Is individualized therapy the future of lupus treatment?

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The main goal of therapy for systemic lupus erythematosus is to achieve remission, as this has a major impact on patient and renal survival. Furthermore, early treatment success has been shown to improve long-term prognosis. Treatment has traditionally followed a standardized schematic therapy. However, studies have shown that treatment response may depend on age, gender, ethnicity and other genetic factors. In addition, data show that mycophenolate mofetil is effective in the treatment of lupus nephritis, and research focusing on the pathogenesis of lupus is ongoing with emerging treatment targets. Thus, the treatment of systemic lupus erythematosus and, in particular, lupus nephritis, is evolving from standardized therapy to an individualized therapeutic approach based on analysis of organ involvement, the patient's background, risk factors and, possibly, cytokine, antibody or cell profiles.

Systemic lupus erythematosus (SLE) is a disease that affects many different organs. The outlook for patients has improved over recent decades, and the 5-year survival rate has increased to approximately 85% [1]. Nevertheless, morbidity and mortality are still important issues. The most common causes of death were active disease and infections initially, and atherosclerosis and cancer after the first year of diagnosis [2,3]. Therefore, treatment will have to focus not only on the initial phase, but also on the years afterwards. An individualized treatment will have to concentrate on different points: the pattern of organ involvement and the severity of the disease, the patient's background (gender, ethnicity, age and comorbidity) and the possible treatment strategies available.

Organ involvement & severity of disease activity

Regarding organ involvement, renal manifestation has a major impact on morbidity and mortality [4]. Therefore, treating lupus nephritis is an important issue and this article will focus on this manifestation.

The assessment of lupus nephritis has improved with the recently updated histological WHO classification [5]. Treatment varies with the different forms of nephritis; for example, lupus nephritis class I and II does not require immunosuppressive treatment. Data on the treatment of class V are sparse, as only small studies are available and no clear evidence-based recommendations can be given [6]. Severe forms of kidney involvement are histologically defined by proliferative changes (lupus nephritis class III or IV) also reflected in the activity index [7]. The majority of therapeutic efforts have focused on this group of patients, with a progressive course of the disease leading to terminal renal failure in approximately 25% of the patients after 10 years of follow-up [4,7]. Korbet and colleagues have shown the importance of achieving remission, as both patient and renal survival at 5 and 10 years are greatly reduced if remission is not achieved [4]. Houssiau and colleagues have shown the importance of an early response, as the greater the reduction in creatinine and proteinuria at 6 months of treatment, the better the patient's long-term renal outcome [8]. The current accepted standard of care for induction treatment of proliferative lupus nephritis is monthly intravenous cyclophosphamide (dose: 0.5–1 g/m^2) together with steroids. The regimen was developed in the 1970s and 1980s in trials by the NIH but has been changed in the subsequent years. Alternative cyclophosphamide regimens have been evaluated. Houssiau and colleagues have shown that a low-dose fixed cyclophosphamide regimen for 3 months followed by azathioprine is successful in a group of Caucasian patients with lupus nephritis, and preserves renal function in most patients (after a median follow-up of 73 months, renal function was permanently impaired in 20% of the low-dose group and in 23% of the high-dose group patients) [9].

Although cyclophosphamide has improved outcome in terms of progressive renal disease [10], mortality was not influenced when compared with a regimen with steroids alone [11]. The reasons involve acute adverse effects such as severe infections [12]. In addition, long-term toxicity, such as permanent infertility and secondary malignancies, has to be taken into account.

Keywords: biological, lupus nephritis, mortality, mycophenolate mofetil, systemic lupus erythematosus

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Moreover, this regimen seems to be less effective in non-Caucasian populations (low remission rate of only 14.3 and 18.2% in the studies by Ginzler and colleagues [13] and Ong and colleagues [14], respectively, including mainly non-Caucasian patients) with a higher incidence of lupus nephritis [15] and a high level of disease activity [16,17].

