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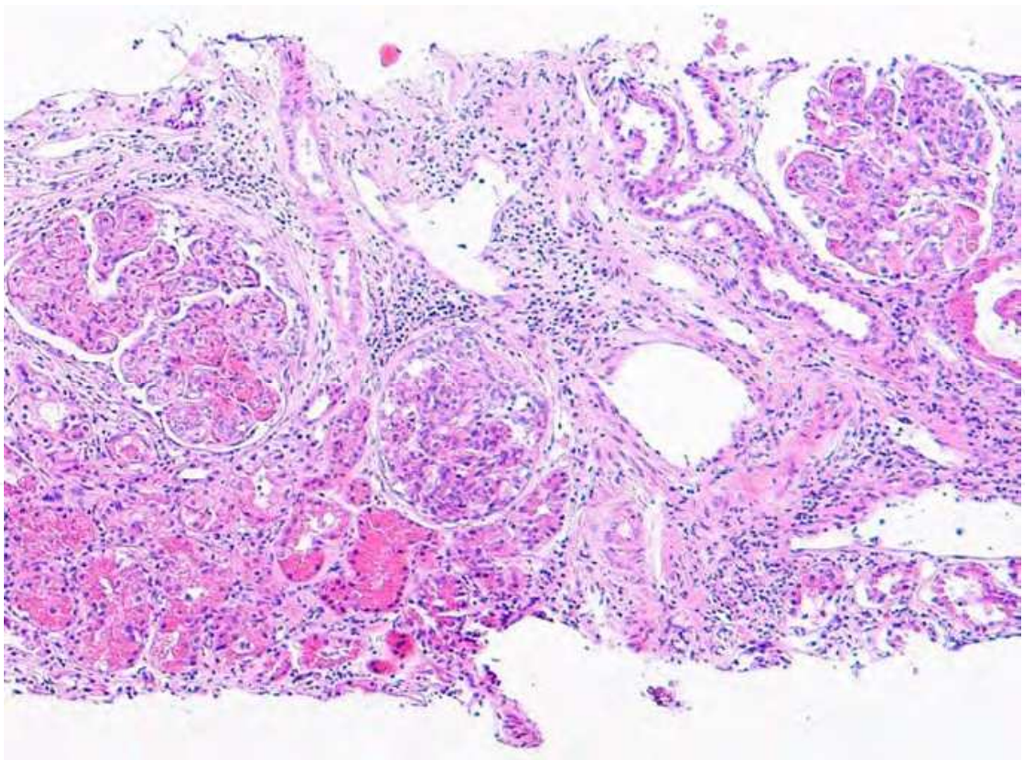
New Therapeutic Strategies in Lupus Nephritis

Natasha Jordan and Yousuf Karim
Louise Coote Lupus Unit, St Thomas' Hospital, London
United Kingdom

