The overall aim of this thesis was to provide a behavioural medicine perspective on SLE by investigating both clinical care for patients with SLE and their well-being. Therefore, this thesis included studies which described optimization of SLE diagnosis and treatment and studies investigating the impact of SLE on patients’ psychological functioning. The five main results of this thesis are:

1. Repeat renal biopsies during a lupus nephritis flare are only advisable in the case of a non-proliferative lesion in the original biopsy (chapter 2). The majority of patients with proliferative lesions in the reference biopsy have proliferative lesions in a repeat biopsy of either the same or a closely related class, which has no therapeutic consequences and frequently makes repeat biopsies unnecessary.

2. Concentration controlled dose adjustments with a target MPA-AUC$_{0-12}$ of 60-90 mg*h/l appears to result in optimized drug exposure and an optimal renal outcome in patients with proliferative lupus nephritis (chapter 3).

3. Type of treatment for proliferative lupus nephritis may not only influence HRQoL (chapter 4), but also patients’ perceptions of treatment effectiveness (chapter 6). In addition, SLE in general and immunosuppressive treatment for SLE specifically have a negative influence on sexual functioning (chapter 5).

4. Specific illness-related cognitions and emotions which are not assessed by questionnaires may be revealed by patients’ drawings (chapter 6).

5. Intentional and unintentional non-adherence is common in SLE patients and associated with both cognitions and emotions (chapter 7).

These main results show that a selective repeat renal biopsy policy and therapeutic drug monitoring do not hamper renal outcome and may even reduce treatment burden. However, also low dose immunosuppressive treatment remains burdensome. This burden is reflected by a lowered HRQoL and lowered sexual functioning. In view of limitations in the extent to which immunosuppressive treatment can be further lowered, patients’ illness perceptions may be targeted to enhance psychological functioning. In addition, treatment outcome may benefit from illness
perception modification through a beneficial effect of positive (i.e. more adaptive) treatment perceptions on level of treatment adherence.

Disease outcome is generally regarded as an important determinant of good patient care. One could argue that the correct diagnosis and treatment are essential steps in achieving a good disease outcome and therefore important for good patient care. In the case of SLE patients with lupus nephritis, classification of lupus nephritis and the subsequent treatment are indeed important parameters of disease outcome and good patient care. However, good patient care includes more than the management of disease parameters. It also comprises consideration of the patient’s management of the illness itself and how illness influences everyday functioning and feelings of well-being. In addition, there is a reciprocal relationship between disease characteristics and patients’ well-being. This perspective is in line with the biopsychosocial model which states that the relationship between disease characteristics and patients’ well-being is reciprocal and multifactorial and that therefore the patient and not the disease should be the centre of focus. The studies included in this thesis aimed to derive at a patient centered perspective on SLE.

Repeat renal biopsies in the classification of lupus nephritis

Although a renal biopsy can be necessary to decide on the optimal treatment for lupus nephritis, this procedure is risky and burdensome for patients. Hence, it would be desirable to keep the number of biopsies to a minimum. However, numerous authors advise serial renal biopsy in the management of lupus nephritis. This advice is based on the finding that transformations from one WHO class to another are frequent, i.e. between 26-75%. Chapter 2 reports on a study that also found a frequent class switch of 49%. However, 84% consisted of a switch from one proliferative form to another. A switch between class III and IV (with or without an additional class V) was the most frequent (54.2%). A predominance of transitions between class III and IV (with or without an additional class V) has been reported in several studies. The detection of these transformations within the proliferative group does not have clear therapeutic
consequences and does not justify the performance of repeat biopsy during a flare. On the contrary, this thesis does report a significant class switch to proliferative forms in patients with non-proliferative lesions in their reference biopsy. Hence, repeat renal biopsy may be preserved for patients with non-proliferative lesions in their original biopsy. In these cases it remains uncertain which treatment strategy to follow and a biopsy should be considered.

