When biologics should be used in systemic lupus erythematosus?

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Summary

Recently, the use and evaluation of biologics increased in systemic lupus erythematosus (SLE). However, no international recommendation is available concerning the use of biologics with regards to the subset of patients who should be treated, the optimal time to treat, the objective of treatment and the manner to discontinue it. To address these complex questions, we focused on biologics already evaluated in at least two published randomized controlled trials. We summarized the results of these trials and available observational data in registries. Taking into account the clinical evidence, we proposed some guidance on the way biologics could be used in SLE. Many areas of uncertainty persist and require intensifying efforts from the academic world to set up new trials, and develop international recommendations.

In 2013, a group of 34 international experts steered by The European League Against Rheumatisms (EULAR) proposed the first recommendations for optimizing the therapeutic strategy in systemic lupus erythematosus (SLE) in a treat-to-target approach [1]. Interestingly, their 11 recommendations did not discuss the conditions of use of biologics in SLE. Three biologics are currently available, abatacept and rituximab which are off-label in SLE, and belimumab, the sole marketed biologic for SLE to date. Many more biologics and other new immunomodulatory drugs are currently evaluated. However, a crucial question remains: when these biologics should be used?

“When” refers to distinct questions: what kind of subset of patients (pattern of clinical manifestations/early or refractory diseases) should be treated with biologics? For what aims:

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to induce, maintain remission, and/or to have a corticosteroid-sparing effect? When to start and when to stop them? [2]. Unfortunately, the answers to these questions cannot be easily extrapolated from observational data, which allow the study of real-life use but prevent any definitive conclusion regarding efficacy. The interpretation of the results of randomized trials, with pre-specified design and strict inclusion/exclusion criteria, is also complex. Therefore, very few recommendations on the use of biologics have been proposed [3–7]. We will summarize the current evidence and controversies on the use of biologics in SLE. We will focus on biologics that have already been evaluated in at least 2 published randomized controlled trials (RCTs).

**Biologics mainly targeting B cells**

**Inhibition of BAFF**

**Belimumab**

This monoclonal antibody against BAFF (B cell activating factor of the TNF family), also termed BlyS-specific inhibitor, is the only approved biologic for the treatment of SLE. BAFF is a crucial cytokine for B, but also T cell activation, and BAFF inhibition results in the depletion of naive, activated B cells, and plasma cells, but not in that of memory B cells or T cells. Two large phase III randomised controlled trials were performed. The study of Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS-52) trial included 865 patients with moderate-to-severe disease and positive ANA and/or antiDNA who were randomised to receive intravenous belimumab 1 or 10 mg/kg or placebo [8]. A higher response rate was observed in belimumab-treated patients. A second trial of very similar design (BLISS-76) was conducted in 819 patients and ran for 76 weeks. At week 52, patients treated with belimumab 10 mg/kg had greater responses than with placebo [9]. The rate of serious infections and cancers in the controlled phase of randomized trials was similar between belimumab and placebo [10,11]. The follow-up open extension phases did not reveal any signal either, but the number of patients and the duration of follow-up are too limited (< 2000 patient/year). Data from registries on tolerance in “real life” are expected soon. The randomized studies evaluated the efficacy of belimumab using new outcome criteria, the SLE Response Index (SRI), which has 3 components: the SLE Disease Activity Index (SLE-DAI) that documents the improvement of overall disease activity, the British Isles Lupus Assessment Group (BILAG) that documents that no domain of the disease worsened and a physician’s global assessment that provides confirmation by clinicians. There has been a great debate on the choice of this novel SRI endpoint, but it should be noted that the SLE-DAI would also have shown a superiority of belimumab over placebo [12]. There was a significant steroid-sparing effect of belimumab in BLISS-52 but not in BLISS-76. Coming back to the optimal target patient population for belimumab, some baseline characteristics of the patients enrolled in these 2 RCTs should be considered: the number of previous conventional immunosuppressants is not mentioned; patients with severe lupus nephropathy or central nervous system (CNS) involvement were excluded; patients had to have a SLEDAI greater or equal to 6 and approximately half of them had a SLEDAI greater or equal to 10; a minority of patients were concomitantly treated with mycophenolate mofetil (MMF); 70% and 44% of patients had a baseline corticosteroid dosage greater than 7.5 mg/d in BLISS-52 and in BLISS-76, respectively. A higher disease activity was associated with a greater difference between belimumab and placebo [13]. No baseline specific biomarker, except high anti-double strand DNA (dsDNA) and low complement, was associated with a better response to belimumab [14]. Of interest, baseline serum BAFF was not a predictor of clinical response. The serum increase of complement levels could already be observed 8 weeks after the initiation of belimumab and represents a predictive factor of good response. Of course, many areas of uncertainty remain, as it is always the case for a new drug. Whether belimumab is best suited to induce or maintain remission, its efficacy on severe lupus nephropathy and CNS involvement, long-term safety, especially in current practice, interest and safety of co-medications such as MMF, will have to be answered by new trials. The approval of belimumab was rather broad and applies to a quite large proportion of patients with SLE (moderate-to-severe lupus with autoantibodies, despite standard therapy). At this time, taking into account the clinical evidence, areas of uncertainty, and the price of the drug, a 6-month trial of belimumab could be proposed to patients with persistently active mucocutaneous and/or musculoskeletal manifestations of SLE, high levels of anti-dsDNA and low complement, requiring a continuing need for corticosteroids (prednisone > 7.5 mg/d) after failure or intolerance of hydroxychloroquine and at least another immunomodulatory drug.