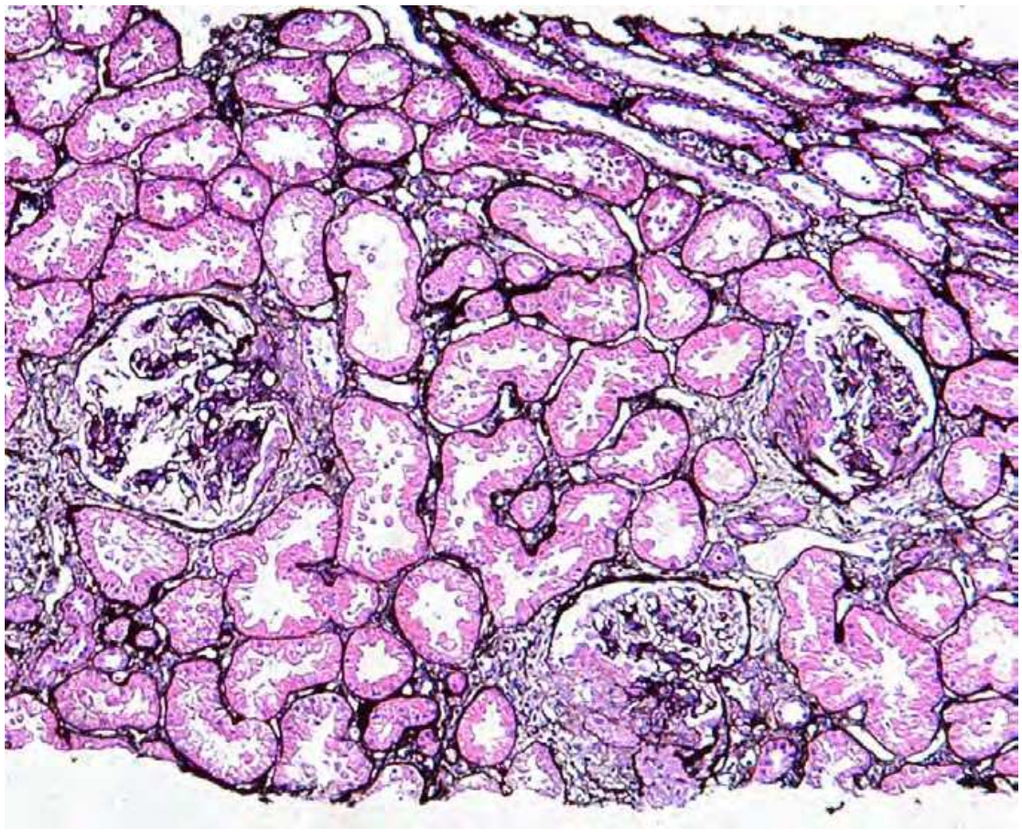
1. Introduction

Lupus nephritis remains a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). Despite overall advances in the clinical management of lupus nephritis in recent decades with earlier recognition of disease and optimization of the currently available immunosuppressive regimens, an estimated 10-15% of patients progress to end-stage renal disease (ESRD) requiring dialysis and/or renal transplantation (Mavragani et al, 2003). Proliferative lupus nephritis (International Society of Nephrology/Renal Pathology Society classes III & IV) is the most aggressive variant of nephritis; figures 1 and 2 illustrate the histology of Class IV nephritis.



(Courtesy Dr Fahim Tungekar)

Fig. 1. Class IV global proliferative lupus nephritis



(Courtesy Dr Fahim Tungekar)

Fig. 2. Class IV segmental proliferative lupus nephritis

The rate of progression to ESRD is likely to be even higher patients of Afro-Caribbean descent (Dooley et al, 1997). Commonly used therapeutic agents such as corticosteroids, cyclophosphamide, mycophenolate mofetil and azathioprine have certainly improved clinical outcomes, however a significant proportion of lupus nephritis patients have refractory disease and the potential side effects of these therapies are significant.
A recent retrospective review of lupus nephritis patients over a 30 year period (1975-2005) showed that five year mortality decreased by 60% between the first and second decades but remained unchanged over the third decade. The rate of progression to ESRD also reached a plateau in the third decade. These results suggest that the benefits of conventional immunosuppressive therapies have been maximized and if further improvements in lupus nephritis outcomes are to be achieved, novel therapeutic targets must be developed (Croca et al, 2011).

2. B-cell depletion therapies

Lupus nephritis involves a complex interplay of immunologic disturbances with renal damage resulting from production of pathogenic autoantibodies and immune complexes, which activate complement leading to infiltration of inflammatory cells in the kidney. B lymphocytes play an integral role in this process, they are the precursors of plasma cells that

Class of therapy	*Agent*	*Mechanism of action*	*Clinical Stage*	*Result or Outcome*
B-cell depletion	Rituximab	anti-CD20 chimeric Moab	Phase III	EXPLORER & LUNAR trials failed to meet primary end-points
	Ocrelizumab	anti-CD20 fully humanized Moab	Phase III	Clinical trial suspended
	Epratuzumab	anti-CD22 fully humanized Moab	Phase III	Study ongoing
B-cell survival factors	Belimumab	anti-BLys fully humanized Moab	Phase III	BLISS (52 and 76) FDA approved
	Atacicept	TACI-Ig fusion protein	Phase II/III ongoing	Trial temporarily discontinued, now resumed
T-cell co-stimulation	Abatacept	CTLA-4-Ig fusion protein	Phase II	Failed to meet primary end-point, further trials ongoing
	CD40L	BG9588 IDEC-131	Phase II	Study discontinued due to thromboembolic events Negative trial
Cytokine targets	Tocilizumab	Il-6 fully humanized Moab	Phase I	Well tolerated in phase I trial, further trials pending
	Infliximab Etanercept	anti-TNF-α chimeric Moab TNF-receptor-IgG fusion protein	no controlled trials no controlled trials	
	Medi-546	Interferon-α Moab	Phase I	Trials ongoing
Complement therapies	Eculizumab	anti-C5 fully humanized Moab	Phase I	Safe & well tolerated in phase I trial, no further studies to date

Moab, monoclonal antibody, BLys, B lymphocyte stimulator, TACI-Ig, transmembrane activator and calcium modulator and cyclophylin ligand interactor-immunoglobulin, TNF-receptor-IgG, tumour necrosis factor-receptor-immunoglobulin

Table 1. Summary of emerging biologic therapies in systemic lupus erythematosus

produce these pathogenic autoantibodies and they also function as antigen presenting cells to T lymphocytes. Thus B lymphocytes represent a rational therapeutic target in lupus nephritis. By far the most clinical experience in targeting B-lymphocytes to date has been in the form of B-cell depletion therapy (BCDT). Rituximab, a monoclonal antibody against the cell surface protein, CD20 has been in use clinically for the past decade. Alternative forms of BCDT are under development and in ongoing clinical trials.

