Lupus Nephritis: From Pathogenesis to Targets for Biologic Treatment

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Immune complex · Belimumab · Interferon · Systemic lupus erythematosus · Abatacept · Proteinuria

Abstract
Background/Aims: Lupus nephritis is an organ manifestation of systemic autoimmunity. Current treatment algorithms are still based on unselective immunosuppressive drugs. There is hope that highly selective biological drugs could be as or even more effective but less toxic. A profound understanding of the pathogenesis of lupus nephritis is necessary to identify the optimal molecular targets. Methods: PubMed and www.clinicaltrials.gov were searched using 'lupus nephritis' as the key word. Results: The pathogenesis of lupus nephritis is based (1) on the mechanisms that lead to loss of tolerance against nuclear autoantigens, i.e. systemic lupus, and then (2) on the mechanisms of immune complex-induced intrarenal inflammation. Systemic lupus develops when genetic variants allow autoimmunization against nuclear autoantigens, e.g. by impairing lymphocyte depletion via apoptosis, opsonization, and rapid phagocytic clearance. This allows endogenous nucleic acids to directly activate Toll-like receptors on dendritic cells or B cells, a process that drives IFN-α-driven immunity, antigen presentation, and the activation of autoreactive lymphocyte subsets. Activation of B cells and their maturation to plasma cells promotes autoantibody production and subsequent immune complex glomerulonephritis. Complement and numerous proinflammatory cytokines drive the inflammatory process that can cause kidney injury, scarring, and chronic kidney disease. Conclusion: Systemic lupus is more a variable syndrome than a single disorder based on heterogeneous genetic variants and complex aberrant immune alterations. This makes it less likely that a single specific biological drug will be as efficient as currently used unselective immunosuppressive drugs. Autoantibody production and intrarenal immune complex formation are the hallmark of lupus nephritis. However, kidney injury and scarring also result from local amplification of tissue inflammation. Therefore, a combination of unselective immunosuppressive and biological drugs that block immune cell recruitment or proinflammatory cytokines may be promising to improve disease outcomes in lupus nephritis.

Introduction

Biological drugs have significantly improved outcomes in many autoimmune disorders, but so far clinical trials have failed to demonstrate any significant benefit of biological drugs in lupus nephritis. This is surpris-
ing because all autoimmune disorders, including systemic lupus erythematosus (SLE), are based on anti-
gen-presenting cells that trigger the activation and pro-
liferation of autoreactive lymphocyte subsets. So what
distinguishes the pathogenesis of SLE from other auto-
immune disorders? Why do clinical trials often fail to
validate drug efficacy previously demonstrated in pre-
clinical experiments or uncontrolled cohort studies?
Disease heterogeneity is an important factor that distin-
guishes SLE from other autoimmune disorders and
which remains a challenge for clinical trial design. Ge-
nome-wide association studies have documented that
numerous different genetic alterations, each of them
conferring only a minor risk contribution, are present in
SLE patients. This implies that SLE is rather a clinical
syndrome that develops from different combinations of
genetic alterations that cause systemic autoimmunity
through different avenues of immune dysregulation.
This may explain why some but not all patients benefit
from biological drugs that modulate highly selective tar-
gets. Nonetheless, to move beyond unselective immuno-
suppressiv drugs in lupus nephritis management, it is
necessary to identify common pathways in the patho-
genesis of SLE and lupus nephritis. In this review, we
briefly summarize current concepts of disease patho-
genesis in SLE and lupus nephritis and present molecu-
lar and cellular targets for biological drugs to improve
disease outcomes.

