Clinical Immunology 206 (2019) 42–52

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Cytokine targets in lupus nephritis: Current and future prospects

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ARTICLE INFO

Keywords:
Autoimmune diseases
Kidney
Lymphocytes
Autoantibodies
Biologics
Personalized medicine

ABSTRACT

Despite advancements in the care of lupus nephritis, a considerable proportion of patients may respond poorly or flare while on conventional immunosuppressive agents. Studies in murine and human lupus have illustrated a pathogenic role for several cytokines by enhancing T- and B-cell activation, autoantibodies production and affecting the function of kidney resident cells, therefore supporting their potential therapeutic targeting. To this end, there is limited post-hoc randomized evidence to suggest beneficial effect of belimumab, administered on top of standard-of-care, during maintenance therapy in lupus nephritis. Type I interferon receptor blockade has yielded promising results in preliminary SLE trials yet data on renal activity are unavailable. Conversely, targeting interleukin-6 and interferon-γ both failed to demonstrate a significant renal effect. For several other targets, preclinical data are encouraging but will require confirmation. We envision that high-throughput technologies will enable accurate patient stratification, thus offering the opportunity for personalized implementation of cytokine-targeting therapies.

1. The burden of lupus nephritis and unmet needs

Kidney disease develops in approximately 20–40% of patients with systemic lupus erythematosus (SLE) and represents one of the most severe disease complications. Currently, both the ACR [1] and the EULAR/ERA-EDTA [2] recommend a diagnostic kidney biopsy in SLE patients who manifest persistent proteinuria above 0.5 g/day, especially when glomerular hematuria or urine casts are coexistent. During the past decades, there has been notable progress in the understanding and management of LN (reviewed in [3,4]). A number of new immunosuppressive and biologic agents have been added in the therapeutic armamentarium and specific treatment goals have also been introduced aiming to improve long-term renal and patient outcomes [5,6].

Notwithstanding, several unmet needs still exist such as the fact that the selection of first-line immunosuppressive agent (usually, mycophenolate or cyclophosphamide) is largely empirical and not based on the underlying pathophysiology of kidney disease. Next, only half of patients with active LN will demonstrate complete renal response (usually defined as reduction of baseline proteinuria to < 0.5 g/day) after 6 months of immunosuppressive treatment [7]. Moreover, a sizeable number of patients may not respond to one or more agents or may experience relapse of LN after initial response [8], which necessitate repeated courses and/or switching treatment. Importantly, unabated kidney inflammation results in tissue scarring and organ dysfunction. In this regard, a recent systematic review has indicated stable or even worsening worldwide trends of end-stage renal disease (ESRD) in patients with LN with most recent 10-year ESRD rates estimated to range 15–20% [9]. Finally, and despite efforts to introduce 'steroid-free' protocols, [10] glucocorticoids are still considered an

Abbreviations: ACR, American College of Rheumatology; APRIL, A PRoliferation-Inducing Ligand; ARHP, Association of Rheumatology Health Professionals; BAFF, B cell activating factor; BILAG, British Isles Lupus Assessment Group; BLyS, B Lymphocyte Stimulator; CCL, C-C Motif Chemokine Ligand; CsA, Cyclosporin A; CyC, cyclophosphamide; CXCL, chemokine [C-X-C motif] ligand; eGFR, Estimated Glomerular Filtration Rate; ERA-EDTA, European Renal Association- European Dialysis and Transplant Association; EULAR, European League Against Rheumatism; Fn14, fibroblast growth factor-inducible-14; IL, Interleukin; IL18bp, IL-18 binding protein; IgG, Immunoglobulin G; IFN, Interferon; IFN-α, Interferon alpha; IFNAR, I IFN-α receptors; IV, intravenous; JAKs, JAnus Kinases; LN, Lupus nephritis; MCP-1, monocyte chemoattractant protein 1; MMF, mycophenolate mofetil; NIH, National Institutes of Health; RCT, randomized controlled trial; SIGIRR, Single Ig IL-1-related receptor; SLE, Systemic Lupus Erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SoC, Standard of Care; SOCS3, suppressor of cytokine signaling 3; SRI, Systemic Lupus Erythematosus Responder Index; STAT, signal transducers and activators of transcription; Tfh, follicular T-helper cell; Th-17, T helper 17 cell; TACI, transmembrane activator and CAML interactor; TWEAK, Tumor necrosis factor-like weak inducer of apoptosis; Treg, regulatory T cell; UPCR, Urine Protein to Creatinine Ratio

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https://doi.org/10.1016/j.clim.2018.08.013
Received 19 April 2018; Received in revised form 21 July 2018; Accepted 31 August 2018
Available online 02 September 2018
1521-6616/

essential component of existing therapeutic regimens due to their fast onset of action. Consequently, patients with LN are at increased risk for steroid-related comorbidities and/or organ damage. The above-mentioned issues have stimulated vigorous efforts for the identification of novel therapeutic targets that are pertinent to immunopathogenesis of LN.

In this review, we provide a brief overview of the current treatment options in LN including recent studies on the use of multi-target protocols. We then focus on cytokines that are implicated in LN and have been targeted in preclinical or clinical studies, and we summarize the existing evidence for their efficacy. We conclude with our perspective on how technological advances and high-throughput approaches might facilitate the identification and/or prioritization of cytokines to be targeted in patients with LN.

2. Current standard of care in lupus nephritis

2.1. Induction therapy

Current standard treatment in patients with proliferative forms of LN (class III and IV) includes a combination of glucocorticoids with immunosuppressive agents. Typically, treatment regimens are combined initially with three consecutive pulses of intravenous methylprednisolone in order to promptly control kidney inflammation and reduce cumulative glucocorticoid exposure. This is followed by oral prednisone (or equivalent) starting at 0.5–1 mg/kg/day for 4 weeks, gradually tapered to a dose of ≤10 mg/day by 4–6 months [2].