2.1 Rituximab (Anti-CD20)

CD20 is a cell surface protein expressed on B lymphocytes from the early pre-B cell until mature B cell stages of development, but is not present on hematopoietic precursor stem cells or plasma cells.The CD20 antigen was first targeted in the immunotherapy of B cell lymphomas (Grillo-Lopez et al, 1999) (Hainsworth et al, 2000) and, subsequently in rheumatoid arthritis (RA) (Edwards et al, 2004). Rituximab is a chimeric mouse/human monoclonal antibody against the B cell-specific antigen CD20, a cell surface protein believed to function in B cell cycle initiation and differentiation. Rituximab induces cell lysis via antibody-dependent cell-mediated cytotoxicity and activation of complement leading to B-cell depletion in the peripheral blood and bone marrow (Reff et al, 1994).

Open trials of rituximab over the past decade have shown encouraging results in active and refractory SLE including lupus nephritis (Leandro et al, 2002) (Looney et al, 2004) (Leandro et al, 2005). However the failure of rituximab to meet its primary and secondary end points in randomized controlled trials of non-renal SLE (EXPLORER) and lupus nephritis (LUNAR) has been disappointing (Merrill et al, 2010). Issues with study design, concomitant use of high dose steroid and other immunosuppressive therapies and the relatively low severity of disease in patients enrolled need to be taken into account when interpreting the results of these trials.

A number of case reports and open-label studies have reported successful treatment of lupus nephritis with rituximab. Vigna-Perez et al reported an open study of 22 LN patients receiving rituximab (0.5 to 1.0 g at Days 1 and 15). This was added to existing treatment consisting of different combinations of azathioprine, mycophenolate, cyclophosphamide and corticosteroids. Significant reduction of disease activity and proteinuria was seen ($P<0.05$). One patient died from invasive histoplasmosis at day 70 (Vigna-Perez et al). Clinical improvements have also been seen using rituximab in membranous lupus nephritis (Jónsdóttir et al, 2010) (Jónsdóttir et al, 2011).

Pepper et al reported the use of rituximab as induction therapy followed by maintenance mycophenolate mofetil in a cohort of eighteen patients with proliferative lupus nephritis. A significant decrease in proteinuria from a mean protein: creatinine ratio (PCR) of 325 mg/mmol at presentation to 132 mg/mmol at 1 year ($p = 0.004$) was demonstrated and this combination of sequential therapy allowed a reduction or total withdrawal of maintenance corticosteroids (Pepper et al, 2009).

The French Autoimmune and Rituximab (AIR) registry reviewed one hundred thirty-six patients who received this treatment for SLE. Articular, cutaneous, renal, and haematologic improvements were noted in 72%, 70%, 74%, and 88% of patients, respectively. Severe infections were noted in 12 patients (9%), with most severe infections occurring within the first 3 months after the last rituximab infusion. Five patients died, three due to severe infection ($n = 3$) and two due to refractory autoimmune disease. Overall response was observed in 71% of patients and among these, 41% experienced a relapse of disease but responded after retreatment with rituximab in 91% of cases (Terrier et al, 2010).

Sangle et al noted progression to ESRD in five patients with severe proliferative, crescentic lupus nephritis (mean activity score 12/24, mean crescents 38%) with raised serum creatinine (mean 278 µmol/l) treated with rituximab, after failure of other immunosuppressive drugs (Sangle et al, 2007). This may reflect that the timing of rituximab therapy in the course of disease may be important for its efficacy.

The degree of B-cell depletion achieved is far more variable in SLE patients treated with rituximab as compared to those with RA or lymphoma (Gunnarson et al, 2007) (Sutter et al, 2008). However the degree and duration of B-cell depletion in SLE patients does correlate to some extent with clinical response and those who fail to deplete tend to have a poorer clinical response (Albert et al, 2008).

The most common adverse effects associated with rituximab therapy are mild to moderate infusion reactions. Two SLE patients treated with rituximab developed progressive multifocal leukoencephalopathy (PML) which should be interpreted in the context of the known 20 patients with SLE reported to have developed PML and had not received rituximab therapy (Calabrese et al, 2007).

