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Biologic Therapy in Lupus Nephritis

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Abstract
This position paper critically analyzes the available controlled data regarding biologic therapy in lupus nephritis (LN). Rather than an exhaustive review of all published evidence, the stress is put on the unmet medical needs in LN, the design of trials aimed at testing the effect of a biologic in LN, the possible reasons for LN trial failures and the future of biological therapy in LN.

Why Do We Need Biologics in Lupus Nephritis?

Lupus nephritis (LN) is a feared disease manifestation of systemic lupus erythematosus, affecting between 30 and 60% of the patients [1], with a higher prevalence in childhood-onset cases. While most patients can be successfully treated in the short term with current immunosuppressants, the long-term outcome is not so bright. Thus, in our own inception cohort of biopsy-proven LN (LOULNIC; Louvain Lupus Nephritis Inception Cohort), we are pleased to claim that only 4% suffer from end-stage renal disease after a mean follow-up of 6.5 years. Yet, 17.5% of these patients have some degree of renal impairment (defined as eGFR <60 ml/min/1.73 m²) [Houssiau et al., unpubl. data]. Since most of these patients are currently below the age of 40, it is anticipated that a significant percentage of them will eventually develop end-stage renal disease. Although we still partially ignore why some LN patients do not respond to therapy, the consensus is that an early response to induction immunosuppressive therapy has a high positive predictive value for a good long-term renal outcome [2]. In this respect, the fact that only a relatively small proportion of LN patients achieve complete renal remission at 6–12 months stresses the need for additional or alternative approaches, of which biologics might play a pivotal role by improving early complete remission rates. A second reason why biologics should be tested in LN stems from the side effects of current immunosuppressive regimens. One should keep in mind that most of the damage observed in systemic lupus erythematosus is related to the use of glucocorticoids (GC) [3, 4]. The possibility that biologics might display a major GC-sparing effect is not farfetched, as suggested by recent data obtained with an oral steroid-free regime combining rituximab (RTX) and mycophenolate.
nolate moefitil (MMF) (RITUXILUP regime) [5]. Thirdly, biologic therapy might be of interest to reduce the rate of renal flares, which are quite common despite maintenance immunosuppression with low-dose GC, azathioprine or MMF, and have a deleterious impact on long-term renal outcome, mainly in case of nephritic flares.

**How to Run a LN Trial Aimed at Testing a Biologic?**

From a theoretical viewpoint, four different designs can be (have been) tested. First, biologics can be evaluated as an ‘add-on’ induction therapy superimposed to the standard of care (SOC). In this setting, patients receive GC and another immunosuppressant [MMF or intravenous cyclophosphamide (CY)], and either placebo or the study drug. Unless the primary endpoint is set far enough from baseline (at least 1 year, ideally 2), much of the effect might be driven by SOC, mainly by GC, which may obscure the potential benefit of the study drug, in case the biologic agent, except if the study drug is a wonder drug. The other possible drawback is to cumulate adverse events, some of which could be wrongly assigned to the study drug instead of SOC. In other words, in an add-on approach, both efficacy and toxicity might well be driven by SOC. A second design is a modified draft of an add-on protocol in which the dose of GC is reduced to a minimum. The aim of this ‘low-dose/no GC’ approach, used in the RITUXILUP regime, is to avoid the aforementioned pitfalls [5]. While this might be game-changing, it should be stressed that it still needs to be tested in a controlled trial [6]. A third possibility is to test biologics in patients who do not display a sufficient level of response in terms of reduction of proteinuria after 3–6 months of SOC, i.e. in patients suffering from refractory disease, or at least experiencing a suboptimal response to induction therapy. Actually, this is how RTX has been (is still) used by lupologists in clinical practice. Many series – again uncontrolled – indicate that RTX might be efficacious in this niche indication, as also suggested by registry data [7–9]. The ATLAS (anti-TWEAK) and the RING (RTX) trials are testing this approach. One advantage of this design is that the dose of GC is mostly reduced by the time the biologic is introduced, which may contribute to reduce toxicity and increase the chance of unmasking the effect of the study drug. Lastly, biologics could be tested as long-term maintenance therapy, as already alluded to. This design is, however, unlikely to be tested by pharma trials, as it requires a long observation period (at least 3 years).