**Atacicept**

Atacicept is a receptor construct that inhibits both BAFF and APRIL. A clinical trial of atacicept with MMF and high dose corticosteroids in lupus nephritis was stopped after the enrolment of 6 patients due to 3 hypogammaglobulinemias and 2 pneumonias in 4 patients. Actually, the decrease of serum IgG had already started before atacicept was initiated and could be related to severe nephrotic syndrome in these patients [15]. In a trial evaluating the efficacy of 2 doses (75 and 150 mg twice weekly) of atacicept for the prevention of flares, the primary endpoint was not met in the atacicept 75 mg arm compared with placebo. Treatment was discontinued after the enrolment of 145 patients in the 150 mg arm due to 2 fatal infections (pneumococcus and leptospirosis) but ad-hoc...
analyses showed a reduced risk of SLE flares and increased time to flare [16]. Atacicept caused declines in IgG, IgA and IgM, as well as in naïve and memory B cells. A trial is currently recruiting patients to evaluate the superiority of atacicept 75 or 150 mg, once weekly, over placebo at week 24, using the SRI as primary outcome.

**Other BAFF**
The interest, other BAFF inhibitors are currently evaluated in SLE, such as blisibimod, a peptibody, and tabalumab, a monoclonal antibody that targets both membrane-bound and soluble BAFF.

**B cell depletion**

**Rituximab**
A persistent controversy remains within the medical community concerning the use of rituximab in SLE, given the discrepancy between the negative results of rituximab (RTX) in 2 large controlled studies [17,18] and the abundant observational data suggesting its efficacy. Three different approaches have been considered for the use of RTX in SLE: RTX as an add-on therapy for the induction of remission, evaluated in the 2 randomized controlled studies, RTX included in a corticosteroid-minimal (or corticosteroid-free) regimen analyzed in open studies, and RTX for corticosteroid-dependent and/or refractory subsets of the disease. The two controlled studies concerned lupus nephritis (the LUNAR study, in newly diagnosed or newly relapsed lupus nephritis, as an add-on therapy to MMF and high dose of corticosteroids) and patients with other manifestations of SLE (the EXPLORER study, in which RTX was prescribed as an add-on therapy superimposed to high doses of corticosteroids). Although RTX may truly be ineffective in SLE, there is still a great debate on the reasons why the controlled trials failed to confirm observational data. The reasons reviewed [19] include, among others:

- design of these 2 trials: inclusion criteria (non-refractory patients), insufficient statistical power based on very ambitious effect of RTX (the randomized difference between the treatment and control groups in LUNAR was comparable with that observed in the belimumab trials [12,20]), co-medications (high dose of corticosteroids), MMF instead of cyclophosphamide, this latter when associated to RTX being associated with a higher response than MMF in a systemic review of literature [21], the time frame (primary outcome at 52 weeks) maybe too early for lupus nephritis;
- immunological explanations, since, for instance, B cell depletion can be harder to achieve in SLE than in rheumatoid arthritis.

RING, a European-based randomized controlled trial, has started in 2013 to evaluate the interest of RTX in refractory lupus nephritis, for patients with partial response to induction therapy or patients with grumbling disease despite standard of care [22].

Another very relevant potential interest of RTX could be an early use to minimize oral steroids, which is the main cause of damage in SLE [23]. Three open studies suggested that an early use of RTX might be effective and might allow reducing the burden of steroids [24–26]. A randomized trial entitled RITUXILUP is expected to begin and will compare oral corticosteroid to RTX on a background therapy of MMF plus 2 pulses of methylprednisolone. RING and RITUXILUP demonstrate that clinicians remain confident that RTX might demonstrate its efficacy in SLE. This strong belief is related to the numerous reports on the broad utility of RTX [19] albeit in open-label studies, with very heterogeneous designs. In observational studies, RTX was mainly used for refractory and/or corticosteroid-pendent patients. In our experience [27] and in the Autoimmunity and Rituximab Registry [28], more than 75% of the 136 patients had received at least 2 previous immunosuppressants and required high doses of corticosteroids (greater than 20 mg/d of prednisone). Half of the patients were treated without any other immunomodulatory drug than hydroxychloroquine. The rate of serious infections was 6.6/100 patient/years. Overall, a response (defined as a reduction in the SELENA–SLEDAI score ≥3) was observed in 71% of patients, along with a corticosteroid-sparing effect. RTX was notably effective on articular and renal involvement as well as on autoimmune cytopenia.