The rate of development of human anti-chimeric antibodies (HACAs) is significantly higher in lupus patients treated with rituximab than RA or lymphoma patients who have received this therapy (Smith et al, 2006) (Saito et al, 2005). It is not entirely clear if development of HACAs in rituximab treated lupus patients will lead to reduced efficacy of this medication with repeated use.

A cohort of 76 patients with active SLE refractory to standard immunosuppression have received repeated cycles of rituximab since 2000 with good clinical response and favourable safety profile (Turner-Stokes et al, 2011). The long-term effects of repeated B-cell depletion are unknown, though there is a risk of hypogammglobulinaemia.

Perhaps further randomized controlled trials in moderate to severe lupus patients and a greater understanding from basic science as to why some lupus patients have more profound and long-lasting B-cell depletion will clarify the role of rituximab in SLE and in particular lupus nephritis.

2.2 Ocrelizumab (Anti-CD20)

Ocrelizumab, a fully humanized monoclonal antibody against CD20, is an alternative form of BCDT which entered clinical trials for SLE and rheumatoid arthritis (RA). The potential benefits of this form of BCDT included avoidance of HACA development given its fully humanized structure thus maintaining efficacy and minimizing HACA related side effects. Clinical trials in SLE and RA were suspended in 2010 due to excess deaths due to opportunistic infections and thus no results are currently available for this therapy.

2.3 Epratuzumab (Anti-CD22)

CD22 is a B-cell surface restricted marker and member of a class of adhesion molecules that regulate B-lymphocyte activation and interaction with T lymphocytes. CD22 is expressed in the cytoplasm of pro-B and pre-B cells, and on the surface of maturing B cells (Tedder et al, 1997). CD22 plays a role in inhibition of BCR signaling by controlling calcium efflux in B cells as evidenced by work in CD22-deficient mice (Sato et al, 1998). CD22-deficient mice have reduced numbers of mature B cells in the peripheral blood and bone marrow and these B cells also have a shorter life span and increased apoptosis indicating that CD22 plays a key role in B cell development and survival (Otipoby et al, 1996).

Thus CD22 is an attractive therapeutic target in lupus nephritis. Epratuzumab is a recombinant humanized monoclonal IgG antibody to CD22; it mediates antibody-dependent cellular cytotoxicity and partially depletes B-cells. It is thought that epratuzumab modifies B-cell function without killing them but the precise mechanism of action remains unclear.

Safety of epratuzumab was first demonstrated in clinical trials of non-Hodgkins lymphoma (Leonard et al, 2004). It has also been successfully used in refractory lymphoma in combination with rituximab (Leonard et al, 2005). The main side-effects seen in these studies were infusion reactions.

An open-label non-randomized trial of epratuzumab in mild to moderate SLE showed promising results with consistent improvement observed in all patients enrolled for the 12 week duration of the study, average 35% depletion in B-cell levels, and no evidence of HACA development. The duration of response in this study was very heterogeneous for different BILAG domains, precluding any firm conclusions from being drawn about the specific impact of epratuzumab on lupus nephritis (Dorner et al, 2008). A phase III trial of epratuzumab in patients with moderate to severe SLE is underway.

3. Targeting B-cell survival factors

3.1 Belimumab

BLyS (B lymphocyte stimulator) also known as BAFF is a member of the TNF superfamily and plays an essential role in B-cell survival and development (Stohl et al, 2003). It binds to three different membrane receptors: BCMA (B cell maturation antigen), BAFFR (BR3) and TACI (transmembrane activator and calcium modulator and cyclophylin ligand interactor). Mice deficient in BLyS have reduced levels of mature B cells and immunoglobulins (Schiemann et al, 2001). Overexpansion of BLyS in transgenic mice leads to expansion of B-cells, hypergammaglobulaemia and autoimmune disease (Mackay et al, 1999).

Belimumab is a fully humanized monoclonal antibody against BLyS, which can cause depletion of circulating B cells however less profoundly than anti-CD20 monoclonal antibodies such as rituximab. Belimumab was approved by the FDA for treatment of SLE in March 2011, the first lupus drug to be approved since hydroxychloroquine and corticosteroids were approved in 1955. The safety and effectiveness of belimumab was demonstrated in two clinical trials (BLISS-52, and BLISS-76) that randomized a total of 1684 patients to receive either belimumab or placebo in combination with standard therapy (Wallace et al, 2009) (Jacobi et al, 2010). Treatment with belimumab plus standard therapy reduced disease activity and steroid use.

However, there are reservations regarding the effectiveness of belimumab in the more severe organ manifestations of SLE as patients with active lupus nephritis and central nervous system (CNS) disease were not studied. Study participants of African American descent did not significantly respond well to belimumab, which is also of concern.