**Therapeutic drug monitoring in lupus nephritis**

Several treatments have been shown to be effective in achieving a good renal outcome in lupus nephritis, but treatment for lupus nephritis in general is burdensome because of frequent and serious side effects. Mycophenolate mofetil (MMF) has recently been established as an effective drug in both the induction and maintenance treatment of lupus nephritis. However, studies into the pharmacokinetics of MMF have suggested that results with MMF may be further improved through therapeutic drug monitoring. Although several studies have proposed guidelines for therapeutic target ranges for MMF therapy in SLE patients, no study reports on the application of these guidelines in a concentration controlled treatment. Chapter 3 describes a study where concentration controlled treatment with a target MPA-AUC$_{0-12}$ of 60-90 mg*h/l resulted in exposure within the target range in a sample of SLE patient with proliferative lupus nephritis. Although MPA-AUC$_{0-12}$ levels were low with a mean of 46.5 mg*h/l before dose adjustment, MPA-AUC$_{0-12}$ levels increased to an average of 69.3 mg*h/l after dose adjustment. In addition, the individualized dosing regimen was associated with a good renal outcome with 87.5% of patients showing a partial or complete response after 12 months of treatment.

**Health-related quality of life (HRQoL)**

A negative effect of pharmacological therapy for SLE on HRQoL has been reported previously, but mostly for medication groups only (e.g., immunosuppressants or glucocorticosteroids). Differences between certain variants within medication groups or differences in treatment schedules have only been investigated by two previous
studies.\textsuperscript{20,21} Comparison of CYC with MMF\textsuperscript{20} and CYC with AZA\textsuperscript{22} showed a lower physical and social functioning and higher treatment burden in the CYC groups. Chapter 4 shows that patients who were treated according to a low dose CYC and MMF protocol showed a non-significant improvement in physical and psychological functioning compared with patients in a high dose CYC only group. Hence, with regard to immunosuppressants CYC appears to have a more negative effect on HRQoL than other cytotoxic drugs and remains burdensome when low dosages are given.

**Sexual functioning**

Sexual functioning is a subdomain of HRQoL that has been shown to be important for patients with SLE, but which has been studied infrequently. Chapter 5 shows that nearly 50\% of SLE patients reported a lower sexual functioning because of their SLE. This is consistent with a general negative effect found in previous studies that have addressed sexual functioning in SLE patients.\textsuperscript{23-29} The focus in previous studies with regard to predictors of sexual functioning has been on medical and socio-demographic factors, which have been shown to have associations with sexual functioning in patients with SLE.\textsuperscript{23,26,28} However, this thesis showed that when also psychological factors are included, patients’ illness perceptions appear to play a more important role in the negative impact on sexual functioning than disease or socio-demographic characteristics. This is consistent with comparable research in patients with other chronic medical illnesses\textsuperscript{30}, strengthening the relevance of Engel’s biopsychosocial model\textsuperscript{1} which forms the theoretical basis of this thesis.

**Illness perceptions**

The findings in chapter 6 suggest that type of treatment for proliferative lupus nephritis influences perceptions of treatment effectiveness. Patients who were treated with low dose CYC rated their treatment as more helpful than patients with a high dose CYC treatment. An effect of treatment on illness perceptions has not been studied previously in patients with SLE. Moreover, illness perception assessment in SLE patients in general has been scarce. Although previous studies are difficult to compare because of the
use of non-standardized measures, general findings are that patients hold negative perceptions\textsuperscript{31-35} and that their perceptions are susceptible to change.\textsuperscript{36,37} The results of this thesis are in line with these previous findings.

**Drawings**

Patients’ drawings of their illness have been shown to uncover additional information on illness perceptions in various patient populations\textsuperscript{38-40}, including patients with SLE.\textsuperscript{41} More importantly, drawing characteristics have been shown to predict physical recovery better than medical parameters (e.g. recovery after myocardial infarction).\textsuperscript{42} Also in this thesis, SLE patients’ drawings of their kidneys provided additional information on their perceptions of damage to their kidneys due to lupus nephritis and the extent of improvement due to treatment. Drawing characteristics were not associated with measures of renal outcome.