Immunosuppression with either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) is generally commenced in addition to corticosteroids. Three different regimens of CyC have been used [1,2]: 1) the high-dose regimen, consisting of monthly intravenous pulses of CyC dosed at 0.5–1 g/m^2 for 6 months, 2) the low-dose intravenous regimen, dosed at 500 mg every 2 weeks for a total of six doses and, 3) oral CyC at 1–1.5 mg/kg per day for 2–4 months. The two intravenous dosing regimens have shown to be equally effective for both short-term remission induction and long-term kidney-function preservation, with better efficacy/toxicity ratio for the low-dose one [11]. MMF with a target dose of 2–3 grams per day orally (or equivalent dose of enteric-coated mycophenolic acid) for 6 months, is considered to be non-inferior to intravenous CyC for induction therapy in proliferative (class III or IV) forms of LN, based on several randomized controlled trials and their meta-analysis [7,12–14].

Patients with pure class V nephritis and nephrotic-range proteinuria are generally treated with prednisone (0.5 mg/kg/day) plus MMF for 6 months [1,2,15]. In a pooled analysis of two randomized controlled trials (RCTs), patients with pure membranous lupus nephritis showed similar results with MMF plus daily prednisone as with high-dose intravenous CyC plus prednisone [16]. Thus, MMF may be preferred over CyC in most cases to avoid gonadal toxicity. Alternatively, calcineurin inhibitors (ciclosporin, tacrolimus) may be used [2], whereas there is little evidence regarding the effectiveness of the low-dose CyC regimen [17].

2.2. Maintenance therapy

For patients who respond after induction treatment, maintenance immunosuppressive therapy should follow to consolidate the renal response and prevent flares, using either azathioprine (2 mg/kg/day) or MMF at a lower dose (2 grams daily). In European patients who received induction therapy with low-dose CyC, the MAINTAIN trial showed comparable long-term efficacy of MMF versus azathioprine [18,19]. Conversely, the multiracial ALMS study found that MMF was superior to azathioprine in renal survival and preventing renal flares [20]. Treatment should be continued for at least three years, as early discontinuation is linked to increased risk of renal flares [21,22].

2.3. Adjunct therapy

The concomitant use of antimalarials such as hydroxychloroquine by LN patients is recommended to reduce the occurrence of renal flares and organ damage including cardiovascular damage [23,24]. Additional agents include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers in patients with residual proteinuria > 50 mg/mmol or hypertension, statins, vitamin D, calcium supplements and anti-bone resorptive agents for osteoporosis prevention [1,2].

3. Cytokine targeting strategies in lupus nephritis

The pathogenesis of LN is complex and is generally thought to begin by the glomerular deposition of immunocomplexes that are formed by autoantibodies directed against DNA and glomerular antigens (reviewed in [4,25,26]). These immunocomplexes may activate the complement cascade, Fc-receptor-bearing innate immune cells and kidney parenchymal cells, thus inducing the local production of cytokines, chemokines and subsequent recruitment of inflammatory cells. In particular, a number of cytokines have been implicated in LN due to their distinct effects on infiltrating immune cells, activation and differentiation of immune cells [27] and interference with kidney endothelial and parenchymal cells (detailed below). Their involvement is further supported by genetic studies showing that cytokine gene variants (e.g. B-cell activating factor [BAFF] [28]) or their upstream/downstream regulators (e.g. interferon regulatory factor [IRF]-5) contribute to increased risk for LN [29,30]. The aforementioned evidence provides rationale for developing and testing cytokine-targets strategies in patients with LN.

3.1. Multitarget combination therapy

Calcineurin inhibitors (CNIs) include cyclosporine A, tacrolimus (FK506) and more recently, voclosporin. Although CNIs do not directly target any cytokine molecules, nevertheless, they block T-cell activation and reduce Th1 and Th2 inflammatory cytokines, particularly IL-2, TNF, IL-1β, IFN-γ, IL-6 and IL-10 [31,32]. Their clinical use has been restricted by the relatively high frequency of adverse effects. Nonetheless, recent evidence has revamped interest on this class of drugs pertaining to their possible inclusion – as part of multi-drug regimens – in the therapeutic armamentarium of active LN. Bao et al. [33] (Table 1) first compared CyC against a regimen consisting of MMF and tacrolimus – both regimens combined with glucocorticoids – in refractory mixed class V + IV LN. The MMF/tacrolimus combination was superior in inducing complete remission at 6 and 12 months. Cortés-Hernández et al. [34] added tacrolimus to background MMF therapy in 17 LN patients who were refractory to induction therapy, with 12 of them achieving clinical response after 24 months.

Driven by these results, Liu et al. [35] performed a randomized, open-label, multicenter study to compare the combination of tacrolimus (4 mg/day) and MMF (1 g/day) against intravenous monthly pulses of CyC (0.75 g/m^2) in Chinese patients with new-onset class III to V LN. Patients who received multitarget therapy had significantly higher complete remission rates after 6 months of therapy as compared to those on CyC (45.9% versus 25.6%). In patients who achieved at least partial response, the multitarget regimen was continued as maintenance therapy, whereas CyC-treated patients continued with azathioprine [36]. During the 18 months period, the two groups had similar rates of relapses and renal function [36].

More recently, the results of the placebo-controlled AURA-LV (Aurinia Urinary Protein Reduction Active – Lupus with Voclosporin) phase IIb study were announced [37]. In this trial, voclosporin – a novel oral CNI with more predictable pharmacokinetics and potentially less metabolic adverse effects [38] – was used at two different doses (23.7 mg or 39.5 mg, twice a day) together with MMF (2 g/day) and

Table 1
Recent studies on multitarget therapy (combination of mycophenolate with calcineurin inhibitor) in patients with lupus nephritis.