Additional studies need to be conducted to definitively determine the safety and efficacy of belimumab in the more severe complications of SLE particularly lupus nephritis.

3.2 Atacicept

An alternative therapeutic approach targeting B cell survival is atacicept, a recombinant fusion protein containing the ligand-binding domain of the transmembrane activator and calcium modulator and cyclophilin-ligand interactor receptor (TACI) and the Fc portion of human immunoglobulin (IgG1). Atacicept inhibits B-cell stimulation by binding to both

BLys and a profileration-inducing ligand (APRIL). Atacicept is believed to selectively impair mature B cells and plasma cells with less impact on progenitor and memory B cells (Nestorov et al, 2008). A phase I study has demonstrated the safety and tolerability of atacicept in patients with mild to moderate SLE (Pena-Rossi et al, 2009). A phase II/III study of atacicept in LN is ongoing and due to be completed in 2012. The study was temporarily discontinued due to decreased immunoglobulin levels in study participants and now has been resumed. Of note, a phase II trial of atacicept in multiple sclerosis was discontinued due to increased disease relapse and new lesions on MRI brain imaging in the study subjects.

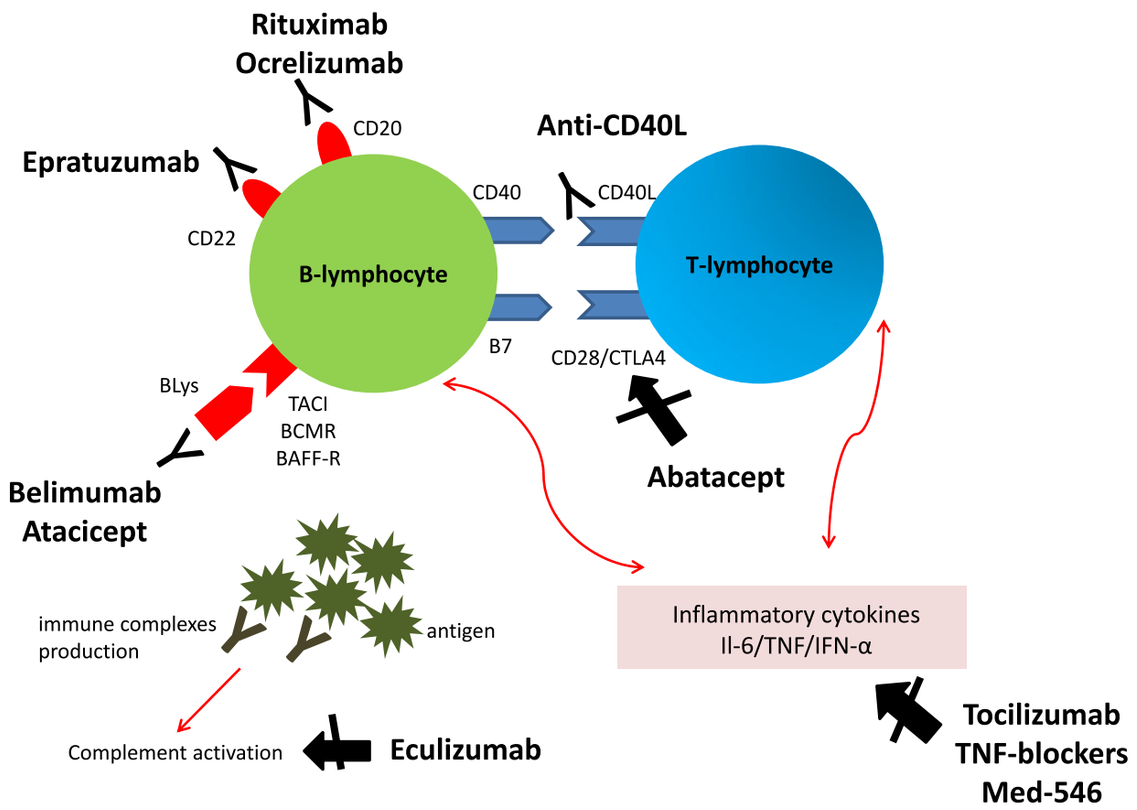


Fig. 3. Mechanisms of action of novel agents

4. Blockade of T-cell co-stimulation

4.1 Abatacept

Immunological tolerance can be induced by blockade of co-stimulatory interactions between T and B lymphocytes. The most well characterized T lymphocyte co-stimulatory ligand is CD28, a glycoprotein which interacts with the co-stimulatory receptors B7-1 (CD80) and B7-2 (CD86). Stimulation of this pathway occurs when naive T cells encounter an antigen presenting cell with the appropriate major histocompatibility complex class II bound antigen, resulting in T lymphocyte proliferation and differentiation (Ledbetter et al, 1990). CTLA4 (cytotoxic T-lymphocyte antigen) is expressed on activated T cells and interacts with B7 with higher affinity than CD28 resulting in a negative feedback mechanism that inhibits T cell activation (Scheipers et al, 1998) (Reiser et al, 1996) (Brunet et al, 1987).