**Treatment adherence**

Adherence to treatment is an important factor in achieving successful treatment outcomes. Although the mean self-reported adherence level in chapter 7 of 86.7% implies good adherence, patients’ also reported frequent intentional and unintentional non-adherence. Non-adherence has been reported frequently in studies with SLE patients\textsuperscript{43-49}, but a distinction between intentional and unintentional non-adherence has been only made once.\textsuperscript{43} The previous finding that unintentional non-adherence was more common than intentional non-adherence\textsuperscript{43} is also supported by the findings in chapter 7. In contrast to the earlier study\textsuperscript{43}, this thesis also investigated predictors of unintentional non-adherence. Problems with cognitive functioning, concerns about potential side effects and age were the best predictors of unintentional non-adherence.

**Clinical implications and future research**

In studies with patients with SLE, the focus has mainly been on improving disease characteristics such as renal outcome and disease activity. Although research into patients’ well-being is increasing over the last few decades, this thesis also showed that
several aspects of psychological functioning for patients with SLE are only beginning to be uncovered. The studies included in this thesis aimed to give more insight in the reciprocal relationship between disease characteristics and well-being in patients with SLE. The results point in the direction of several recommendations to influence this relationship in a positive way and for the focus of future research.

First of all, a restrictive repeat renal biopsy policy may reduce the number of repeat renal biopsies and therefore reduce treatment burden. Current renal biopsy policies are often based on results from studies existing of protocol renal biopsies. However, in clinical practice biopsies are performed on account of a clinical manifestation of a lupus nephritis flare. Chapter 2 describes one of the few studies that performed repeat biopsies based on clinical characteristics. Given this study’s results and its implications, more such studies are needed to confirm the results. In addition, the participant group in chapter 2 consisted mostly of individuals of Caucasian descent, so that a similar study with patients of other ethnicities should be performed. For example, patients with SLE of African descent have a more aggressive course of disease and poorer outcomes which may influence preferred biopsy policy.

Secondly, therapeutic drug monitoring allows making early adjustments in medication dosages in order to minimize the occurrence of adverse and toxic effects and to maximize renal outcome. Although therapeutic drug monitoring requires frequent blood sampling, the early detection of too high or too low drug concentrations may result in an overall reduction of treatment burden. Future studies are needed to investigate the actual effects on patient experience. In addition, randomized controlled trials comparing fixed dose to therapeutic drug monitoring would be necessary to confirm the superiority of an individualized dosing regimen.

Thirdly, the finding that SLE has a great impact on patients’ HRQoL highlights the need to address this issue regularly. Patients may feel hesitant to introduce problems with psychological functioning themselves, especially when the focus is on medical aspects. Moreover, it has been shown that patients are more likely to report problems with sexual functioning if physicians inquire about such problems. But besides making problems with psychological functioning open to discussion, disease specific measures of HRQoL can be
useful to assess the most important problems and their impact. Although several measures of HRQoL have been developed for use with SLE patients, cross-cultural validation is often missing and these measures in general do not include an adequate assessment of sexual functioning. Future studies are needed to address these issues.

Furthermore, besides discussing psychological problems, the results of this thesis highlight the importance of adequate doctor-patient communication. Chapter 6 showed that patients with SLE in general hold negative illness perceptions. Such negative emotions and cognitions have been associated with poor outcomes, such as a lowered sexual functioning (chapter 5) and low adherence levels (chapter 7). Therefore, improving psychological functioning in patients with SLE starts with uncovering patients’ specific emotional and cognitive perceptions about their illness. Besides the use of short questionnaires, drawings have been shown to be a successful tool to reveal patients’ unique illness perceptions (chapter 6). Knowing these perceptions will enable doctors to fine-tune their communication to address patients’ specific needs and concerns.

Lastly, this thesis showed a negative influence of treatment on both HRQoL and illness perceptions. Not only adjustments in pharmacological treatment should be sought to lower this burden, but also non-pharmacological methods to improve HRQoL and illness perceptions should be applied. Psychological interventions aimed at enhancing HRQoL have been shown to be successful in patients with different chronic diseases, but implementation in SLE patients and its effect on HRQoL have not been studied. A previous study did find a positive effect of cognitive behavioural therapy on patients’ illness perceptions. More positive illness perceptions may not only have a beneficial effect on psychological functioning, but also on treatment adherence. Illness perceptions modification in SLE patients should therefore be addressed in future studies.
REFERENCES