Author (Year)	Study type	Multitarget regimen	Study population	Primary endpoint	Results	SAE
Bao et al. (2008)	RCT	MMF (0.91 g/d) plus tacrolimus (3.65 mg/d)	40 patients with class V + IV LN, randomized 1:1 to induction therapy with multitarget therapy or IV CyC	CR	Higher rate of CR with multitarget therapy than IV CyC at 6 months (50% vs. 5%) and 9 months (65% vs. 15%)	Most adverse events were less frequent in the multitarget therapy group. No deaths.
Lanata et al. (2010)	Case series	MMF (2.8 g/day) plus tacrolimus (3.4 mg/day)	7 patients (3 class III + V, 2 class IV, 1 class II + V, 1 class IV + V), refractory to MMF	CR (± 10% of normal values of proteinuria	CR (n = 1), PR (n = 3)	Diabetic ketoacidosis (n = 1), pneumonia (n = 2), muscle pain (n = 2)
Cortés-Hernández et al. (2010)	Observational study	MMF (2-3 g/d). Tacrolimus (0.075 mg/kg/d) was added if intolerance or lack of efficacy after ≥3 months of MMF	70 patients (class III, IV, V)	CR at 6, 12 and 24 months and at the end of the follow-up period	Tacrolimus was added to 17 (24%) patients., CR: 35%, PR: 35%	Pulmonary tuberculosis (n = 1)
Liu et al. (2015)	Randomized, open-label, multicenter study	MMF (1 g/d) plus tacrolimus (4 mg/d)	368 patients (class III, IV, V, III + V, and IV + V) randomized 1:1 to induction therapy with multitarget or IV CyC	CR (24 weeks)	Higher CR rates with multi-target (45.9% vs. 25.6% with IV CyC)	Similar incidence of SAE in the two arms
Choi et al. (2018)	Retrospective study	MMF plus tacrolimus	29 patients (class III, IV, V) who failed to standard induction therapy or flared after intitial response	CR, PR at 6 and 12 months	CR: 15.4% at 6 months, 25.9% at 12 months; PR: 38.5% at 6 months, 29.6% at 12 months	Hair loss (10.3%), headache (10.3%), leukopenia (6.9%) and herpes zoster infection (6.9%)
Jesus et al. (2018)	Case series	MMF (2.25 g/d) plus cyclosporin (2.9 mg/kg/d)	6 patients, resistant to induction therapy with IV CyC or MMF	CR, PR at 6 months	CR (n = 4), PR (n = 1)	No SAE
AURA-LV study (2017)	RCT (placebo-controlled)	MMF (2 g/d) plus voclosporin (low dose: 23.7 mg BID, high dose 39.5 mg BID)	265 patients (class III, IV, V)	CR (6 months)	CR rate was significantly higher in the low dose voclosporin versus the control group (32.6% vs. 19.3%)	SAEs were numerically higher in the voclosporin groups
Sakai et al. (2017)	Prospective, single-arm, open label pilot study	Tacrolimus (3 mg/d) plus low dose IV CyC	15 patients (class III, IV, III/IV + V)	CR (6 months)	CR: 80%	Increase in serum creatinine (n = 3); premature ovarian failure (n = 1)

glucocorticoids as induction therapy for active LN. At 48 weeks, 23.9% of patients on the control arm achieved complete renal response as comparted to 49.4% of the low-dose and 39.8% of the high-dose voclosporin groups. Renal function was stable in all groups of patients [37]. A phase III trial (NCT03021499) for voclosporin in LN is currently underway.

3.2. Existing anti-cytokine biological agents

3.2.1. The role of B-cells and BLyS/BAFF blockade

B-cell hyperactivity and production of autoantibodies are considered hallmarks in SLE pathogenesis. Accordingly, targeting B-cells and B-cell function has long been considered a rationale therapeutic approach. In the context of MRL-Fas*lpr* lupus-prone mice, B-cells were found to be indispensable for kidney inflammation; notably, transgenic mice which do not secrete immunoglobulin still exhibited significant interstitial nephritis and vasculitis, although to less extent as compared to wild-type MRL-Fas*lpr* strains, underscoring an important role for B-cell functions other than autoantibody production [39]. By inactivating the adaptor protein MyD88 (that mediates toll-like receptor[TLR-]7/9 signaling) specifically in B-cells, Teichmann et al. [40] showed that MRL-Fas*lpr* mice had diminished nephritis and reduced antibody-independent interstitial T-cell infiltrates, suggesting that autoreactive B-cells can directly activate nephrotoxic T-cells. More recent evidence implicates B-cell–intrinsic factors such as T-bet, STAT1 and IL-6 in local activation of follicular helper T-cells (T_{FH}) and germinal center formation [41,42]. In line with this, intra-renal B-cell infiltrates resembling secondary lymphoid tissue have been characterized in patients with LN, with the majority of B-cells showing a mature non-antibody producing phenotype with antigen presenting ability [43].

Critical to the enhanced B-cell activation and differentiation in SLE is BAFF (B-cell activating factor), also known as BLyS (B-lymphocyte stimulator), a cytokine/growth factor that belongs to the TNF superfamily. Together with another family member named APRIL (a proliferation-inducing ligand), BAFF promotes B-cell survival by upregulating anti-apoptotic proteins, drives immunoglobulin (Ig) class switching and plasma cell differentiation [44]. Serum BAFF concentrations correlate positively with disease activity in SLE patients [45]. Moreover, an immunohistochemistry study in kidney biopsies from patients with active proliferative LN demonstrated increased levels of APRIL, BLyS, and BAFF-receptor (BAFF-R) in the interstitial compartment, whereas APRIL was also expressed in mesangial cells [46]. Likewise, diseased kidneys from NZB/NZW F1 lupus mice display significantly increased BAFF expression which is predominantly produced by infiltrating activated dendritic cells and macrophages [47].