Abatacept is a fusion protein consisting of CTLA-4 combined with the Fc portion of human IgG1 (CTLA-4-Ig). Combination therapy of CTLA-4-Ig and cyclophosphamide has been demonstrated to significantly reduce proteinuria, autoantibody titres and mortality in murine models of lupus nephritis (Daihk et al, 2001), (Finck et al, 1994).
Abatacept has been used successfully in the clinical management of RA and psoriasis (Genovese et al, 2008) (Mease et al, 2011). A randomised double blind placebo controlled trial has evaluated the clinical efficacy and safety of abatacept in 175 lupus patients. These patients had primarily serositis, musculoskeletal and dermatologic features and the trial was not specifically designed to examine the role of CTLA-4-Ig in lupus nephritis. The primary end-point of the study was the proportion of patients with a new flare of SLE (defined as BILAG score of A or B adjudicated as a flare in any organ system). The primary end point was not met. However when reassessed considering only BILAG A flares, 40.7% of patients in the abatacept group experienced a flare after initiation of steroid taper as compared to 54.5% in the placebo group. (Merrill et al, 2010). A clinical trial of abatacept in combination with cyclophosphamide in lupus nephritis is ongoing.

4.2 Anti-CD40 ligand

CD40 ligand (CD40L, CD154) is a transmembrane glycoprotein belonging to the TNF superfamily and is expressed on CD4 T-cells and activated platelets. It binds with CD40 on the surface of B-cells, macrophages and dendritic cells and this interaction between CD40/CD40L plays a pivotal role in B-cell class switching (Davidson et al, 2003). CD40L is overexpressed in murine lupus and monoclonal antibodies against CD40L have successfully treated murine lupus nephritis (Early et al, 1996).
Two humanised anti-CD40L monoclonal antibodies (IDEC-131 and BG9588) have entered clinical trials in SLE patients. Treatment of 85 SLE patients with IDEC-131 failed to demonstrate clinical efficacy over placebo at 20 weeks (Kalunian et al, 2002). An open-label study of 28 patients with proliferative lupus nephritis treated with BG9588 showed reduced anti-dsDNA titres and increased complement levels but was discontinued prematurely due to thromboembolic events (Boumpas et al, 2003). Given the unexpected side effects and lack of efficacy demonstrated in these studies, it is unlikely that anti-CD40L will progress to larger clinical trials in lupus nephritis.

5. Cytokine therapies

5.1 Anti-interleukin-6

Multiple cytokines have been implicated in the pathogenesis of SLE; among these is interleukin-6 (Il-6), a pleiotropic cytokine with both proinflammatory and anti-inflammatory properties. Evidence from murine models of lupus supports the role of Il-6 in the pathogenesis of lupus nephritis. Exogenous IL-6 increases autoantibody production and accelerates progression of nephritis in both the NZB/NZW and BXSB lupus mouse models (Ryffel et al, 1994) (Yang et al, 1998). On the contrary, injection of lupus prone mice with an IL-6 monoclonal antibody decreases anti-dsDNA levels and proteinuria and reduces mortality (Liang et al, 2006) (Mihara et al, 1998). In SLE patients, IL-6 levels have been shown to correlate with disease activity and anti-dsDNA titres. (Chun et al, 2007) (Linker-Israeli et al, 1991). Urinary excretion of IL-6 is increased in those with proliferative forms of lupus nephritis and this excretion is reduced following cyclophosphamide therapy (Peterson et al, 1996) (Tsai et al, 2000).

Tocilizumab is a fully humanized monoclonal antibody against the α-chain of the IL-6 receptor and prevents binding of IL-6 to both membrane bound and soluble IL-6 receptor. A phase I trial over a 12 week period has demonstrated the safety and tolerability of tocilizumab in lupus patients. Five of the twelve patients recruited to this study had renal disease at baseline, all of whom had moderate levels of proteinuria which remained unchanged throughout the duration of the study. There was however a reduction in the number of patients with active urinary sediment and a decrease in anti-dsDNA antibody titres (Illei et al, 2010). The short duration of the study renders it difficult to draw any firm conclusions as to the longer term effects of tocilizumab in lupus nephritis. The principal side effect noted in the study was neutropenia, which was dose related and white cell counts normalized on discontinuation of therapy. Randomized controlled trials of tocilizumab in lupus nephritis are awaited.

