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REVIEW

Special Issue: Novel Diagnostic and Therapeutic Approach Options in Lupus Nephritis

New Treatment Options in Lupus Nephritis

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Abstract
The aim of this study is to report major recent progresses in the treatment of lupus nephritis (LN). Results of controlled randomized trials are discussed in view of the unmet needs in the field. Current treatments of LN are not satisfactory, with a disappointing proportion of 20–30% of patients achieving complete renal response within 6–12 months, and 5–20% developing end-stage kidney disease within ten years. Two drugs (belimumab and voclosporin) have been officially registered by the medical agencies as add on treatment of LN, a first-in-history success after decades of use of non-registered drugs and trial failures. Other targeted therapies (obinutuzumab and anifrolumab) are currently tested in Phase III trials, after interesting results in Phase II studies. Unanswered questions related to the use of these new drugs are discussed. Recent trials have opened new avenues for the treatment of LN which will hopefully reduce the rate of chronic kidney disease.

Keywords Lupus nephritis · Treatment · Targeted therapies · Outcome

Introduction

Lupus nephritis (LN) is the most common severe disease manifestation of systemic lupus erythematosus (SLE). Renal involvement is described in 35–60% of patients. At least 20% of patients suffering from LN will evolve to chronic kidney disease (CKD), defined by an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, and 5–20% will require renal replacement therapy (Maroz and Segal 2013; Pons-Estel et al. 2011), with increased morbidity and mortality, not to mention a huge socio-economic burden.

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Pathophysiology of LN in a Nutshell

As nicely summarized in a recent review by Ann Davidson's laboratory (Maria and Davidson 2020), LN is not considered anymore as only a glomerular disease (glomerulonephritis) but rather as a disease affecting all kidney compartments (pan-nephritis). The glomerular component, known for decades, is due to subendothelial, subepithelial and mesangial deposition of circulating immune complexes (IC). The subendothelial IC induce endothelial dysfunction and recruitment of immune cells, such as T cells and macrophages, in the glomerular tuft, while subepithelial (and mesangial) IC damage podocytes, which play a central role to maintain glomerular integrity. Besides this glomerular component, in which the kidney can be considered as a passive victim of circulating IC, inflammation and damage in the tubulointerstitium (TI) have been more recently shown to play a critical role. Thus, resident macrophages located next to the tubules and the tubular capillaries are also activated by IC. This process leads to the release of renal antigens which are presented to local immune effectors, such as dendritic cells, thereby inducing a local immune response, illustrated by the presence, in the TI, of tertiary lymphoid structures containing $CD21^+$ follicular dendritic cells. TI inflammation further leads to hypoxia, fibrosis and tubular atrophy. Most

importantly, several studies have reported that the long-term prognosis of LN is largely influenced by the degree of TI inflammation, fibrosis and atrophy (Daniel et al. 2001; Pagni et al. 2016; Pamfil et al. 2018).

Current Treatment Strategies

Humans start losing podocytes (and thereof nephrons) around the age of 40, thereby causing an average eGFR decrease of 0.7 ml/min/m^2/year. This process is considerably accelerated by an episode of LN. Since the disease mostly starts in young (female) adults (and sometimes in children), the risk of developing CKD and even end-stage kidney disease (ESKD) early in life is high. The treatment of LN should therefore be compared to a sprint race against irreversible nephron loss, with as ultimate goal to avoid CKD up to several decades after the initial kidney injury.

The current treatment paradigm to prevent CKD in LN is based on a sequential approach, which consists of an initial (induction) treatment to induce a response and a subsequent (maintenance) treatment to maintain the response and to avoid flares. Based on these principles, therapeutic recommendations for LN have been developed and updated in 2019 by a joint initiative of the European League Against Rheumatism and the European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) (Fanouriakis et al. 2020). The task force recommends the use of intravenous (IV) methylprednisolone (MP) pulses followed by a moderate dose of oral prednisolone (0.3–0.5 mg/kg/day), promptly tapered to $\leq$ 5–10 mg/day by three months. Mycophenolate mofetil (MMF; 2–3 g/day) or low-dose IV cyclophosphamide (CYC), prescribed according to the Euro-Lupus regimen (6 × 500 mg q2w) (Houssiau et al. 2002) are recommended as first-choice induction treatment. Similar choices were recently proposed by the Kidney Disease: Improving Global Outcomes (Rovin et al. 2021a).