Besides augmenting systemic autoimmunity, the mechanism by which enhanced BAFF contributes to kidney inflammation in SLE remains elusive (Fig. 1). It is presumed that BAFF may sustain the intrarenal survival of long-lived plasma cells and autoantibodies production

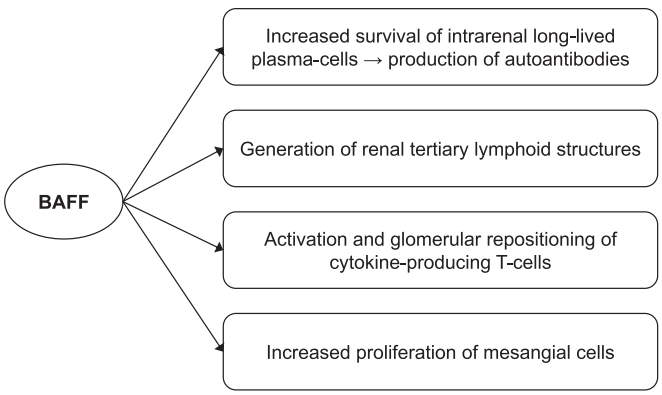

Fig. 1. Outline of the kidney-specific pathogenic effects of BAFF in SLE.

Table 2
Cytokine-targeting treatments in lupus nephritis.

Currently available or being tested in patients
- BAFF blockade (belimumab, blisibimod, ataticept)
- Type I IFN
- IL-6 (sirukumab, PF-04236921)
- IL-23/17 (ustekinumab)
- IFN-γ blockade (AMG 811)
- JAK inhibitors (bariticinib, tofacitinib)
- Exogenous IL-2 (aldesleukin)

Possible future treatments
- IL-21 blockade
- IL-1 family blockade
- TWEAK/Fn14 blockade

[48]. However, introduction of the BAFF transgene into autoimmune-prone B6.*Sle1* and B6.*Nba2* mice resulted in severe glomerular pathology by 3 months of age that was not fully explained by circulating levels of IgG anti-chromatin and/or anti-double-stranded DNA antibodies or renal deposits of these autoantibodies [49]. Other studies have suggested an important role for BAFF in inducing renal tertiary lymphoid structures and regulating the position of T cells within the glomeruli [50]. B-cell–independent effects of BAFF have also been suggested [51] such as the induction of inflammatory, cytokine-producing T cells [50] and BAFF-R–mediated proliferation of mesangial cells [52].

3.2.1.1. Belimumab (anti-BAFF mAb). The first drug that was used to inhibit the BAFF/APRIL pathway was belimumab, a human monoclonal antibody specific for soluble BAFF (Table 2). The BLISS-52 [53] and BLISS-76 [54] studies demonstrated superiority of belimumab versus placebo – both administered on top of conventional therapy – in inducing clinical response and preventing flares in patients with moderately active SLE. Notably, none of these trials was designed to specifically assess the efficacy of belimumab in renal disease. Nonetheless, more than 20% of included patients had baseline proteinuria > 0.5 g/24h and more than 16% had renal involvement according to the SELENA-SLEDAI index [55]. Post-hoc analysis indicated that belimumab treatment reversed renal activity parameters in a greater number of patients as compared to placebo. Specifically, at 52 weeks, proteinuria levels were reduced by an average 28% in placebo versus 48% and 39% in the 1 mg/kg and 10 mg/kg belimumab arms [55]. Also, renal flares occurred in a smaller number of belimumab- than placebo-treated patients. The abovementioned differences were more prominent in the subset of patients who were on background treatment with MMF, with renal SLEDAI improvement rates 28% in placebo versus 63% in belimumab 10 mg/kg group [55].

More recently, a systematic review identified 11 studies, both randomized and non-randomized, which included 234 SLE patients with renal involvement who received belimumab [56]. Notwithstanding the heterogeneity across studies regarding the therapeutic protocols and renal assessment methods, 55% of patients showed evidence of response. However, it is hard to draw robust conclusions due to critical methodological issues, unavailable kidney biopsy data, and possible reporting bias [57]. Nonetheless, belimumab might be considered in some patients who are receiving chronic maintenance immunosuppressive therapy for LN and manifest residual proteinuria (> 0.7–1 g/24h) or are unable to reduce the dose of glucocorticoids to less than 7.5 mg/day. To this end, the efficacy and safety of belimumab in active LN is currently assessed in a phase III randomized placebo-controlled trial, the BLISS-LN trial (NCT01639339).

3.2.1.2. Other inhibitors of the BAFF/APRIL axis. Tabalumab is another anti-BAFF antibody that neutralizes both membrane and soluble forms BAFF. Two large phase III studies [58] [59] evaluated the efficacy and safety of subcutaneous tabalumab in moderate-to-severe SLE. In spite of

favorable effects on B-cell–related immunological parameters, a clear superiority of active drug versus placebo was not demonstrated. Neither of the two trials included patients with severe renal involvement and analysis of renal parameters showed no significant effect of tabalumab on renal flares, proteinuria and eGFR [60].

The “peptibody” blisibimod is also a BAFF antagonist that selectively binds to both soluble and membrane-bound BAFF and inhibits the interaction of BAFF with all three receptors, namely BAFF-receptor, B cell maturation antigen (BCMA), and transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) [61]. A large phase III RCT was performed to assess the efficacy of subcutaneous blisibimod versus placebo in SLE patients with SELENA-SLEDAI ≥10 on standard-of-care therapy [62]. Although the trial did not meet its primary endpoint, in patients with baseline proteinuria ≥0.5g/24h, a significantly higher percentage of blisibimod-treated subjects achieved > 50% reduction in proteinuria and/or reduction of proteinuria to < 0.5g/24hr, and/or proteinuria levels ≤3 times the upper limit of normal [62].