5.2 Anti-TNF-α therapies

Anti-TNF therapies (infliximab, adalimumab, etanercept) have become the mainstay of therapy in RA, psoriatic arthritis and ankylosing spondylitis. However the role of anti-TNF blocking agents in the treatment of SLE remains controversial. TNF is overexpressed in the serum, kidneys and skin of SLE patients and high serum levels of TNF correlate with lupus disease activity (Herrera-Esparza et al, 1998) (Aringer et al, 2005) (Zampieri et al, 2006) (Gabay et al, 1997). Murine models provide further evidence of the role of TNF in lupus nephritis. Both MRL/lpr and NZB/NZW lupus mouse models overexpress TNF and this correlates with renal inflammation suggesting potential benefit in TNF blockade in SLE (Boswell et al, 1988) (Yokoyama et al, 1995) (Brennan et al, 1989).

However it is well established that patients treated with anti-TNF therapies develop autoantibodies similar to those seen in clinical lupus and the concern is that these agents when used in SLE patients could induce lupus flares. Anti-nuclear (ANA) antibodies develop in up to 50% of patients treated with anti-TNF agents and anti-dsDNA antibodies in 5-14% (Aringer et al, 2008) (Charles et al, 2000). It should be pointed out that these are mainly IgM antibodies. 0.5-1% develop high affinity IgG antibodies to ds DNA (Charles et al, 2000). The development of clinical lupus-like syndromes in anti-TNF treated patients is rare and in those who do develop this, manifestations are for the main part mild (De Bandt et al, 2005). The development of lupus nephritis as a complication of TNF-induced lupus has been reported but is extremely rare (Mor et al, 2005) (Stokes et al, 2005) (Neradova et al, 2009). New onset anti-phospholipid antibodies have also been noted in individuals treated with TNF blockers and associated vascular events have been documented (Aringer et al, 2008). The development of human anti-chimeric antibodies (HACAs) is also of concern in this patient population and these antibodies are more likely to develop in individuals with SLE given the autoimmune nature of the disease and potentially lead to an increased rate of infusion reactions.

Small cohorts of SLE patients treated with TNF blockers including those with lupus nephritis have been published but as of yet no controlled trials have been conducted (Aringer et al, 2004) (Aringer et al, 2009). In four out of six lupus nephritis patients treated with anti-TNF therapies in an open-labeled study there was a significant sustained reduction in proteinuria following an induction regimen of four infusions of infliximab. Repeated infusions did not confer any additional benefit for these patients (Aringer et al, 2004) (Aringer et al, 2009).

Most lupus patients in these reports were treated with the chimeric monoclonal antibody infliximab, less is known about the clinical impact of the TNF receptor fusion protein, etanercept or the fully humanized TNF monoclonal antibodies adalimumab or golimumab. Overall no firm conclusions can be drawn as regards the use of TNF blockade in lupus nephritis. There may be potential in using these agents, perhaps the fully humanized forms as an induction therapy in lupus nephritis and randomized controlled trials would be needed to clarify the role of anti-TNF therapy in the treatment of SLE.

5.3 Targeting Interferon-α

The concept of interferon-α playing a role in SLE pathogenesis has been noted in the literature since the 1970's. There is a clear association between IFN activity and elevated anti-dsDNA titres and reduction in complement levels, commonly used parameters of clinical lupus activity. Further evidence of the relationship between IFN and lupus stems from the clinical observation that patients receiving recombinant IFN-α for the treatment of hepatitis C or malignancies may develop a lupus-like syndrome and develop autoantibodies. Microarray gene expression analysis has shown wide spread activation of IFN-inducible genes in lupus patients (Baechler et al, 2003) (Crow et al, 2003). IFN pathway activation has been associated with renal disease in lupus (Kirou et al, 2005). IRF5, a lupus susceptibility single nucleotide polymorphism with the highest odds ratio after the MHC plays a pivotal role in IFN pathways and toll-like receptor signaling (Graham et al, 2006). Hence, targeting IFN pathways is a valid therapeutic strategy in lupus patients.

A number of clinical trials of monoclonal antibodies specific for various IFN-α isoforms are ongoing to establish the safety of these agents. An anti-IFN-α monoclonal antibody has been shown to inhibit the IFN signature in peripheral blood mononuclear cells and skin in lupus patients (Yao et al, 2009). This group has proposed a scoring method based on expression of type I IFN-inducible mRNAs, which may divide SLE patients into two distinct subgroups. This might enable type I interferon-inducible genes to be used as biomarkers to identify patients who might respond better to anti-type I IFN treatment (Yao et al, 2011).

Blockade of the IFN receptor is another potential therapeutic target. Given the role of IFN-α in the host defense against viral infection, close clinical monitoring is mandatory in the development of any potential agents targeting this pathway.