Optimal nephroprotection is strongly recommended with renin–angiotensin system (RAS) inhibitors, weight control, reduced salt intake, optimal blood pressure control, avoidance of smoking and of nephrotoxic drugs. Hydroxychloroquine (HCQ), initially developed as treatment of cutaneous and joint involvement, is yet another important drug in LN since it reduces the risk of renal flares, ESKD and death (Pons-Estel et al. 2009).

Once a response is obtained, maintenance immunosuppressive therapy with MMF or azathioprine (AZA) is recommended. MMF should be pursued if this drug was used as induction therapy. In case of initial therapy with Euro-Lupus IV CYC, maintenance should continue with either MMF or AZA. Maintenance immunosuppressive treatment should be kept for at least 3 years. Steroid should be withdrawn in patients with complete response, in the absence of extra-renal manifestations.

Rituximab, a B-cell depleting anti-CD20 monoclonal antibody, is advised in refractory cases, based on several retrospective series. Alas, the corresponding LUNAR trial was not conclusive (Rovin et al. 2012).

More attention should be paid to nonadherence to therapy, quite common in chronic diseases in general and especially in lupus nephritis. Repeated measurements of whole blood HCQ titers might be very helpful in identifying nonadherent patients, who would be otherwise considered as refractory cases and be exposed to treatment escalation with more immunosuppression and possibly additional adverse events (Costedoat-Chalumeau et al. 2007, 2019). Improving adherence to therapy is difficult and requires a multidisciplinary approach involving nurses, psychologists and other health professionals, as well as newer e-technologies (Costedoat-Chalumeau and Houssiau 2021).

Last but not least, LN should be diagnosed as soon as possible by very regular assessments of proteinuria. When proteinuria is detected, the immune process is already at work in the kidneys for several months, if not several years. This probably explains why some patients with "newly" diagnosed LN already display some chronic damage in the initial biopsy, such as glomerular scarring and tubulointerstitial fibrosis. These chronic changes might jeopardize the efficacy of standard immunosuppressants and of the new targeted therapies discussed here.

Limitations of Current Treatment Regimens

Although patient and kidney survival rates have greatly improved compared to the last century, thanks to the use of steroids and other immunosuppressants, it should be emphasized that complete renal remission (CRR), defined as a proteinuria $\leq$ 0.5 g/day, is achieved in only 20–30% of patients after 6–12 months of treatment (Wofsy et al. 2015). Interestingly, a recent study demonstrated that LN patients who do not experience CRR have a 3-folds higher risk of CKD and a 10-folds higher risk of ESKD (Pirson et al. 2021). Flares occur in 20–35% of LN patients (El Hachmi et al. 2003). Even more worryingly, as already mentioned supra, nearly 20% of patients suffering from LN will develop CKD and 5–20% will require renal replacement therapy after 15 years (Maroz and Segal 2013; Pons-Estel et al. 2011). In addition to these suboptimal results, the adverse effects of current treatment regimens, particularly of steroids, greatly contribute to reduced quality of life, irreversible organ damage (such as vertebral crush, osteonecrosis, cataract, skin atrophy, etc.), morbidity and mortality. Taken together, these figures illustrate the need for newer approaches. We discuss three such approaches: treat-to-target, switch from sequential to combination therapy (with two drugs officially labeled

for LN as add-on treatment) and the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Treat-to-Target Concept

The treat-to-target concept stems from the assumption that achieving a given target early after disease onset and initial therapy will ensure a good long-term outcome, in casu an absence or renal impairment. The complexity and heterogeneity of LN makes such a target more difficult to define than in hypertension, diabetes mellitus or rheumatoid arthritis. For years, especially based on our own work, we have used a clinical target, namely proteinuria decrease. Yet, based on several recent investigations, again including our own, we propose that one should switch from a clinical to a pathological target, through per-protocol repeat kidney biopsies performed after one year of treatment.

In two studies, we were able to demonstrate that reducing proteinuria to ≤ 0.7–0.8 g/day after 12 months of treatment displays an excellent positive predictive value for a good long-term kidney outcome, i.e. an absence of renal impairment after seven years of follow-up (Dall'Era et al. 2015; Tamirou et al. 2015). This was confirmed in a real-world LN series collected in South America (Ugolini-Lopes et al. 2017). Thus, at the bedside, one can reassure a patient who reaches this target that she/he will remain free of CKD. Alas, the negative predictive value is very low since two thirds of patients not reaching this target will still (and fortunately) achieve the same goal. The problem is therefore to identify, as early as can, those very patients who have not reached the clinical target and who will experience a poor long-term renal outcome, for whom a change in therapy might be appropriate.