Finally, atacicept (TACI.Ig) is a soluble recombinant fusion protein that blocks both APRIL and BAFF. The APRIL-LN study was a phase II/III randomized, placebo-controlled trial that evaluated atacicept in combination with high-dose glucocorticoids and MMF in active LN [63]. Unfortunately, the study was terminated prematurely due to the occurrence of serious infections. Notably, atacicept has demonstrated efficacy in patients with moderately severe SLE [64], therefore justifying its further investigation also in LN.

3.2.2. Type I interferon blockade

Interferons belong to a family of cytokines that comprise three major classes: type I (alpha and beta), type II (gamma) and type III (lambda). Each type binds to its specific receptor activating multiple signaling pathways that lead to the transcription of hundreds of genes within the target cells. SLE patients are characterized by overexpression of genes induced by type I IFNs (IFN-I), which comprise the so-called ‘IFN signature’ [65–67]. Expression level of these genes in the blood correlates with SLE activity and severity, including active renal disease [68–70].

IFN-I are thought to contribute to SLE primarily through their pleiotropic actions on various innate and adaptive immunity cells, thus resulting in increased T-cell proliferation and activation, impaired function of regulatory T-cells, enhanced B-cell differentiation, activation of monocytes and dendritic cells. The aforementioned effects can provide an inflammatory cellular milieu within the kidney and promote tissue injury (Fig. 2). In addition, IFN-I may enhance the renal deposition of immunocomplexes without necessarily increasing systemic humoral autoimmunity [71]. Notably, renal resident cells including mesangial and epithelial cells, both produce and respond to IFN-I by upregulating IL-6 and TNF expression [72,73] and facilitating the recruitment of neutrophils and monocytes [74]. Other local effects of IFN-I include activation of glomerular endothelial cells, which results in increased albumin permeability [75], and of podocytes and parietal epithelial cells, which may be linked to glomerulosclerosis [76]. To this end, immune-histochemical studies [72] and transcriptome analysis [77] of renal tissue from active LN patients have detected type I IFN signature in infiltrating dendritic cells and renal tubular epithelial cells, associated with tubulointerstitial injury and chronic damage. Further, overexpression of IFNα confers resistance of LN in NZB/NZW F1 mice to treatment with CyC, anti-CD40-ligand antibody or costimulation blockade (CTLA4.Ig) [78]. In line with this, genetic deficiency [79,80] or pharmaceutical blockade of type I IFN receptor (IFNAR) [81] protects or ameliorates LN in mouse models.

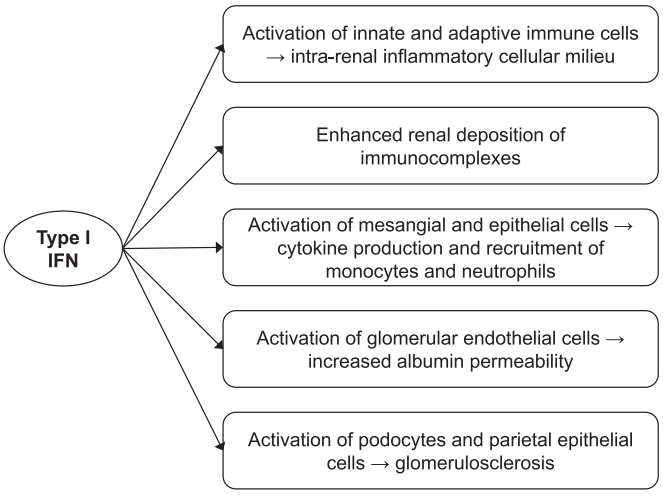

Fig. 2. Outline of the kidney-specific pathogenic effect of type I IFN in SLE.

Sifalimumab is a fully human monoclonal antibody that neutralizes multiple IFN-α subtypes. In a phase IIb trial, it demonstrated good efficacy and safety in extra-renal, moderate-to-severe SLE [82]. In contrast, the anti-IFN-α monoclonal antibody rontalizumab failed to meet its endpoints in a placebo-controlled study [83]. More recently, researchers have prepared an IFNα immunogen (IFNα kinoid) that endogenously induces transient neutralizing anti-IFN-α antibodies [84]. Kinoid-vaccinated lupus mice displayed reduced disease activity – including proteinuria, histological renal lesions, and death – which correlated with serum inhibitory IFNα bioactivity. In humans, a placebo-controlled, phase I/II dose-escalation study has been performed to compare different doses of IFN-kinoid or placebo in 28 women with mild-to-moderate SLE [85]. Further clinical trials are eagerly awaited.

Anifrolumab is a monoclonal antibody that targets IFNAR. A recently completed phase IIb trial in active SLE demonstrated higher response rates with anifrolumab as compared to placebo [86]. The difference between active drug and placebo was even greater among patients with high IFN gene signature. However, patients with active nephritis were excluded, hence there is currently no evidence regarding the renal effects of the drug. Nonetheless, considering the major role of type I IFN in the initiation and potentiation of lupus autoimmunity, it is anticipated that anti-IFNAR might demonstrate benefit also in renal disease presumably by reducing immunocomplexes deposition, tubulointerstitial injury and fibrosis.

3.2.3. IL-6 blockade

Interleukin-6 (IL-6) regulates a variety of immune cells such as it promotes B-cell maturation into Ig-secreting plasma cells. It also skews T helper cell differentiation into pathogenic Th17 (IL-17 producing) versus Treg (regulatory) T-cells [87]. IL-6 has been implicated in SLE and elevated serum levels have been described in patients with active SLE [88]. In murine models, exogenous IL-6 exacerbates lupus glomerulonephritis, while deficiency or targeting IL-6 has the opposite effect [89–91]. More recent evidence suggests that B-cell–derived IL-6 is crucial for the activation of follicular helper T-cells in germinal centers, which subsequently augment lupus humoral responses and glomerulonephritis [41].