Mycophenolate mofetil (MMF) has emerged as a potential alternative induction treatment to cyclophosphamide [13,14,18,19]. The largest completed randomized trial is the study by Ginzler and colleagues including 140 patients [13]. In an intention-to-treat analysis, 21 (30%) patients who received intravenous cyclophosphamide and 37 (52%) of those who received MMF achieved complete or partial remission (significant difference, $p < 0.005$). Patients who received MMF had a lower rate of severe infections and deaths during follow-up after induction therapy than those who received intravenous cyclophosphamide. MMF has also been successfully used to maintain remission [18,20]. All randomized trials and several uncontrolled open-label studies suggest that MMF is at least as effective as cyclophosphamide [13,14,18–21]. However, as the studies by Chan and colleagues include Chinese patients [18,19], the studies by Ginzler and colleagues [13] and Contreras and colleagues mostly involved Hispanic and black patients [20] and the study by Ong and colleagues involved Malay and Chinese patients [14], positive results regarding the potential of MMF to induce remission were found for mainly nonwhite patients. Regarding toxicity, the administration of MMF was less likely to result in death, severe infection or leukopenia, and amenorrhea occurred less frequently, although the differences did not always reach statistical significance [13,18,20] (diarrhea seems to be more common with MMF [13]). The hospitalization rate was also reduced [18,20]. Recent studies regarding the quality of life resulted in superiority for MMF compared with cyclophosphamide treatment [22,23]. In addition, a model simulating the costs of an induction treatment of patients with lupus nephritis showed that MMF was more cost effective than cyclophosphamide [23]. Taken together, these results would lead to the conclusion that MMF should at least be used in nonwhite patients with proliferative lupus nephritis. However, these studies have been relatively small and with a limited follow-up. Therefore, many questions still need to be answered. The ongoing Aspreva Lupus Management Study (ALMS) is aiming to provide such data. More than 350 patients are randomized to receive, in addition to prednisolone, intravenous cyclophosphamide (0.5–1 g/m^2) or MMF (3 g/day; minimum 2 g/day) for induction, followed by azathioprine or MMF for maintenance therapy. The first results of the induction phase did not show a superiority of MMF [24]. Subgroup analyses need to be performed to see if a special group of patients had an improved remission or partial remission rate with one of the different regimens. This seems especially important as patients with different ethnicity and patients of class V nephritis (membranous lupus nephritis) have been included. A recent investigation assumes that the incidence of those patients is increasing (43% of biopsies done between 1999 and 2007 showed class V lupus nephritis) [25]. Until now, treatment in membranous lupus nephritis concentrates primarily on the inhibition of the renin–angiotensin system and the reduction of secondary risk factors. The immunosuppressive approach includes drugs such as cyclosporin A, MMF, azathioprine, cyclophosphamide or even rituximab [26–29]. An individualized approach in membranous lupus nephritis still seems to be far in the future.

Age, gender, ethnicity & socioeconomic status

Age & gender

As the prevalence and the severity of SLE varies with age, gender and ethnicity, these factors will have to be taken into account for an individualized treatment approach. Moreover, arising data suggest that the socioeconomic situation of the patient has an important influence on outcome.

It has been shown that age is negatively associated with high levels of disease activity (systemic lupus activity measure-revised [SLAM-R] score >10) [16]. Disease activity has important implications regarding outcome in terms of damage accrual and mortality. In accordance with these results, Bastian and colleagues have recently shown that younger age is associated with renal involvement and with the risk of new or worsening proteinuria [17]. Some 5 years earlier, Mosca and colleagues could already demonstrate that a younger age at the time of renal biopsy correlates with the occurrence of renal flares [30], which are considered to be an important risk factor for end-stage renal disease [31]. Whereas young patients seem to need a more aggressive or longer lasting immunosuppressive protocol, treatment in older patients should be reduced, taking into

account the lower disease activity and the higher susceptibility for infections (a patient treated with oral cyclophosphamide aged 65 years has a 50% chance of developing a severe infection and the risk further increases to approximately 70% at the age of 70 years [12]). As older patients have a higher incidence of venous thrombotic events [32,33], prophylaxis is an important issue in this patient group.

