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# New drugs in systemic lupus erythematosus: when to start and when to stop

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## ABSTRACT

*Survival of patients with systemic lupus erythematosus (SLE) has greatly improved compared to earlier decades. However, this improvement appears to have reached a plateau. In addition, damage accrual appears to have an important impact on patient prognosis. In this scenario a number of new drugs targeting different pathways of the immune response are being developed, and some are already available in clinical practice. In clinical practice and in clinical trials, the indications for treating SLE patients with new drugs are active or refractory disease despite standard-of-care treatment. While RCTs are able to document the capacity of new drugs to control the disease in selected patients, many important questions arise from clinical practice and at present are largely unanswered. When should we start a new drug? Should this drug be introduced early, as are anti-TNF drugs in rheumatoid arthritis? Perhaps some drugs should be initiated only after a patient's incomplete response? How many traditional drugs should be used and for how long, before considering a new therapy? Should we stop an effective drug and if yes, when and how?*

*Additional studies and data derived from registries and observational studies will give valuable evidence to answer these questions. In this article, we review indications for the use of new drugs in SLE, and examine existing data on patient outcome after withdrawal, focusing our attention on rituximab and belimumab.*

## Introduction

A number of variables such as early diagnosis, improved monitoring, optimisation of therapeutic protocols and management have led to great improvements in the survival of patients with systemic lupus erythematosus (SLE) compared to earlier decades (1-5). However, this

improvement appears to have reached a plateau as no significant changes in patient survival have been observed over the past 2 decades. Patients with SLE continue to have a mortality risk greater than three times higher than the general population (1, 2). Damage accrual, particularly neuropsychiatric and renal damage, as well as other factors such as cardiovascular diseases (CAD), appear to have an important impact on patient survival (2, 6).

## Unmet needs in SLE treatment

The reduction of long term mortality, optimised control of disease activity, reduction of damage and minimisation of use and dosage of glucocorticoid (GC) therapy have been identified, among others, as targets for the treatment of SLE (7). However, with currently available protocols, complete remission of disease activity is relatively rare – reported in 25–30% of patients, or fewer if clinical and serological remission are considered (8-13). On the contrary, the majority of patients experience either chronically active disease or disease flares. Similarly, damage accrual remains. In the SLICC inception cohort, for example, damage accrual during the first 5 years of disease has been described in about 50% of patients, mostly related to GC therapy (14). Recent data show that the incidence of end-stage renal disease (ESRD) due to lupus nephritis remained unchanged between 1999 and 2004 (15). Finally, despite the correlation between the cumulative GC dose and damage accrual, GC are still used in the long-term treatment of SLE patients, and only few attempts to guide the treating physician in their tapering or withdrawal have been published (16-18).

These data highlight the limits of existing therapeutic options used to control SLE. In this scenario, a number of new drugs targeting different pathways of the immune response are being devel-

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oped, and some are already available in clinical practice.

In this article, we review indications for the use of new drugs in SLE, and examine existing data concerning patient outcome after withdrawal. We have focused on rituximab and belimumab, as the majority of data are available concerning the use of these two drugs, both from randomised controlled trials (RCT) as well as from clinical practice.

### **New drugs in the treatment of SLE** *Rituximab and SLE*

The first reports concerning the use of rituximab (RTX) in the treatment of SLE were case reports and small series in which the drug had been used for the treatment of patients with severe organ involvement refractory to traditional drugs. Over the past 10 years, clinical evidence has accumulated supporting the efficacy of RTX in the treatment of SLE (19-28). However, two large randomised studies aimed at assessing the efficacy of RTX in the treatment of moderate-to-severe SLE (29) and lupus nephritis (30) have failed to reach their primary end point.

At present, from the existing literature, we can derive that RTX has been used to treat active refractory patients, *i.e.* patients with active disease despite treatment with immunosuppressive drugs (31, 32).

Disease activity was treated both as persistent disease activity as well as disease flare and in the different reports is assessed with validated indices as well as physician judgment. The most common types of organ involvement treated with RTX were kidney, central nervous system (CNS), articular, and haematological.

The majority of patients had been treated previously with GC, antimalarial drugs and at least one immunosuppressive drug, although about half of the patients had incomplete responses to at least two immunosuppressive drugs. In some cases, RTX was used because of intolerance to traditional drugs, particularly cyclophosphamide. Recently, data have been reported concerning the treatment of 50 patients with lupus nephritis with a steroid-avoiding protocol (Rituxilup), suggesting that chronic

treatment with steroids could be avoided in patients treated with mycophenolate mofetil and RTX. If these data are confirmed, RTX could represent an important option to spare GC in lupus nephritis (33).