In addition, kidney parenchymal cells, including podocytes, endothelial, mesangial and tubular epithelial cells, have all been shown to express IL-6 under certain inflammatory conditions. Podocytes in particular, demonstrate inducible expression of the IL-6 receptor (IL-6R) and IL-6 promotes the proliferation of podocytes in autocrine fashion [92]. Intriguingly, podocyte-derived IL-6 might exert anti-inflammatory effects on glomerular endothelial cells by upregulating the expression of suppressor of cytokine signaling 3 (SOCS3) [93]. Other reports, however, have suggested that IL-6 acts on endothelial cells to promote not only vasoconstriction (by increasing the expression of angiotensin II type I receptor) [94] but also inflammation (by increasing the expression of surface adhesion molecules and chemoattractant molecules) [95]. Finally, mesangial cells exposed to the combination of IL-6 and

soluble IL-6R exhibit increased levels of monocyte chemoattractant protein 1 (MCP-1) which can enhance monocyte infiltration in the kidneys [96]. Together, the contribution of IL-6 tissue-specific effects to LN pathogenesis requires further studies.

To this end, initial studies using the RA-approved agent tocilizumab, which blocks IL-6 receptor, suggested beneficial effects in SLE skin and joint disease, followed by reduction of circulating activated T and B cells, plasmablasts/plasma cells and IgD-CD27+ post-switched memory B cells [97,98]. Disappointingly, two trials that tested anti-IL-6 monoclonal antibodies in patients with active SLE and LN, failed to demonstrate superiority over placebo. Specifically, Rovin et al. [99] assessed the efficacy and safety of sirukumab in patients with class III or IV LN who were receiving concomitant immunosuppressive treatment (including MMF, azathioprine, corticosteroids). Treatment with sirukumab was not superior to placebo and resulted in an unacceptable safety profile. PF-04236921, a fully human monoclonal anti-IL-6 antibody, failed to reach its primary endpoint in patients with active SLE [100].

3.2.4. IL-23/17 axis blockade

IL-17 is a pro-inflammatory cytokine with multiple immune and non-immune effects [101]. The main producers of IL-17 are a specialized subset of T lymphocytes, known as Th17 cells, which are generated from CD4+ T-cells under the effect of certain cytokines, particularly IL-23. Culminating evidence suggests an important role of IL-17/Th17 in SLE and LN (reviewed in [102]). IL-17–deficient lupus-prone mice are protected from glomerulonephritis despite unaffected autoantibodies production [103]. Likewise, B6.*lpr* mice deficient in IL-17 receptor (IL-17RA) were protected from IFN-I-dependent crescentic glomerulonephritis [104]. However, other studies have suggested less important role of intra-renal Th17/IL-17 immune responses in the MRL/lpr and NZB/NZW mouse models of lupus glomerulonephritis. The discrepant results might be partially explained by different murine genetic backgrounds and experimental settings. Similar to other cytokines, IL-17 can also exert direct effects on kidney resident cells. Thus, IL-17F directly induces the renal expression of neutrophil-attracting chemokines CXCL1 (chemokine [C-X-C motif] ligand 1) and CXCL5 [105]. Moreover, in mouse mesangial cells, IL-17 upregulates pro-inflammatory cytokines such as CCL2 (C-C Motif Chemokine Ligand 2), CCL3, and CCL20 [106].

In humans, serum IL-17 concentrations correlate with general and renal SLE activity [107] and lupus-affected kidneys are infiltrated by IL-17+ T-cells [108]. A clinico-histopathological study in active LN showed that baseline serum IL-17 levels were significantly higher in patients with persisting active nephritis on repeat biopsy after treatment, and at follow-up, serum IL-23 were higher in non-responders versus responders [109].

Aforementioned evidence provides basis to target the IL-23/IL-17 axis in SLE including LN. Accordingly, a phase II study has evaluated the efficacy and safety of ustekinumab, a monoclonal antibody targeting the common subunit (p40) of IL-12/IL-23, in active SLE [110]. At week 24, ustekinumab-treated patients had significantly higher SRI-4 response rate as compared to the placebo group (60% versus 31%). Data regarding the possible effects of ustekinumab on kidney disease are yet unavailable.

3.2.5. IFN-γ

IFN-γ is a type II IFN that has been clearly implicated in the pathogenesis of SLE and LN as illustrated in studies with lupus-prone mice deficient in either IFN-γ [111] or its receptor [112,113]. By studying the *sanroque* lupus model, Lee *et al.* demonstrated a pathogenic role of IFN-γ signaling in T cells associated with accumulation of Tfh cells, spontaneous germinal center, autoantibody formation, and glomerulonephritis, and these effects were reversed by IFN-γ blockade [114]. Notably, other studies have also highlighted a critical role of B-cell–intrinsic IFN-γ signaling in promoting the generation of Tfh cells and pathogenic humoral responses in murine lupus [115,116]. Based on these results, a fully human monoclonal anti-IFN-γ antibody (AMG 811) was tested against placebo in SLE patients with and without LN [117]. The former group included patients with biopsy-proven active class III or IV nephritis and persistent proteinuria > 1 g/24hr despite ≥12 weeks of standard-of-care induction treatment. Unfortunately, treatment with AMG 811 had no significant effect on proteinuria, lupus serology or molecular biomarkers [117].