As 90% of the patients developing lupus are women (e.g., see the LUpus in MInority populations: NAture v Nurture [LUMINA] cohort), predominantly during their childbearing years, there is no doubt regarding the influence of gender and hormones. Male SLE patients present with atypical cutaneous manifestations (widespread discoid lupus erythematosus and papular and nodular mucinosis were significantly more common [34]) and have been reported to develop more serositis, seizures and thrombotic events [35]. By contrast, musculoskeletal involvement was less frequent [35]. Renal involvement developed more often in men, and the risk of renal end-stage disease was highest in men with an early onset of the disease [36]. In addition, Andrade and colleagues demonstrated that organ damage was more frequent, of higher magnitude and occurred early in the course of the disease [35], leading to a poorer long-term prognosis. A reduced survival rate was also seen by others (77% in men compared with 92% in women after a median observation of 5.4 years) [33]. The fact that men have a less favorable long-term prognosis than women, emphasizes the importance of early diagnosis. Studies will have to show if a more aggressive and/or longer immunosuppressive treatment may prevent deleterious events, increasing the survival of men with SLE. At present, no studies have incorporated or even considered different therapeutic strategies.

The dominance of women in their childbearing age is already influencing therapeutic considerations. Thus, cyclophosphamide-induced ovarian toxicity is an important issue. It is heralded by the onset of irregular or infrequent periods, and may progress to amenorrhea, permanent infertility and premature ovarian failure with elevated levels of gonadotropins and decreased levels of estradiol leading to physical and emotional consequences. Despite many publications, no data are available allowing for reliable prediction of gonadal toxicity. In women, permanent infertility arises in most after total doses greater than 25 g [12]. However, the incidence of ovarian failure depends on age, and older women are more likely to progress to premature ovarian failure after therapy because they have a smaller number of oocytes at initiation. In one study of patients with lupus nephritis, cyclophosphamide administration resulted in ovarian failure in all women older than 30 years, in approximately 50% of those aged 20–30 years and in 13% of patients younger than 20 years [37]. Recently, Manger and colleagues have described comparable results [38]. Administration of a gonadotropin-releasing hormone analogue in women with severe SLE was associated with a significant reduction in premature ovarian failure [39]. Nevertheless, an increasing number of women with the desire to have children refuse to take an alkylating agent, especially since positive results of MMF have been published. However, MMF has been shown to be teratogenic and it should be discontinued prior to pregnancy [40].

Ethnicity & socioeconomic status

Multiethnic studies have shown the influence of ethnicity on the incidence, clinical manifestation and outcome in SLE. The incidence is significantly higher in nonwhite racial groups [41]. African and Hispanic ethnicity has been associated not only with a greater prevalence, but with a more severe disease [42]. Alarcon and colleagues reported that renal involvement occurred in 45% of Texan Hispanics, 11% of Puerto Rico Hispanics, 46% of African–Americans and 18% of Caucasians. Socioeconomic status accounts for only 14.5% of this variance [15]. This ethnical difference also refers to the severity of renal involvement. In a group of patients in the UK, Adler and colleagues reported that 62% of black patients progressed to end-stage renal failure compared with 19% of white or Asian patients [43]. These data are reminiscent of results published in the USA, where African–American patients had a more aggressive lupus and a more progressive renal disease [44]. Renal survival was significantly worse in black compared with white patients. The 5-year renal survival was 95% in white patients, whereas black patients showed a progressive decline with a survival rate of only 58% [44]. Racial differences were independent of age, hypertension control and activity or chronicity indices on renal biopsy [44]. Although the structure of the healthcare system in the USA makes it more difficult to determine whether the cause for this renal failure is genetic or socioeconomic, the

data from the UK, where healthcare is free at the point of entry, suggest that some cases of renal failure may be genetically predetermined.