Recent studies, performed by three different groups, have revealed a mismatch between clinical and pathological responses after induction therapy. Thus, Zickert et al. (2014) showed, through per-protocol repeat kidney biopsies performed after induction therapy, irrespectively of the clinical response, that almost one third of patients with CRR displayed histological signs of active LN. Using a similar design, Malvar et al. (2017) showed that 50% of patients with CRR had an activity index (AI) > 3 on post-induction kidney biopsy performed after 6 months. Parodis et al. (2020), in an analysis of the per-protocol repeat kidney biopsies performed in our Louvain incident LN cohort after 12–24 months of treatment, further emphasized this mismatch. While there was a slight correlation between the amount of proteinuria measured at the time of repeat biopsy and the activity index, two groups of patients could be identified. Some had no signs of renal activity despite the persistence of significant proteinuria likely due to chronic damage. The risk for those patients, with chronic damage and no inflammation, is over-treatment. Others, despite having low-grade proteinuria had an AI > 3, with a risk of under-treatment. Interestingly, repeat kidney biopsies portended relapse and long-term renal outcome. Thus, renal flares were more common in patients with an AI > 3 (mainly in the glomerular compartment), while CKD was associated with a chronicity index > 3 (mainly linked to the TI compartment).

On the whole, we would recommend to perform systematic repeat kidney biopsies in LN after one year of treatment. We have designed an international protocol (http://www.rebiolup.com), discussed in another paper of this series, aimed at testing the hypothesis that knowledge of the results of the control biopsy and subsequent treatment changes, will increase the rates of CRR and thereby improve long-term outcome.

A Paradigm Shift: From Sequential to Combination Therapy

Results of two recent Phase III randomized controlled trials have opened a new avenue in the treatment strategies of LN. Two drugs (belimumab and voclosporin) have indeed been labeled by the medical agencies for use in LN as add-on (combination) therapy, a first-in-history success contrasting with that fact that none of drugs recommended so far for use in LN (vide supra) were registered.

Belimumab (BEL) is an anti-BLyS/BAFF monoclonal antibody initially registered more than 10 years ago for non-renal SLE patients as add-on therapy based on six randomized controlled trials (Brunner et al. 2020; D'Cruz et al. 2019; Furie et al. 2011; Navarra et al. 2011; Stohl et al. 2017; Zhang et al. 2018). Based on a post hoc analysis of patients randomized in the two pivotal trials who displayed some degree of proteinuria (not full-blown LN) and who improved on BEL (Dooley et al. 2013), a Phase III LN trial was designed (BLISS-LN) (Furie et al. 2020). Patients were treated with BEL or placebo (PBO) on top of standard of care (SOC), i.e. steroids and either MMF or Euro-Lupus IV CYC. After 104 weeks, the primary endpoint (primary efficacy renal response), mainly driven by proteinuria (≤ 0.7 g/day), was achieved in 32 and 20% of BEL and PBO patients, respectively. CRR (proteinuria ≤ 0.5 g/day) was achieved by 43 and 30% of BEL and PBO patients. These differences were statistically significant. Importantly, the eGFR slope between month 6 and 24 was statistically reduced in BEL patients. The mechanisms underlying this effect could be unraveled by repeat kidney biopsy studies performed after BEL treatment. More patients in the BEL group took ≤ 7.5 mg/day of prednisone at week 104, thereby indicating a steroid-sparing effect. Time to first renal flare from week 24 onwards was statistically longer in BEL patients. BEL significantly improved serological markers such as

anti-DNA antibodies and complement levels. This said, no statistically significant benefit could be demonstrated on top of IV CYC, in Class V LN and in patients with African ancestry, although the numbers were likely small to unmask a significant difference. Adverse events were not more common in the BEL arm.