3.2.6. JAK inhibitors

Janus kinases (JAKs) transduce intracellular signals that converge from cell membrane receptors for multiple cytokines (except for IL-1, IL-17 and TNF) and growth factors, therefore representing a potential therapeutic target in autoimmune diseases [118]. Currently, a number of different JAK inhibitors are being tested or have already been approved for the management of RA and other inflammatory diseases. The 'net' immunologic and clinical effect of JAK inhibitors largely depends on the potency and specificity to antagonize one or more of the four JAKs (JAK1–3, TYK2) in various immune cells. Ikeda *et al.* [119] evaluated tofacitinib, which preferentially inhibits JAK3 and JAK1, in the NZB/W F1 mouse model of SLE and observed reductions in anti-dsDNA antibodies, decreased proteinuria, and amelioration of nephritis as compared with control littermates. These improvements were accompanied by reduction of IFN gene signature. Similar results were described in the MRL/*lpr* lupus-prone where tofacitinib resulted also in increased endothelium-dependent vasorelaxation and endothelial differentiation [120]. Another group has also administered CP-690,550, a more selective JAK3 inhibitor, in NZB/W F1 mice and found significant reductions in serum anti-dsDNA titres and in C3 and IgG deposition in glomeruli, followed by decreased T-cell and macrophage kidney infiltration [121]. Based on these findings, a randomized Phase II trial comparing baricitinib (JAK1/2 inhibitor) versus placebo (NCT02708095) has been conducted in moderately active SLE patients with predominant skin and joint disease but the results have not yet been released. A potential advantage of JAK inhibitors is their ability to inhibit multiple cytokines, yet their clinical efficacy in SLE and LN remains to be seen.

3.2.7. Restoration of IL-2

Regulatory T-cells (Tregs) comprise a subpopulation of T-cells that act as self-regulators of the immune system, by down-regulating the activity of effector T cells and suppressing autoreactive T-cells. Their survival depends on the abundance of interleukin-2 (IL-2). There is robust evidence to support that SLE patients exhibit defective production of IL-2 and that their CD4+ T-cells respond poorly to IL-2, which both may contribute to defective Treg function [122,123]. Accordingly, the concept of administering low-dose IL-2 to induce the survival/expansion of Tregs and potentially ameliorate autoimmune responses has emerged. This has been supported by experimental evidence where exogenous IL-2 treatment in the form of IL-2/anti-IL-2 complexes resulted in effective and sustained expansion of CD4+CD25+Foxp3+ Tregs and reduction in pathogenic IFN-γ+CD4+ and IL-17A+CD4+ T cells in the kidneys and spleen [124].

To this end, a number of small studies have assessed the safety and efficacy of IL-2 treatment in patients with active refractory SLE. Humrich *et al.* [125] reported a case of successful and rapid induction of remission with low-dose IL-2 therapy in a 36-year-old female SLE patient with active arthritis, myositis, skin rash and serological activity, refractory to several treatments. Next, a first phase I/IIa trial in active SLE patients demonstrated restoration of Treg defects following IL-2 therapy [126]. Moreover, an open-label trial with 38 patients with SLE who were administered low dose IL-2 therapy reported impressive SRI responses (89.5% at week 12) [127]. At this point, a new clinical trial is currently recruiting SLE patients (NCT03312335) who will receive a total of 4 cycles of subcutaneous injection of aldesleukin (Proleukin®, Interleukin-2), each cycle consisting of 5-day courses of injections.

3.3. Novel anti-cytokine targets in lupus nephritis

3.3.1. IL-21

IL-21 is a cytokine produced in excessive amounts by Tfh and plays a critical role in germinal center formation, maturation and Ig-class recombination of B-cells [128]. It additionally activates other immune cell subsets such as CD4+ and CD8+ T-cells. In Tregs, IL-21 signaling stimulates the mTOR pathway, and disrupts the autophagy, differentiation, and regulatory function [129]. Several studies have established a pathogenic role of the IL-21/IL-21-receptor (IL-21R) axis in murine LN, and its manipulation has proven beneficial [130–133]. Conversely, human data are still circumstantial [134]. Nevertheless, blockade of IL-21/IL-21R could represent a novel therapeutic approach in LN.

3.3.2. IL-1 family

IL-1 family cytokines are crucial mediators of inflammation and have been implicated in SLE and LN. IL-1a and IL-1b mRNA is overexpressed in glomerular macrophages of MRL-*lpr* lupus-prone mice [135]. Both NLRP3, the protein complex which mediates IL-1b maturation, and mature IL-1b protein were found increased in mice suffering from glomerulonephritis compared to wild type mice [136]. IL-18 protein levels were also found elevated in SLE patients compared to healthy controls and correlated positively with LN [137].

Signaling triggered from IL-1 cytokines is tightly regulated by decoy receptors and IL-1-receptor (IL-1R) antagonists. IL-1Ra levels were significantly increased in active LN versus inactive LN patients, and both patient groups exhibited increased IL-1Ra compared to healthy donors [138]. Moreover, IL-18 binding protein (IL-18bp) mRNA levels were significantly lower in peripheral blood mononuclear cells of patients with LN, although IL-18bp secretion did not differ between active LN and active non-renal SLE patients [139]. An additional layer of regulation of IL-1 signaling are intracellular molecules such as the single Ig IL-1-related receptor (SIGIRR). Lech *et al.* [140] have demonstrated enhanced pristine-induced LN in SIGIRR–deficient mice, confirming the pro-inflammatory role of IL-1.