However, the socioeconomic status itself is a prognostic factor. Lack of health insurance and poor social support has been shown to be associated with high level of disease activity (SLAM-R score >10) [16].

New treatment strategies

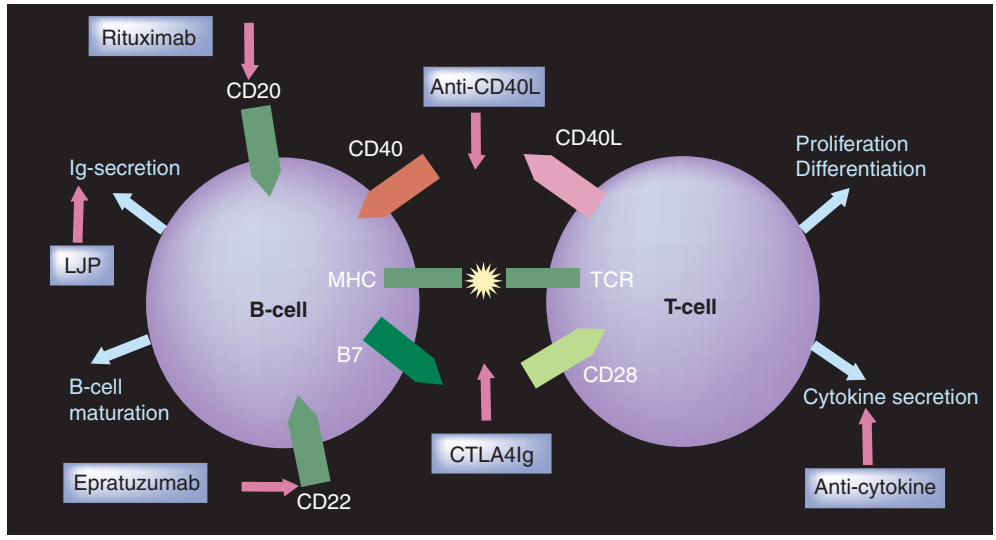
The main goal of therapy for SLE, and especially for lupus nephritis, is to achieve and maintain remission, as this has a major impact on patient and renal survival [4,31]. This has traditionally been achieved with intravenous cyclophosphamide, but recent data give the impression that, for example, MMF is as effective as, and causes fewer adverse events than, cyclophosphamide [13,14,18–21]. Research to find new treatment targets is ongoing. The key for effective alternatives may lie in the pathogenesis of lupus nephritis. Many studies in mice have provided important information regarding the role of B and T cells, as well as costimulatory molecules (CD40 ligand, B7 and CD28), immunoglobulins and CD20, which is characteristic of B cells. This information has led to the development of a variety of potential new treatment approaches (Figure 1). Possible future therapies include monoclonal antibodies against CD20 (rituximab), CD22 (epratuzumab) and antibodies interfering with the costimulatory molecules and therapies targeted at cytokine secretion, immunoglobulin secretion, B-cell maturation and T-cell proliferation and differentiation.

Rituximab has already shown promise in patients with active proliferative lupus nephritis, which suggests that B-cell depletion may be successful [45–48]. The target of rituximab is the cell-surface antigen CD20, which appears early in the maturation of B cells and is expressed throughout the stages of B-cell development [40]. Importantly, in terms of toxicity, plasma cells do not express CD20 cell-surface antigens, which means that these cells are not depleted during treatment with rituximab [45]. Looney and colleagues published the first results with rituximab in patients with SLE; they found variable levels of B-cell depletion using different doses and showed that rituximab had no effect on disease activity in patients who did not have a depletion of B cells [46]. Subsequently, many small studies have been undertaken, with around 100 patients now treated with rituximab overall. The results of these, and larger studies by Sfikakis and colleagues and Leandro and colleagues [47,48], are promising, but data from long-term trials are awaited to determine the long-term prognosis and possible parameters to predict or influence treatment response.