For clinicians in a practice setting where off-label use of RTX is possible, it would seem reasonable to consider this option in patients with lupus nephritis who have failed conventional therapy (cyclophosphamide and/or MMF [3,4,29]), and in patients with severe lupus manifestations despite standard of care, including severe CNS involvement, refractory autoimmune cytopenia and refractory arthritis [3]. For refractory arthritis, we would suggest the use of RTX only in patients requiring persistent and high dose corticosteroid therapy after failure or intolerance of hydroxychloroquine and at least another immunomodulatory drug.

**Ocrelizumab**
Another anti-CD20 monoclonal antibody, ocrelizumab, was studied in lupus nephritis with background MMF or EUROLUPUS regime (cyclophosphamide 500 mg × 6 then azathioprine) but the trial was stopped early due to an imbalance in the rate of serious infections in patients treated with ocrelizumab and MMF. In a subgroup analysis, there was a greater treatment effect of ocrelizumab when combined with the EUROLUPUS (cyclophosphamide) regime [30].

**Anti-CD22 monoclonal antibody: epratuzumab**
Epratuzumab is a humanized monoclonal antibody targeting CD22, a transmembrane protein expressed on mature B cells that influences migration and activation. The mechanism of action of epratuzumab is not fully elucidated yet, but it selectively inhibits B cell activation by inducing CD22 internalisation.

Epratuzumab was first evaluated in 2 RCTs in which patients received standard of care plus epratuzumab (360 or 720 mg/m²) or placebo in 12-week cycles for up to 48 weeks (ALLEViate-1 and -2 studies). These two trials, which enrolled an overall population of 90 patients, which were discontinued prematurely because of interruption in drug supply [31], showed lower BILAG scores at week 48. The EMBLEM phase IIb trial evaluated the efficacy of 5 regimes of epratuzumab in moderate-to-severe lupus (excluding severe CNS or renal manifestations). The primary outcome, evaluated at 12 weeks, was a novel composite primary endpoint, the BILAG-based Combined Lupus Assessment (BICLA). A significant clinical improvement was observed in patients who received a cumulative dose of 2400 mg (600 mg weekly or 1200 mg every other week). No safety signal was observed. Epratuzumab induced only a partial reduction in B cell levels, without decreases in immunoglobulin levels [32]. Two large phase III RCTs are ongoing, expected to include an overall population of more than 1500 patients with moderate-to-severe disease activity, and no severe renal or CNS involvement.

**Abatacept**

Abatacept is a selective T cell co-stimulation modulator that binds to CD80 and CD86, expressed on antigen-presenting cells, and thereby blocking its interaction with CD28, expressed on T cells, modulating T cell activation. Abatacept was evaluated in three RCTs, two of them concerning lupus nephritis, one of them other lupus manifestations, and the results of the three trials were all negative. In the non-renal trial [33], inclusion criteria required a flare in one of the three organ systems: mucocutaneous, musculoskeletal or serositis. The patients were all started on prednisone (30 mg/d), and were randomised to receive abatacept or placebo. The primary outcome was the proportion of patients who flared following tapering of glucocorticoids. After 1 year, around 80% of patients had flared in both groups. Severe flares (defined as a new BILAG A) were somewhat less frequent in the abatacept group (41% versus 55%), and several patient-reported outcomes were significantly better with abatacept. The limitations of this trial include the high dose of steroids used and the known poor agreement between experts on mild/moderate flares. In the first trial of abatacept in lupus nephritis, abatacept (10 or 30 mg/kg) was added to MMF and high dose of steroids [34]. There was no significant difference with regards to time to complete renal remission, the primary outcome of the trial. However, the definition of complete remission was rather restrictive, and a reanalysis using several other definitions of complete or partial renal response was therefore performed [35]. Interestingly, when applying the definition of response used in the LUNAR trial of rituximab, a response rate was achieved in the abatacept group in more than 20% of patients versus only 6% in placebo. Thus, the results of the 3d RCT of abatacept (the ACCESS trial) in lupus nephritis were eagerly awaited, all the more as abatacept was evaluated on an Euro-Lupus background including intravenous cyclophosphamide [36]. The complete remission rate at 6 months was similar in the abatacept and in the placebo group. Blinded evaluations at later time points are still ongoing. Of note, and converse to rituximab, very little observational information is available regarding the efficacy of abatacept in real life. To date, the literature does not support the use of abatacept in lupus, although its use could be perhaps proposed after failure of belimumab in patients with severe lupus-related arthritis requiring high dose of steroids.

**Conclusions**

Recently, the use and evaluation of biologics increased in SLE. Numerous other biologics, including inhibitors of interferon signaling [37] and other new immunomodulatory drugs or therapeutic vaccines [38] are currently evaluated. Previous clinical trials emphasized both the potentials and pitfalls in the development of biologics. Many areas of uncertainty persist and require intensifying efforts from the academic world to set up new trials, as proposed by an academic-based network, called the Lupus Nephritis Trial Network.

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**References**

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