IL-33 is a newly described IL-1 cytokine which is expressed in a variety of tissues, including kidneys, predominantly by epithelial and endothelial cells, and it is released upon damage. IL-33 serum levels were found increased in SLE compared to healthy individuals [141]. Also, Mok *et al.* [142] monitored increased levels of soluble ST2 (sST2, decoy receptor of IL-33) in SLE serum however, this could not discriminate LN versus non-renal SLE patients. The possible involvement of IL-33 in SLE pathogenesis was highlighted using a monoclonal anti-IL-33 antibody in MRL/*lpr* lupus-prone mice; IL-33 blockade led to significant improvement of glomerular inflammation and vasculitis, as well as reduced kidney deposition of IgG and C3 [143]. Since IL-33 is released upon cell death and considering that neutrophil cell death by formation of extracellular traps (NETs) is a prominent feature in SLE and LN pathogenesis, [144] we have further demonstrated the presence of interferogenic IL-33–decorated NETs in the tubulo-interstitial space in kidneys from patients with active proliferative LN [145]. Notably, IL-33 deficiency reduced tubular cell injury and subsequent renal neutrophil infiltration in experimental kidney ischemia-reperfusion injury [146]. To conclude, several IL-1 family members and their regulators have been implicated in the pathogenesis of experimental LN and could therefore, be further evaluated as novel drugable targets.

3.3.3. TWEAK

TWEAK (Tumor necrosis factor-like weak inducer of apoptosis) and its receptor Fn14 (fibroblast growth factor-inducible-14) belong to the TNF/TNF-receptor cytokine family, are induced in injured tissues and mediate inflammatory effects in both resident epithelial and immune cells. Compelling evidence implicates TWEAK/Fn14 in the pathogenesis of acute and chronic kidney injury in non-immune and immune–mediated disorders (reviewed in [147]). Regarding LN, kidney Fn14 protein and mRNA levels were both significantly increased in MRL/lpr mice at 22 weeks of age as compared to unaffected MRL/MpJ mice [148]. Concordantly, patients with active LN display increased urinary excretion of TWEAK which correlates with renal disease activity [149]. More convincingly, Fn14–deficient mice were less prone to lupus kidney disease with less kidney IgG deposition, IL-6, MCP-1, RANTES, IP-10 and macrophage infiltration as compared to wild-type littermates [150]. *In vivo* administration of anti-TWEAK neutralizing antibody in lupus mice resulted in diminished kidney inflammation and proteinuria without ameliorating the production of autoantibodies. Collectively, TWEAK/Fn14 might represent a novel therapeutic approach towards the reduction of renal inflammation and damage in SLE.

4. Critical appraisal and future prospects

As many as 30–40% of patients with active proliferative LN may not respond to existing immunosuppressive therapies, or they can experience flares, which necessitate intensification or re-initiation of treatment including corticosteroids [3,151]. Moreover, repeat kidney biopsy studies have demonstrated persistence of active inflammatory lesions and accrual of chronic damage even in patients with good clinical response and low-grade residual proteinuria [152]. Pertinent to these, worldwide trends of SLE-associated ESRD have reached a plateau that exceeds 10–15% [9]. Although the introduction of ‘multi-target’ regimens could prove a useful option in cases of refractory or severe nephrotic nephritis, the long-term effects on the disease immunobiology and kidney function remain elusive [153]. These regimens are also prone to the limitations and harms of the individual immunosuppressive compounds. Consequently, there is merit in developing biologic therapies that target specific soluble mediators and cytokines involved in LN pathogenesis. To date, available data exist only for belimumab (anti-BAFF antibody) [55], pending the conclusion of the BLISS-LN trial, and sirukumab (anti-IL6 antibody), which however failed to demonstrate superiority over placebo [99]. For several other putative targets, we are eagerly waiting their validation in preclinical and clinical studies.

In this context, a number of challenges should be considered. First, to ensure statistical power, trials need to include a sufficient number of patients. Notably, in recent epidemiological studies, prevalence of nephritis among white SLE patients ranges 10–30% with incidence rates of 0.45–0.60 per 100,000/year [154,155]. Consequently, LN trials often require to be multicentric, recruiting patients across the globe. However, a potential risk of this strategy is the inclusion of patients managed in diverse clinical settings and health care systems, and this might affect patient prognosis. Second, trials in SLE and LN have repeatedly suffered from methodological hurdles, particularly the fact that the difference between active drug and placebo may have been blunted by high background therapy (e.g. high-dose MMF, high-dose oral steroids). Also, the selection of endpoints can impact on the trial results. An illustrative example is the abatacept in LN (ACCESS) trial where use of alternative definitions of renal response led to different results than those published in the original trial [156]. To this end, assessment of the flare rate or per-protocol repeat kidney biopsy could unravel additional insights regarding drug effectiveness, irrespective of the response in proteinuria.

Shall cytokine-targeting therapies be available in the clinic, an additional challenge would be how to choose the most suitable treatment for each individual with LN. Until now, candidate patient profiles are usually derived based on the baseline characteristics (demographic, histological, clinical) of the trial participants or post-hoc data analysis [157]. Further insights might be derived from experimental studies which delineate the mode of action of each treatment. Thus, BAFF blockade might alleviate renal disease by inhibiting the activation and differentiation of memory B-cells, as compared to IL-17 blockade which presumably reduces kidney-infiltrating T-cells without impacting on humoral responses [103]. Other cytokine-targeting therapies (e.g.

TWEAK/Fn14) could exert renoprotective effects by altering the function of renal epithelial cells [150]. Towards applying a personalized-medicine approach, novel high-throughput technologies might be particularly relevant. Supposedly, their application (e.g. transcriptome analysis) in the blood, urine or affected kidney could enable the *a priori* stratification of LN patients according to underlying pathophysiology, therefore assisting the selection of most appropriate therapy [158]. In conclusion, we remain optimistic that continuous progress in biology and genomics, coupled with preclinical and clinical studies and improvements in their design, will eventually expand the therapeutic armamentarium in LN.

Acknowledgments

This work was supported by Special Research Account of the University of Crete (grant no. 4718) and the Greek Rheumatology Society and Professional Association of Rheumatologists (grant no. 644). Spyros Georgakis is supported by the "LUPUSCARE: Precision care in Systemic autoimmunity: an integrated multi-tissue/level approach for Systemic LUPUS Erythematosus (SLE)" (grant no. 742390).

Declarations of interest

None.

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