Anti-dsDNA antibodies correlate with flares of lupus nephritis and may represent another therapeutic target. Therapy with LJP 394 (Riquet®), which is a construct of four 20-mer dsDNA epitopes [49] and crosslinks anti-dsDNA antibodies in solution or on the B-cell surface, thus inducing apoptosis or anergy, reduces flares [49]. Concerns exist over the safety of injecting antigens into a patient with autoimmune disease. However, in a randomized, placebo-controlled study, patients who received placebo had three-times as many renal flares as patients treated with LJP 394 and had a shorter median time to renal flare, but only when the drug bound with high affinity to the patient's anti-dsDNA antibodies [49]. Thus, a patient will have to be tested before this treatment may be applied.

Studies are already recruiting for many of the new drugs and those in preparation. They will hopefully provide more information regarding prognostic parameters and predictors of treatment response, eagerly awaited to better classify patients, not only because of their gender and their ethnical background, but also because of their immune status (e.g., selected HLA alleles and Fcγ-receptor polymorphisms, single nucleotide polymorphisms of functionally important cytokines and others) [50–52]. Capuano and colleagues recently described that renal expression of hepatocyte growth factor and TGFβ1 predicts renal outcome at 6 months after therapy with cyclophosphamide and steroids with a predictive value of 94%, whereas activity and chronicity index were not able to discriminate between poor versus favorable outcome [53]. In the future, microarray experiments producing profiles of gene expression may identify pathogenic, diagnostic and prognostic markers, and may also reflect the drug-response profile, which may help clinicians in monitoring disease activity [54]. Thus, Alcorta and colleagues recently described specific leukocyte gene-expression profiles in patients with lupus nephritis distinct from those of patients with antineutrophil cytoplasmic autoantibody-associated vasculitis, rheumatoid arthritis or healthy volunteers. A subset of SLE signature genes was upregulated in activated T cells. The authors concluded that monitoring changes in the expression of specific genes may be a tool to help quantify disease activity during treatment [55]. The dream of an individual 'response test' for different treatment strategies may become reality.

Figure 1. Potential future targets and drugs in the management of systemic lupus erythematosus.



Ig: Immunoglobulin; MHC: Major histocompatibility complex; TCR: T-cell receptor.

Accelerated arteriosclerosis

Beyond the initial phase of the disease course of SLE, cardiovascular death is the main cause of mortality [2,3], and this must also be addressed if long-term outcomes are to be improved. Many patients with SLE have subclinical atherosclerosis quite early in the disease course, and the risk of coronary artery disease at any level of traditional cardiovascular risk factors is higher than in the general population [56]. In a Toronto cohort of 665 patients, 33 (27%) of the 124 deaths overall were the result of cardiovascular disease but only 20 (16%) deaths were the result of active lupus [2]. In a Danish cohort of 523 patients, 35 (29%) of the 122 deaths were caused by active lupus, 32 (26%) by cardiovascular disease and 25 (20%) by infections [3]. Doctors thus need to be aware of the phenomenon of accelerated arteriosclerosis in patients with SLE so that they can act now to prevent patients needing bypass surgery for coronary artery disease in 20 years time.