**Why Have LN Trials Failed Thus Far?**

Table 1 lists the randomized controlled LN trials in which a biologic agent has been tested and summarizes the major conclusions. So far, results have been reported for anti-CD20 RTX (LUNAR trial) [10], anti-CD20 ocrelizumab (OCR; BELONG trial) [11], CTLA4-Ig abatacept (ABA; BMS and ACCESS trials) [12, 13], anti-BLyS (B lymphocyte stimulator)/APRIL (A proliferation-inducing ligand) receptor construct atacicept (ATA) [14], antigen-presenting cell modulator laquinimod [15] and anti-IL6 sirukumab [16]. None of these trials reached its primary endpoint. While the reasons for these failures are obviously speculative, three scenarios can be sketched.

First, some drugs turned out to be more toxic than anticipated, at least in combination with the other immunosuppressants used in these trials. Thus the BELONG trial was terminated early because of an imbalance in serious infections in OCR–treated patients versus placebo–treated patients when the study drug was combined with MMF [and not to Euro-Lupus (EL) intravenous CY] given as background immunosuppressive therapy [11]. Of note, many more MMF patients had received ≥1 g intravenous methylprednisolone compared to EL patients, suggesting that increased intravenous GC use might explain the increased infection rate observed in patients treated with the combination of OCR and MMF. Another example of premature termination for toxicity is the ATA LN trial, in which patients received placebo or ATA on a background of GC and MMF [14]. The trial was interrupted after the enrollment of only 6 patients (2 placebo and 4 ATA). Three out of the 4 ATA patients developed severe hypogammaglobulinemia (serum IgG <3 g/l) and all three suffered from severe infection (*Haemophilus influenzae* pneumonia, *Legionella pneumophila* pneumonia and *Bacillus bacteremia*). Interestingly, the results of a nonrenal lupus ATA flare prevention trial were recently released and the high-dose ATA group was also prematurely terminated because 2 patients died of severe infection, despite normal serum IgG levels [17]. It may be that combined blockade of BlyS and APRIL really explodes the infectious risk. Yet, experienced clinical lupologists are well aware that LN patients are extremely exposed to severe infection within the first weeks of therapy and that fatal cases are – alas – not so infrequent, even within the frame of conventional immunosuppressive treatment.