Voclosporin (VOC) is a calcineurin inhibitors (CNI), like tacrolimus and ciclosporin. These drugs display an immunosuppressive effect (by decreasing interleukin-2, interferon (IFN)-γ and tumor necrosis factor-α production by T cells) and a unique ability to stabilize the actin cytoskeleton of podocytes (through preventing dephosphorylation of synaptopodin) and thereby to reduce proteinuria (Chan 2015). Voclosporin has a favorable pharmacokinetic profile (no need for drug monitoring) and a neutral effect on lipids and glucose metabolism, in comparison with other CNI. CNI have been used in LN for many years, especially in Asian patients, mostly in combination with MMF (Liu et al. 2015). After the successful Phase II AURA-LV trial (Rovin et al. 2019), VOC was tested in another positive Phase III trial (AURORA) (Rovin et al. 2021b), which led to approval by the U.S Food and Drug Administration (FDA). Patients were treated with VOC (23.7 mg bid or PBO) on top of steroids and MMF. Of note, the steroid tapering regimen was very stringent with a target of 2.5 mg/day of prednisone at 16 weeks. The primary endpoint (CRR at week 52) was achieved in 41% of VOC patients and 23% of PBO patients. As anticipated by the mode of action of CNI, the reduction of proteinuria was very prompt. VOC displayed efficacy over different ethnic groups, including patients with African descent and Hispanics/Latinos. eGFR remained stable in both groups. No significant effect was noticed on serological biomarkers. Adverse events were not more common in the VOC arm.

The two newly approved drugs are compared in Table 1.

Other targeted therapies are currently tested in combination with SOC in Phase III trials after favorable initial signals from Phase II studies, such as obinutuzumab (OBI) and anifrolumab (ANI).

OBI is an anti-CD20 monoclonal antibody approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma. Compared to rituximab, OBI induces a stronger peripheral B-cell depletion likely related to greater antibody-dependent cytotoxicity, reduced internalization and greater direct cell death effect. In the *NOBILITY* Phase II trial, patients (mainly Hispanics) were treated with OBI or PBO on top of MMF and steroids. CRR rates at week 52 (primary endpoint), 76 and 104 were 23%, 18% and 23% in the PBO group and 35% ($p=0.11$), 38% ($p=0.011$) and 41% ($p=0.026$) in the OBI arm. Peripheral blood B-cell depletion ($CD19^+$ count ≤ 5 cell/µl) was achieved at week 52 in 94% of OBI-treated patients. Adverse events were not more common on the OBI arm (Furie et al. 2022). In the currently recruiting Phase III trial (*REGENCY*), patients receive OBI on week 0, 2, 24, 26, 50 and 52, with a primary endpoint (CRR) evaluated at week 76.

ANI is an anti-IFN-α and β receptor subunit 1 (IFNAR1) monoclonal antibody, blocking the activity of all Type 1 IFNs (α, β, ε, κ, ω). Based on the pivotal role played by these cytokines in the pathophysiology of SLE (Banchereau and Pascual 2006; Blanco et al. 2001), ANI was successfully tested in two non-renal trials: TULIP-1 (Furie et al. 2019) and TULIP-2 (Morand et al. 2020). These results lead to recent approval of ANI by the FDA in non-renal SLE and prompted a Phase II controlled study in LN (*TULIP-LN*). In this trial, patients were given PBO or ANI, the latter following a basic (lower) or an intensified (higher) regimen, on top of MMF and steroids. Only patients receiving the intensified regimen displayed more clinical responses (CRR) compared to PBO patients. Differences in the pharmacokinetics (lower serum concentrations) and pharmacodynamics (less inhibition of the Type 1 IFN gene signature) likely explained the absence of effect of the basic regimen (Jayne et al. 2021a). A Phase III trial is in the pipeline in which the intensified ANI regimen will be used.

Needless to say, drugs targeting the complement, such as C5aR antagonists or Factor B inhibitors could have a major effect on LN. These drugs, by working very downstream in the cascade, might display a prompt effect, allowing stringent reduction or even avoidance of steroids, as recently demonstrated in ANCA-associated vasculitides (Jayne et al. 2021b).

SGLT-2 Inhibitors

While this paragraph may seem inappropriate because the lack of specific data in LN, we believe that the results of a recent trial performed with dapagliflozin (DAPA), a SGLT-2 inhibitor, in CKD patients deserves our utmost attention (Heerspink et al. 2020). In the DAPA-CKD trial, 4,304 patients with an eGFR between 25 and 75 ml/min/1.73 m^2 of body surface area and albuminuria were treated with DAPA (10 mg/day) or PBO. Most patients (67%) suffered from diabetes mellitus. While LN and vasculitis patients were excluded, patients with other glomerular diseases, such as IgA nephropathy, were included. The primary endpoint of the trial was a sustained decline in the eGFR of at least 50%, ESKD or death from renal or cardiovascular causes. The trial was stopped after 32 months when an intermediate analysis showed a 34% reduction of achievement the primary outcome in the DAPA group (hazard ratio: 0.56; 95% CI 0.45–0.68; $p<0.001$). Our educated guess is that SGLT-2 inhibitors will be of particular interest in glomerular diseases, like RAS inhibitors were 30 years ago. The mode of action of SGLT-2