Table 1. Pathomechanisms in SLE and lupus nephritis

<table>
<thead>
<tr>
<th>Pathomechanisms of autoimmunity outside the kidney</th>
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<tbody>
<tr>
<td>Impaired silent cell death and dead cell removal</td>
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<td>Nuclear particles mimic viruses at viral recognition receptors of the innate immune system</td>
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<td>Antiviral immunity</td>
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<td>Autovaccination leading to persistent antinuclear antibody production</td>
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<td>Flares triggered by transient autoantigen loads or unspecific immune activation</td>
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<th>Pathomechanisms of lupus nephritis inside the kidney</th>
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<td>Immune complex formation and classical complement pathway activation</td>
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<td>Mesangial vs. subendothelial vs. subepithelial immune complexes</td>
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<td>Intrarenal induction of cytokines, chemokines, and adhesion molecules recruits leukocytes</td>
</tr>
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<td>Tertiary lymphoid organ formation inside the kidney, i.e. local immunoglobulin production</td>
</tr>
<tr>
<td>Insufficient regeneration and tissue scarring</td>
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</tbody>
</table>

**Pathogenesis of SLE and Lupus Nephritis**

As we have recently described the current pathogenic
concepts of SLE and lupus nephritis in detail elsewhere
[1], only a brief summary is provided here (table 1).

**Systemic Autoimmunity in SLE**

SLE develops from a loss-of-tolerance for nuclear au-
toantigens as is evident from the presence of antinuclear
antibodies. As tolerance against cell nuclei is normally as-
sured by numerous mechanisms and genes, many different
combinations of genetic and environmental factors
can break tolerance, cause antinuclear antibody positivi-
ty, and eventually trigger SLE. The major checkpoints of
immune dysregulation are described in table 1 and below.

**Impaired Silent Cell Death and Dead Cell Removal.** Ge-
netic variants that impair physiological (immunological-
ly silent) suicide of autoreactive lymphocytes during neg-
ative selection in lymphoid organs drive secondary ne-
crosis and the release of nuclear material into the
extracellular space. Similarly, this is also the case with en-
vironmentally induced tissue cell necrosis, e.g. a sunburn
or a trauma increases the amount of extracellular nuclear
material. In SLE, often genetic variants that impair the
phagocytic clearance of such extracellular nuclear parti-
cles keep nuclear particles in the extracellular space [2].
For example, insufficient phagocytic clearance of extra-
cellular neutrophil traps contributes to this phenomenon
[3].

**Nuclear Particles Trigger Antiviral Immunity via In-
nate Viral Recognition Receptors.** Extragrenular nuclear
particles share structural and molecular similarities with
viral particles and their nucleic acid components can ac-
tivate dendritic cells and B cells via Toll-like receptors 7
and 9 [4]. This specifically triggers the induction of interferon-α and subsequently a ‘pseudo’ antiviral im-
mune response, which accounts for unspecific symptoms of SLE including fatigue, fever, myalgia, and arthralgia
[5].

**Autovaccination Leads to Persistent Antinuclear Anti-
body Production.** Because nuclear autoantigens are pre-
sented in the context of innate immune activation, induced costimulation promotes the activation of T and B cell subsets with specificities for nuclear autoantigens. This process involves B cell maturation and differentiation into plasma cells that produce antinuclear antibodies. Memory T cells and bone marrow long-lived plasma cells assure lifelong immune memory, which cannot be eradicated by standard therapies conceptually like immune memory obtained by previous vaccinations [6]. Unspecific lymphoproliferation drives lymphadenopathy as a manifestation of SLE.

Incident Cell Necrosis or Unspecific Immune Activation Trigger SLE Flares. Sudden massive cell death (sunburn or trauma) or exposure to immunostimulatory agents (e.g. during infections) mimic antigen re-exposure or provide unspecific stimuli of innate and adaptive immunity that may expand autoreactive lymphocyte clones and cause a SLE flare [7].

Intrarenal Pathomechanisms of SLE-Related Nephritis Immune Complex Formation and Classical Complement Pathway Activation. Lupus nephritis does not develop in the absence of antinuclear antibodies [8]. Circulating polyclonal autoantibodies bind to intrarenal nucleosomes and other autoantigens, which leads to local complement activation, cell injury, and subsequent cytokine and chemokine secretion.