6. Complement therapies

6.1 Eculizumab

The importance of the complement system in the pathophysiology of SLE is clear although individual complement components play very different roles in the disease process. Early complement proteins are critical in the clearance of immune complexes and apoptotic material, and their absence predisposes individuals to SLE. Activation of terminal complement is associated with exacerbations of disease, particularly in lupus nephritis. Monoclonal antibodies that specifically inhibit terminal complement activation while preserving early complement function have now been developed. Murine models of lupus nephritis treated with anti-C5 have shown delayed onset proteinuria, improved renal histological findings and longer survival (Wang et al, 1996).

Eculizumab, a monoclonal antibody directed against the complement protein C5, inhibits the cleavage of C5 to C5a and C5b and thus blocks the formation of the terminal membrane

attack complex C5b-9 (Cordeiro et al, 2008). Eculizumab has been approved for use in the treatment of paroxysmal nocturnal haemoglobinuria since 2007 (Dmytrijuk et al, 2008). A phase I trial has shown that eculizumab is safe and well tolerated in SLE, but no clear clinical improvements were evident at day 28 and 56 of the study (Rother et al, 2004). To date there have been no further clinical trials to examine the potential efficacy of this therapy.

7. Conclusion

An increased understanding of the immunopathogenesis of SLE during the past decade has lead to the introduction of several new biologic agents into clinical practice. An array of promising new therapies are yet to emerge or are under development. Conventional immunosuppressive therapies have transformed survival in lupus nephritis, but their use is associated with considerable toxic effects and a substantial subset of patients remain refractory to these agents. There is a clear need for new therapeutic agents that overcome these issues, and biologic agents offer exciting opportunities.

An important consideration in the management of lupus nephritis is that patients of different ethnicities have varying clinical outcomes and response to therapy. As alluded to previously, patients of African American descent are more likely to progress to end-stage renal disease (Dooley et al, 1997). Indeed the response to biologic therapy may well vary according to ethnicity. This was well demonstrated in the ALMS study where the efficacy and safety of mycophenolate mofetil (MMF) and intravenous cyclophosphamide (IVC) as induction treatment for lupus nephritis was examined by race, ethnicity and geographical region. This study clearly showed that Black and Hispanic patients responded better to MMF than IVC (Isenberg et al, 2010). The majority of clinical studies in emerging biologic therapies have not addressed the issue of variable clinical response in different ethnic groups. Of note, belimumab was found to be less efficacious in African American patients in phase III clinical trials (Wallace et al, 2009) (Jacobi et al, 2010).

Several of the studies of emerging therapeutic strategies described in this chapter, while encouraging, have targeted SLE disease manifestations in general rather than focusing on outcomes in lupus nephritis. While many of these therapies show promise for their potential use in SLE in general, randomised controlled trials specifically examining their clinical effects in lupus nephritis are needed. In addition to this, the role of new biologic agents to date may have centred on patients who have been refractory to conventional therapies. There are few clinical trials examining their role as first line induction or maintenance therapy. One exception to this has been the successful use of rituximab as first line induction therapy followed by maintenance mycophenolate mofetil in a cohort of eighteen patients with proliferative nephritis (Pepper et al, 2009).

Although so far many biologics e.g. rituximab have been generally well tolerated, (with the exception of rare but important cases of PML), we must not be complacent regarding toxicity, as we do not yet know the long-term effects of these medications on the immune system. Other biologics have had considerable toxicity, such as anti-CD40L (B59588).

A number of key questions remain. How can these therapies be potentially combined with existing proven treatments and indeed with one another to achieve maximum clinical benefit with minimal side effects? It is unlikely that any of these emerging therapies is going to represent a magic therapeutic bullet for all lupus nephritis patients. As is clear to all physicians dealing with the clinical management of SLE this is a heterogeneous disease and

there is not one ideal regimen for all. With greater understanding of the pathophysiology of lupus particularly from the genetic perspective, the era of personalized therapy may represent perhaps the greatest advance that is yet to come in the treatment of lupus nephritis.

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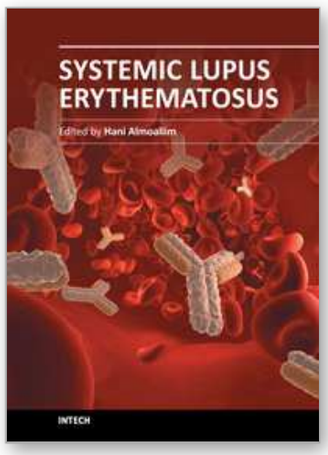

Systemic Lupus Erythematosus

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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