Table 1 Comparison of pivotal belimumab and voclosporin trials in lupus nephritis

Molecule	Trial	Inclusion criteria	Intervention	Baseline characteristics	Primary endpoint	Additional results
Belimumab	*BLISS LN* Phase 3 RCT $n=448$ (224 in BEL group, 224 in PBO group) Duration of 104 weeks	ACR classification criteria for SLE uPCR ≥ 1 ISN/RPS III, IV (± V)	BEL (10 mg/kg) + SOC vs PBO + SOC SOC defined as: **either** induction and maintenance with MMF (1–3 g/day) **or** induction with IV CYC (EL) and maintenance with AZA **plus** CS (1–3 × IV MP 500–1,000 mg) oral prednisolone (≤ 60 mg) HCQ RAS blockade	Mean (SD) uPCR: 3.4 (3.2) Mean (SD) eGFR (ml/min/1.73 m^2): 100.5 (40.2) Patients with eGFR ≥ 60 ml/min/1.73m^2: 83% Median time (IQR) since initial LN diagnosis (years): 0.2 (0.1–3.3)	PERR defined by: uPCR ≤ 0.7 **and** eGFR < 20% below preflare value or ≥ 60 ml/min/1.73m^2 **and** no rescue therapy Patients (%) achieving PERR: 43 for BEL vs 32 for PBO $p=0.03$	Effect consistent over several other endpoints Stringent outcome measures Reduction of kidney flares Reduction of kidney function decline Decrease of serum anti-DNA antibodies Steroid-sparing effect
Voclosporin	*AURORA-1* Phase 3 RCT $n=357$ (179 in VOC group, 178 in PBO group) Duration of 52 weeks	ACR classification criteria for SLE uPCR ≥ 1.5 ISN/RPS III, IV (± V)	VOC (23.7 mg bid) + SOC vs PBO + SOC SOC defined as: MMF (2 g/day) **plus** CS (2 × IV MP 250–500 mg), oral prednisolone (20–25 mg) prompt tapering of steroids RAS blockade	Mean (SD) uPCR: 4.1 (2.7) for VOC 3.9 (2.4) for PBO Mean (SD) eGFR (ml/min/1.73m^2): 92.1 (30.6) for VOC 90.4 (29.0) for PBO Patients with eGFR ≥ 60 ml/min/1.73m^2: 82% VOC 81% PBO Mean (SD) time since initial LN diagnosis (years): 4.6 (5.1) for VOC 4.7 (4.9) for PBO	CRR defined by: uPCR ≤ 0.5 **and** eGFR ≥ 60 ml/min/1.73m^2 **or** eGFR < 20% below baseline eGFR **and** no rescue therapy **and** prednisolone < 10 mg/day Patients (%) achieving CRR: 41 for VOC vs 23 for PBO $p<0.0001$	Low-dose steroid oral regimen achievable Efficacious across ethnic subgroups Trend towards efficacy in pure Class V

ACR American College of Rheumatology, *AZA* azathioprine, *BEL* belimumab, *CRR* complete renal response, *CS* corticosteroids, *CYC* cyclophosphamide, *eGFR* estimated glomerular filtration rate, *EL* Euro-Lupus, *HCQ* hydroxychloroquine, *IQR* interquartile range, *ISN/RPS* International Society of Nephrology and the Renal Pathology Society, *IV* intravenous, *LN* lupus nephritis, *MMF* mycophenolate mofetil, *MP* methylprednisolone, *PBO* placebo, *PERR* primary efficacy renal response, *RAS* renin angiotensin system, *RCT* randomized controlled trial, *SD* standard deviation, *SOC* standard of care, *uPCR* urinary protein to creatinine ratio

inhibitors is complex and only partly understood. In chronic glomerular diseases, the unaffected nephrons suffer from hyperfiltration, which increases sodium reabsorption in the proximal tubule, thereby decreasing sodium levels in the distal tubules and the *macula densa*. This results in further vasodilation of the afferent arteriole through the tubuloglomerular feedback (vicious circle). By blocking sodium (and glucose) reabsorption in the proximal tubule and increasing sodium content in the distal tubule and in the *macula densa*, SGLT-2 inhibitors induce afferent arteriole vasoconstriction, reduce hyperfiltration and restore the tubuloglomerular feedback.