Second, LN trials might have missed their primary endpoint because of poor design. Amongst others, the following criticisms can be raised: (1) wrong definition
<table>
<thead>
<tr>
<th>Reference</th>
<th>Molecule</th>
<th>Mode of action</th>
<th>Trial acronym</th>
<th>Phase Patients, n</th>
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<th>Primary outcome</th>
<th>Conclusions</th>
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<tr>
<td>Rovin et al. [10]</td>
<td>Rituximab</td>
<td>Anti-CD20 B cell depleting mAb</td>
<td>LUNAR</td>
<td>III 144</td>
<td>II/IV</td>
<td>i.v. MP GC MMF</td>
<td>1 g on days 1, 15, 168 and 182</td>
<td>Superior renal response (CR and PR) rate with RTX at week 52</td>
<td>CR+PR rate at week 52 P: 45.8% SD: 56.9%</td>
</tr>
<tr>
<td>Mysler et al. [11]</td>
<td>Ocrelizumab</td>
<td>Fully humanized anti-CD20 B cell depleting mAb</td>
<td>BELONG</td>
<td>III 381</td>
<td>III/IV</td>
<td>i.v. MP GC MMF or EL i.v. CY</td>
<td>400 or 1,000 mg on day 1, week 2, week 16, then q 16 weeks ad week 96</td>
<td>Superior renal response (CR and PR) rate with OCR at week 48</td>
<td>Higher rate of serious infections on MMF background leads to early termination CR+PR rate at week 48 (if ≥32 weeks of Rp) P: 54.7% OCR 400: 56.9% OCR 1,000: 67.1%</td>
</tr>
<tr>
<td>Furie et al. [12]</td>
<td>Abatacept</td>
<td>CTLA-4/Ig fusion protein binding to CD80/86 and inhibiting interactions with CD28</td>
<td>ACCESS</td>
<td>II/III 298</td>
<td>II/IV±V</td>
<td>GC MMF</td>
<td>10/10 group: 10 mg/kg on days 1, 15, 29 and 57 and q month ad 12 months 30/10 group: 30 mg/kg on days 1, 15, 29 and 57; then 10 mg/kg q month ad 12 months</td>
<td>Time to confirmed CR</td>
<td>CR at week 52 P: 8.0% ABA 30/10: 9.1% ABA 10/10: 11.1%</td>
</tr>
<tr>
<td>Frogoso-Loyo et al. [13]</td>
<td>Abatacept</td>
<td>CTLA-4/Ig fusion protein binding to CD80/86 and inhibiting interactions with CD28</td>
<td>ACCESS</td>
<td>II 134</td>
<td>II/IV±V</td>
<td>GC EL i.v. CY followed by AZA</td>
<td>500–1,000 mg at week 0, 2, 4 and then q 4 weeks</td>
<td>CR rate at week 24</td>
<td>CR at week 24 P: 31% ABA: 33%</td>
</tr>
<tr>
<td>Ginzler et al. [14]</td>
<td>Atacicept</td>
<td>Soluble recombinant fusion protein inhibiting BLyS and APRIL</td>
<td>ACCESS</td>
<td>II/III 6</td>
<td>III/IV</td>
<td>GC MMF</td>
<td>150 mg s.c. twice weekly for 4 weeks; then q 4 weeks ad week 52</td>
<td>ALMS response criteria at week 24 (see [33])</td>
<td>ALMS response at week 24 P: 33% LAQ 0.5 mg: 62% LAQ 1.0 mg: 40%</td>
</tr>
<tr>
<td>Jayne et al. [15]</td>
<td>Laquinimod</td>
<td>Antigen-presenting cell modulator; downregulation of proinflammatory cytokines; upregulation of IL-10</td>
<td>ACCESS</td>
<td>IIa 46</td>
<td>IIa</td>
<td>GC MMF</td>
<td>0.5 or 1.0 mg/day</td>
<td>ALMS response criteria at week 24 (see [33])</td>
<td>ALMS response at week 24 P: 33% LAQ 0.5 mg: 62% LAQ 1.0 mg: 40%</td>
</tr>
<tr>
<td>van Vollenhoven et al. [16]</td>
<td>Sirukumab</td>
<td>Anti-IL-6 mAb</td>
<td>ACCESS</td>
<td>II 25</td>
<td>III/IV</td>
<td>GC MMF or AZA</td>
<td>10 mg/kg q 4 weeks ad week 24</td>
<td>% reduction from baseline in proteinuria</td>
<td>P: 43% proteinuria increase SHR 0% proteinuria increase</td>
</tr>
</tbody>
</table>

N = Number of patients; Class = according to ISN/RPS classification; SOC = standard of care; SD = study drug; mAb = monoclonal antibody; i.v. = intravenous; MP = methylprednisolone; GC = glucocorticoids; MMF = mycophenolate mofetil; CR = complete response; PR = partial response; P = placebo; EL = Euro-Lupus; CY = cyclophosphamide; AZA = azathioprine; ALMS = Aspreva Lupus Management Study.
of the primary outcome measure, (2) superiority design required by the medical agencies, (3) too much immunosuppressive comedication (in particular too much GC), (4) statistical power defined on a too ambitious effect (the 11% benefit in favour of RTX in the LUNAR trial did not reach statistical significance, but was within the range of the statistically significant effect of anti-BLyS belimumab in two pivotal nonrenal lupus trials) [18, 19], (5) trial was too short and (6) underestimation of the role of ethnicity, etc. The pivotal importance of choosing the right outcome measure as the primary endpoint has been remarkably illustrated by the reanalysis of the failed BMS ABA LN trial. The very low response rates in each group using the original BMS primary outcome measure [12] led to reanalysis of the data [20]. Using other definitions of renal response, i.e. outcome measures used as primary endpoints in other LN trials, statistically significant and even clinically relevant differences could be unmasked in favor of ABA. The obligation of a superiority design for regulatory purposes is another major reason for ‘failure’. Since no immunosuppressant is currently labelled for LN, a study drug must be shown to be superior to the controlled arm, which is clearly difficult when the comparator is intravenous CY combined to high-dose GC. Rather, a non-inferiority design could also be appropriate and clinically relevant if the trial indicates that the study drug is as good as the control arm but much less toxic. This design was chosen for the RITUXILUP trial, a soon-to-be-running investigator-initiated study, with the hope to demonstrate that LN patients given MMF and RTX will perform as well as patients given MMF and high-dose GC, with less adverse events. Such an approach could position biologics as safer drugs than SOC. That said, the ultimate goal in LN is to prevent renal impairment and renal replacement therapy. Therefore, a new treatment – a fortiori more expensive – should also demonstrate additional efficacy and be validated by a pharmacoeconomic approach. In this respect, the cost of renal replacement therapy is so high that avoidance of only a few cases of end-stage renal disease might be cost-effective in a LN patient population.