Evidence for an association between SLE and accelerated atherosclerosis comes from a variety of sources. In a study by Sun and colleagues, 82% of women with lupus and nonspecific cardiovascular symptoms had myocardial perfusion abnormalities and 43% of women with lupus but no cardiovascular symptoms (age range: 20–46 years) had myocardial perfusion abnormalities, but no definite perfusion abnormalities were found in 24 healthy, age- and sex-matched controls [57]. The evidence is even more striking in terms of the increased prevalence of carotid plaques, intimal/media thickness and endothelial dysfunction (incidence more than five-times as high for carotid plaques and more than double for endothelial dysfunction) [58–60]. The risk of cardiovascular disease is higher in patients with a longer duration of disease and a higher damage index score (a summation of the cumulative effects of disease) [58], and in patients who do experience a vascular event, the mortality is twice as high in SLE as in other patient groups [61]. Simply having SLE accelerates a patient's risk of developing coronary artery disease [56]. Important risk factors include traditional factors that may be specifically relevant in patients with SLE, for example, hypertension, diabetes mellitus, hypercholesterolemia and obesity, as well as risk factors associated with the lupus itself, such as endothelial dysfunction, the inflammatory process, anticardiolipin antibodies and impaired renal function. So how can the accelerated arteriosclerosis be influenced? Possible strategies to reduce the lupus-specific risk include reduction of disease activity to improve endothelial function and reduction of the steroid dose whenever possible [58,60]. Screening and management of the traditional risk factors, which may not have been so important previously, will become more important in the future. Therapy with aspirin or statins may be a possibility to influence lupus-associated and traditional risk factors.

Conclusion & future perspective

The treatment of SLE, and especially lupus nephritis, has traditionally followed a standardized schematic therapy. In the future, management will be individualized. The pattern of organ manifestation already leads to different treatment strategies (e.g., cyclophosphamide is only used in life-threatening manifestations or proliferative lupus nephritis). Studies focusing on patients age, gender, socioeconomic status, genetic background and immune status will bring knowledge to shape a treatment taking into account all these different factors. Data available up to now support the view that young, male patients need a more aggressive and long-term treatment. Nonwhite racial groups seem to respond less well to cyclophosphamide, but may be better off with MMF. Women with the desire to have children refuse to take cyclophosphamide because of its ovarian toxicity. New drugs are emerging and their role will have to be defined in large studies that have just started to include the investigation of genetic variables, for example, polymorphisms, cytokine profiles and drug affinity. The dream of tests predicting response to different treatment strategies may become reality. As mortality is caused less often by active disease, but by side effects and accelerated arteriosclerosis, patient care will focus on the individual risk factors that might be influenced, and early diagnostic procedures will be necessary to prevent cardiovascular events.

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Executive summary

- Treatment of systemic lupus erythematosus (SLE) has followed a standardized schematic therapy. However, studies have shown that response may depend on organ involvement, age, gender, ethnicity and other genetic factors.

Organ involvement & severity of the disease

- Renal involvement has a major impact on morbidity and mortality, and it is important to reach early remission.
- Regarding proliferative lupus nephritis, studies suggest that mycophenolate mofetil is at least as effective as cyclophosphamide but has fewer side effects.

Age, gender, ethnicity & socioeconomic status

- Age has been shown to be negatively associated with high levels of disease activity and younger patients have a poorer prognosis regarding mortality and renal outcome, whereas older patients have a higher risk of developing life-threatening infections. This has to be taken into account when choosing the immunosuppressive regimen.
- Male and/or nonwhite patients have a poorer prognosis for this female-dominated disease and a higher risk of developing end-stage renal disease. A more aggressive and prolonged treatment seems to be necessary.
- Poor socioeconomic status is an independent risk factor and social support is important for successful treatment.

New treatment strategies

- Research focusing on the pathogenesis of the disease has found new treatment targets.
- Possible future therapies will include monoclonal antibodies against B and T cells, costimulatory molecules, cytokines and immunoglobulins.
- Further insight into the genetic background, binding of autoantibodies, cytokine and cell profile will support the dream of a pretreatment test for every patient to predict treatment response.

Accelerated arteriosclerosis

- Besides immunosuppressive treatment, minimizing side-effects and influencing risk factors for the accelerated arteriosclerosis are also important goals.
- Early diagnostic and therapeutic intervention may reduce cardiovascular morbidity and mortality.

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