Many Unanswered Questions

At this stage, the reader might have the impression that the sketch is fully written. Yet, we are left with many unanswered questions. Some of them are listed and commented hereunder.

At best, only 41% of LN patients achieve CRR with current combination therapies, indicating that there is still room for improvement. How can we push these figures further? In line with this goal, much more attention should be paid to adherence to treatment and

non-immunosuppressive therapy, taking lessons from the nephrology world.

How much of the effect of VOC is related to its antiproteinuric properties rather than to actual immunosuppression? This is an important issue which could be addressed by long-term follow-up (even after CNI withdrawal) and by repeat biopsy studies demonstrating regression of glomerular and tubulointerstitial inflammation, not to mention clearance of immune complex deposits.

Will a gain of 10–20% of CRR at 12–24 months translate in less CKD/ESKD in the very long-term? Our data suggest that patients who never achieve CRR have a much poorer renal prognosis. In this respect, increasing CRR rates should positively impact long-term prognosis but only further follow-up will provide us with the answer. It should be stressed that avoidance of only a few cases of ESKD will have a major impact on the personal and global burden of the disease.

Should we prescribe these drugs front up (actually as tested in the trials discussed supra) or wait two to three months before starting them in patients who do not have early signs of response to SOC? In a recent review (Mejia-Vilet et al. 2021), the latter proposal was made for patients not achieving a reduction of proteinuria of at least 25% compared to baseline after 8–12 weeks of induction therapy, with a risk of missing a window of opportunity. In our view, at least in Caucasian patients, most patients experience a prompt early response (a decrease in proteinuria > 25%) likely related to the prompt efficacy of IV MP pulses. If such a rule is applied, these very patients would not benefit from new treatments, which also reduce the flare rate (at least for BEL) and the slope of eGFR decrease. One should not forget that even in experienced referral centers, the rate of CKD is ≥ 20% in the long run.

Will we overtreat patients through widening of the therapeutic armamentarium? Unless we have performant tissue, blood or urine biomarkers capable of identifying at baseline those very patients who will not respond to SOC, it is likely that we shall overtreat a significant proportion of patients. The absence of super-imposed toxicity related to the use of the new drugs is reassuring in this respect, although we need more data on long-term use of VOC, which will be provided by *AURORA-2* (NCT03597464). On yet another note, a pharmaco-economical approach should evaluate the economic burden of combination therapy compared to the possible savings in terms of renal replacement therapy.

What is the efficacy of BEL or VOC in patients with severe renal impairment? Patients with an eGFR < 30 ml/min/m^2 were indeed excluded from *BLISS-LN*, *AURA-LV* and *AURORA*. The use of CNIs in patients with severe renal impairment is not advisable, at least not before their renal function has improved, e.g. after administration of IV MP pulses.

Shall we be able to limit steroid use to IV MP pulses only, as suggested by an uncontrolled series using the oral steroid-free *RITUXILUP* regimen (Condon et al. 2013)? While the *RITUXILUP* trial was early terminated due to recruitment delays, another initiative (*OBILUP*) is in the pipeline testing OBI as add on to MMF in a similar oral steroid-free design (NCT 04,702,256). Avoidance of oral steroids, like in ANCA-vasculitides, would be a milestone achievement given the dire side-effects of steroids which contribute so much to damage accrual (Gladman et al. 2003).

How long should we use these drugs? This pivotal question is unlikely to be solved by the aforementioned pharma trials, which are mostly limited in time. More data on long-term use is available for BEL, at least in non-renal patients.

On yet another note, when several drugs, blocking different pathways, will become available, the next burning question will deal with the choice of the best treatment in a given patient, because "one size will not fit all". Our choice will be guided by patient's extra-renal disease (BEL might be more indicated in case of systemic manifestations), patient's specific toxicity profile, drug availability and reimbursement, etc. Yet, the final clue should stem from identification of the pathways at work in situ through a tissue-based approach. Precise medicine and theranostics will replace the use of rather indirect biomarkers, such as proteinuria, which reflects both inflammation and chronic damage. Transcriptomic (Crickx et al. 2021) and genetic profiling will likely play a role in assessing the individual risk of CKD and allow a tailored approach.

Conclusion

After decades of use of unregistered drugs and after many trial failures, we may now anticipate a better future for patients suffering from LN.

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Declarations

Conflict of interest The authors declare no conflicts of interest related to this work.

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