The Immune Complex Formation Site Determines Lupus Nephritis Outcomes. The polyclonal lupus autoantibody isotypes can localize to different compartments within the glomerulus, which affects the type of histopathological lesion as well as the alterations of glomerular function [9]. Immune complex formation in the mesangium induces mesangio proliferative glomerulonephritis (lupus nephritis classes I and II), which is often mild and rarely progresses to end-stage kidney disease. Subendothelial immune complex formation (lupus nephritis classes III and IV) causes vascular obstruction by endothelial cells (endocapillary lupus nephritis), and pa rietal epithelial cells (crenstic lupus nephritis). Lesions of insufficient repair include podocyte loss-related scarring (FSGS and glomerulosclerosis).

Therapeutic Targets for (Biological) Drugs

The current management of lupus nephritis remains based on steroids, cyclophosphamide, azathioprine, and mycophenolate mofetil, which are all unsel ective immunosuppressive drugs that suppress multiple components of adaptive immunity [10]. These drugs have proven to be efficient in reducing lupus nephritis disease activity, but the long-term outcomes of lupus nephritis have not further improved during the last 30 years. Unselective immunosuppressive drugs are associated with potentially life-threatening infectious complications. Therefore, it remains an unmet medical need to develop new drugs that more specifically interfere with the pathomechanisms of SLE and cause less side effects [11]. In the following we discuss several targets of interest and provide the rationale to explore them for the treatment of lupus nephritis (fig. 1). Past or ongoing clinical trials with target-related drugs are listed in table 2.

Aberrant Cell Death and Insufficient Clearance of Dead Cells
Currently no biological drugs are available that specifically control this aspect of lupus pathogenesis. The prevention of sunburns by avoiding UV light exposure and using sunscreen remains important.

Immunostimulatory Effects of Endogenous Nucleic Acids and IFN-α-Mediated Immunity
Toll-like receptor 7/9 blockade can suppress nucleic acid autoadjuvant-driven disease activity of lupus nephri-
Table 2. Biological drugs for lupus nephritis listed in www.clinicaltrials.gov

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug name</th>
<th>Trial phase</th>
<th>Trial status</th>
<th>Duration, months</th>
<th>Nephritis class</th>
<th>NCT number</th>
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<td>rituximab</td>
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<td>BLYS/BAFF</td>
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<tr>
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<tr>
<td>IFN-γ</td>
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<td>6</td>
<td>III, IV</td>
<td>NCT00818948</td>
</tr>
</tbody>
</table>

Fig. 1. Pathomechanisms and treatment targets in lupus nephritis. 

a Genetic variants of homeostatic lymphocyte death and of the rapid clearance of dead cells predispose to necrotic cell death and a persistence of nuclear particles in the extracellular space. No specific treatments are available at present for this aspect of lupus pathogenesis. The avoidance of sun burns and toxin exposure can help to prevent disease flares triggered by incident episodes of massive cell death. 
b Extracellular nuclear particles containing autoadjuvants like CpG-DNA or immunostimulatory RNA together with other Toll-like receptor ligands released by dead cells activate antigen-presenting cells (dendritic cells and B cells) to present autoantigens together with costimulatory molecules. This process leads to an immune interpretation of the autoantigen as ‘foreign’ and triggers an adaptive immune response, e.g. autoantigen-specific T and B cells. Several biological drugs intend to interfere with this pathomechanism. 
c Circulating autoantibodies bind to their respective autoantigens within the kidney, a process referred to as in situ immune complex formation. This activates complement and other inflammatory mediators that can be targeted with biological drugs to control renal inflammation. IFN-γ, MHC-I, MHC-II (major histocompatibility complex), TNF, and BAF/BLYS.

(For figure see next page.)
Autoantigen Presentation and T Cell Activation

The processing and presentation of autoantigens in the context of costimulation is at the center of every autoimmune disease pathogenesis. Using CTLA-4-Ig to block the interaction between CD80 and CD86 on antigen-presenting cells and CD28 on T cells efficiently suppresses alloimmune T cell activation after kidney transplantation. However, abatacept failed to succeed to reach the primary endpoint in a randomized trial on the induction phase of lupus nephritis classes III and IV, although abatacept therapy had some effects on plasma levels of dsDNA autoantibodies and complement recovery [14]. CD40 and CD40L also promote costimulation, but three trials with anti-CD40L failed to demonstrate efficacy. Abetimus is a drug that modulates autoimmunity via antigen recognition by T cells. Abetimus is composed of a series of linked oligonucleotides, which block the binding of anti-dsDNA antibodies to their autoimmune targets and tolerize B cells with antigen-specificity for DNA. Unfortunately, the results in clinical trials have been very modest. The concept of anti-dsDNA-specific therapeutic interventions does not seem very promising as they target only a very small subset of autoreactive B cells in SLE. Antigen presentation requires peptide processing and loading into HLA molecules, a process that involves a nonredundant role for cathepsin S, the inhibition of which suppresses IgG autoantibody production and prevents lupus nephritis in animal models [15].