Thus, data concerning the use of RTX for SLE are still incomplete; even fewer data are available on the disease course after treatment withdrawal or on a maintenance protocol.

A recent systematic literature review (26) has shown that up to 30% of patients treated with RTX relapse, a mean of 12 months after drug administration. Some authors have suggested the existence of a correlation between B cell reconstitution and disease flares (20, 23, 24).

In the largest series published so far, some patients have been re-treated mainly for disease flares (21, 22). Re-treatment was associated with a good response and safety profile. Therefore, it has been suggested that a maintenance protocol could be developed, with infusions independent from the occurrence of flares. However, no data are available on this aspect to support any choice in clinical practice. Furthermore, although some studies may suggest a correlation between the absolute number of CD19<sup>+</sup> lymphocytes at the baseline and clinical response (23), little information is available concerning predictive factors for relapse that could guide the decision to repeat the treatment or withdraw the treatment. Since the long-term effects of B-cell depletion are not known, and in many patients disease control is stable, it may be suggested that after the first treatment with RTX patients should be followed and monitored for disease activity/flares, to define accordingly if, when, and how there is a need to be re-treated.

### *Belimumab and SLE*

Belimumab is a fully human monoclonal antibody against soluble B-lymphocyte stimulator (BLyS). Based on two large phase III trials results (BLISS-52 and BLISS-76), belimumab has been approved for the treatment of SLE patients with active disease (34-36).

To enter the phase II trial patients were required to meet the ACR criteria for

SLE, have active disease defined by a validated index (SELENA SLEDAI >4), have autoantibodies (also by history) and be taking stable standard-of-care medication for the previous 60 days. These criteria were changed for enrollment in the phase III trial, in which a higher level of disease activity was required (SELENA SLEDAI >6), along with the presence of autoantibodies at screening and a stable standard of care for 30 days before study entry.

A pooled analysis of BLISS-52 and BLISS-76 has shown that factors associated with a better response were higher disease activity, anti-dsDNA positivity, low complement and glucocorticoid therapy. BLISS studies were not designed to define which type of organ involvement would benefit most from this therapy. However, analyses indicated a significant effect for the musculoskeletal and the mucocutaneous domains of both BILAG and SELENA SLEDAI indices (37, 38).

Finally, a reduction in GC dose to  $\leq 7.5$  mg/day (for patients who were on a higher dose at baseline) after 52 weeks was obtained in more patients treated with belimumab; therefore the drug appears to have a steroid-sparing effect.

However, based on inclusion criteria of belimumab RCTs, it is difficult to define when and for whom this drug should be introduced in clinical practice. For example, should belimumab be used only after incomplete response to GC and anti-malarials, or at least one immunosuppressive drug?

We may summarise that available data support the use of belimumab in patients with high disease activity, positive autoantibodies and low complement, in particular in patients with mucocutaneous and articular manifestations.

However, treatment with belimumab might also be considered (i) when disease activity is controlled but patient is receiving a GC dose >7.5 mg/day prednisone or equivalent; (ii) when the use of traditional immunosuppressive drugs is limited by the risk of interaction with additional therapies (*e.g.* anticoagulants and antiepileptic drugs; (iii) in patients with damage and/or intolerance to traditional immunosuppressive drugs (39-43).

No data are available on the use of belimumab in patients with severe active kidney and neurological involvement. Considering the time to response that was observed in the BLISS trials it appears reasonable to continue for at least 26 weeks before withdrawing the treatment for inefficacy, but because the primary outcomes in the trials were measured at 52 weeks some physicians feel that a trial with belimumab could be continued for a full year in selected patients

Finally, no data are available to suggest optimal duration of treatment in responsive patients and a possible tapering strategy.

#### Other biological agents

A number of biological agents are under evaluation in renal and non-renal SLE for their capacity to control disease activity in patients with inadequate response to standard of care (44, 45).

#### Summary

In clinical practice and in clinical trials, new agents are available to treat SLE patients who have active or refractory disease despite standard of care.

While RCTs can document the capacity of new agents to control the disease in selected patients, many important questions arise from clinical practice and at present remain largely unanswered. When should we start a new drug? Should this drug be introduced early, as are anti-TNF drugs in rheumatoid arthritis, or only after documentation that a patient is refractory? How many traditional drugs should be used and for how long, before considering a new therapy? Should we stop an effective drug and if yes, when and how?

Additional studies and data derived from registries and observational studies will provide important information to help answer these questions.

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