on the complications of SLE, including infections.

The assessment of complications in patients with SLE is often difficult, because manifestations attributable to disease activity, chronic organ damage and drug side effects may be present simultaneously. In addition, complications in patients with SLE might be attributed to a combination of causal factors. For example, the development of cardiovascular disease in patients with SLE might be influenced by renal damage and chronic inflammation due to the disease itself, side effects of drugs such as corticosteroids, and by comorbid conditions i.e. hypercholesterolaemia and diabetes mellitus.

Having improved therapy for active lupus disease, the challenge now is to unravel the aetiology of long-term complications of the disease in order to develop strategies to prevent their occurrence.

Aim of the thesis

The studies described in this thesis were performed in outpatients of the rheumatology clinic of the VU University Medical Center, the Jan van Breemen Institute, the Slotervaart Hospital and the Academic Medical Center in Amsterdam: the SLE Cohort Amsterdam.

The main purpose of this thesis was to investigate the disease course of patients with SLE and to assess the prevalence of, and risk factors for three important long-term complications of SLE: 1) osteoporosis, 2) cardiovascular disease, and 3)

infections. Furthermore, the employment status in patients with SLE was evaluated in relationship to organ damage and health-related quality of life.

Chapter 2 presents a review of the results of recent studies on cardiovascular disease, osteoporosis and infections in patients with SLE.

Chapter 3 describes the results of a cross-sectional study on osteoporosis and fractures in patients with SLE. In an attempt to identify patients at high risk for osteoporosis and vertebral fractures, variables associated with low BMD and vertebral fractures were investigated.

The results of two studies on cardiovascular complications in patients with SLE are presented in **Chapter 4 and 5**. Both traditional and non-traditional risk factors for the accelerated atherosclerosis and premature cardiovascular disease have been identified in patients with SLE. In the general population, the role of the nitric oxide pathway and its endogenous inhibitor asymmetric dimethylarginine (ADMA) has been demonstrated in the pathogenesis of cardiovascular disease. Data on the role of ADMA in the development of cardiovascular complications in patients with SLE were lacking in the literature. In **Chapter 4**, the relationship between high plasma ADMA levels and previous cardiovascular events, disease activity and organ damage in patients with SLE is demonstrated. **Chapter 5** describes the results of a study in women with SLE on the prevalence of, and risk factors for the metabolic syndrome, a condition characterized by the clustering of cardiovascular risk factors.

The high frequency of infections in patients with SLE and the suggestion that SLE patients homozygous for variant mannose-binding lectin (MBL) alleles are at an increased risk of acquiring serious infections in comparison with patients who are heterozygous or homozygous for the normal allele, gave rise to a study described in **Chapter 6**. In this chapter, the relationship was investigated between the functional activity of the MBL pathway of complement activation in serum, as measured by three different assays, and the occurrence of infections and major infections in patients with SLE.

Chapter 7 demonstrates the results of a study on work status in patients with SLE of working age, and the relationship of employment status with organ damage and health-related quality of life.

The results of the studies performed in this thesis are summarized and discussed in **Chapter 8**. Moreover, this chapter deals with future studies based on work performed in this thesis.

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