B Cells and Short-Lived Plasma Cells

B cells clearly contribute to SLE and lupus nephritis, which provides a rationale for the use of drugs that deplete CD20+ B cells and short-lived plasma cells such as rituximab, ocrelizumab, or ofatumumab. Uncontrolled studies on refractory lupus nephritis documented response rates of 75% [16], but the randomized placebo-controlled LUNAR trial could not demonstrate any benefit of add-on rituximab on top of a profound immunosuppressive regimen for the induction therapy of incident lupus nephritis classes III–V [17]. However, the clinical efficacy of off-label rituximab use by many centers has maintained the interest in B cell ablation in lupus nephritis [12, 13], but the respective antagonists that are to be tested in clinical trials are more based on nucleic acid formats than biological drugs. In contrast, the anti-IFN-α antibody sifalimumab was reported to meet the primary composite endpoint in a phase 2b trial of nonrenal lupus patients. Data on its efficacy on lupus nephritis are not yet available.

Long-Lived Plasma Cells

Targeting long-lived plasma cells offers the potential of directly modulating antibody-producing cells that maintain humoral immune memory [6]. These cells reside in survival niches in the bone marrow and in tertiary lymphoid organs within the inflamed tissue. They can be targeted by antithymocyte globulin, small molecule proteasome inhibitors, anti-CD138/CD38 antibodies, or by targeting BLyS (B lymphocyte stimulator) or a BAFF-receptor antibody [22].

Mediators of Tissue Inflammation

Tissue inflammation involves numerous proinflammatory cytokines, some of which can now be targeted with biological drugs: TNF-α (infliximab), IL-6 (tocilizumab), IL-12 (ustekinumab), IL-17 (ixekizumab and secukinumab), and TWEAK (BIIB023). TNF blockade with infliximab is able to improve severe lupus nephritis, but holds the risk of enhancing autoimmunity and promoting severe infectious complications [23]. The trans-
continental ATLAS trial that tests TWEAK blockade in the remission phase of lupus nephritis is still ongoing. Macrophage-dependent inflammation is targeted by antimalphage inhibitory factor IgG, for which a safety study in lupus nephritis patients has been completed. Also the CCL2-CCR2 axis is a promising target to limit macrophage-dependent inflammation. Preclinical experiments suggest that adding a CCL2 inhibitor to a low dose of cyclophosphamide is as efficient as high-dose cyclophosphamide, but avoids myelosuppression and lymphocyte ablation [24]. A first trial documented a positive effect on proteinuria using bindarit as a blocker of this pathway [25].

**Summary**

Lupus nephritis develops from extrarenal and intrarenal pathomechanisms. The extrarenal factors include complex combinations of genetic variants in numerous immune pathways that are different in each patient, which may affect success rates of very selective biological drugs in clinical trials. Therefore, treating lupus nephritis with a monotherapy of a selective biological drug should be challenging. Unselective immunosuppressive drugs may remain necessary to suppress the complex interplay of the numerous immune cell subsets that contribute to humoral and cellular autoimmunity in SLE. Lupus nephritis, however, is a classic immune complex glomerulonephritis involving complement-mediated renal inflammation, amplified by infiltrating leukocytes and driven by numerous proinflammatory cytokines. Inflammation-related kidney injury and tissue remodeling cause renal dysfunction and chronic kidney disease in lupus. Therefore, anti-inflammatory biological drugs that limit tissue injury should be attractive combination partners for unselective immunosuppressive drugs that control systemic autoimmunity.

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**References**