The third hypothesis is that some of our educated guesses regarding potential targets are wrong and that the pivotal pathogenic pathways operating in LN have yet to be unraveled. Thus, while the relevance of preclinical lupus models for human LN cannot be overlooked, ‘mice are not merely furry small humans with long tails’, as nicely written by William Stohl in a recent review [21]. It is likely that pathogenic immune mechanisms are at work in LN patients well before the disease becomes clinically detectable, a picture obviously different in murine systemic lupus erythematosus in which very early events can be captured, dissected and targeted. At later (i.e. clinical) stages of the human disease, other molecular pathways may have taken the lead. In this respect, more attention should be paid to the mechanisms leading from reversible immune-mediated inflammation to glomerular and interstitial fibrosis. How the immune system is reconstituted in LN patients after biologic therapy is yet another area of uncertainty, which may be of critical importance for relapses and late outcome. For instance, it is known that serum BLYS levels increase after RTX treatment [22], which might negatively impact the autoimmune repertoire, potentially facilitating renal relapses. The soon to be started CALIBRATE trial (Combination of Antibodies in Lupus Nephritis: Belimumab and Rituximab Assessment of Tolerance and Efficacy) is therefore aimed at testing whether a low-BLYS environment would favour recovery of a nonautoreactive B cell compartment following RTX therapy. Last, but not least, relapses of LN are likely driven by long-lived plasma cells which are not targeted by current immunosuppressive and biologic agents. Proteasome inhibitors have been shown to be efficacious in preclinical models [23], but this approach raises toxicity issues, as autoimmune long-lived plasma cells are unlikely to be specifically targeted by agents like bortezomib.

The Future Might Be Brighter

The preceding paragraphs may make the reader believe that biologics are shooting stars and that the picture is just too sophisticated to see light in the night of biologic therapy in LN. However, the opposite is true, although one should not expect to achieve efficacy in all LN cases with a single wonder drug, because LN is such a complex and pleiotropic disease (compared to rheumatoid arthritis)! There are many reasons for patients, clinicians, investigators and pharma companies to keep the faith. First, we have learned from our mistakes. ‘Old’ drugs, like RTX or ABA, are therefore still studied in LN, with more appropriate designs and outcome measures. Second, at least three LN trials are running: the anti-TWEAK BIIB023 ATLAS trial, the new ABA BMS trial and the anti-BLyS Belimumab LN trial [18, 19]. Other potential LN trials are under discussion, awaiting the results of the corresponding nonrenal trials with anti-CD22 epratuzumab [24], blisibimod (fusion protein between Fc...
portion of IgG and a synthetic peptide sequence that binds to BLYS; PEARL trial) [25], anti-BLYS tabalumab (ILLUMINATE trials) [26], anti-IFNα sifalimumab [27], anti-IFNα AGS-009 [28], anti-IFNα rontalizumab [29], IFNkinoid [30], anti-IFNAR (type I IFN receptor) MED1-546 [31] or rigerimod, an immunomodulating autoantigenic peptide derived from U1-RNP [32]. The third reason for hope is that cooperation among lupologists is more efficient than ever, as demonstrated by the number of investigator-initiated studies in the field of LN, e.g. RITUXILUP, CALIBRATE, RING. Interestingly, these trials were endorsed by the recently launched Lupus Nephritis Trials Network, whose aim is to improve outcomes for LN patients through the conduct of clinical trials designed to prevent chronic kidney disease and the development of clinical trial methodologies that improve and simplify the assessment of therapeutic agents (http://lupusnephritis.org).

Conclusion

While LN trials with biologics have failed so far to reach their primary endpoints, this does not imply that biologic therapy has no place in the bedside armamentarium. Thus, none of us who have successfully treated several desperate LN cases with RTX would hesitate to try the drug in refractory cases, prior to giving up. Hopefully, many other studies, with several ‘first-in-class drugs’, will open new treatment avenues in this threatening disease.

References


