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Review

Upcoming biological therapies in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition with unpredictable course, intermingled with flares and periods of remission. Although the prognosis of the disease has improved in the past decades, current therapies are still associated with treatment-related complications. Recently, there has been major progress in the understanding of the pathogenesis of SLE, paving the way for the development of new biological agents, potentially revolutionizing the treatment of SLE.

This review summarizes available data on novel biological therapies for SLE, focusing on recent results from clinical trials.

As a result of treatment strategies based upon an individualized therapeutic approach, it is hoped that the clinical view of SLE will change from a severe autoimmune disease to a condition in which significant damage, mortality and treatment related complications can be prevented in the majority of SLE patients.

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition heterogeneous from clinical and immunological point of view, with variable and unpredictable course, intermingled with periods of flares and remission. For decades, the therapy for SLE has been based on glucocorticosteroids, hydroxychloroquine, and immunosuppressive agents [1]. These approaches have been related to a remarkable

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improvement in the prognosis of SLE. However, the occurrence of refractory disease and adverse effects related to conventional therapies such as glucocorticoids and cytotoxic agents still represent a challenge for physicians, requiring the development of more efficacious treatments with a higher safety profile in SLE.

Rituximab and, more recently, belimumab are the most extensively used biological agents in SLE.

Although the results of two randomized controlled trials suggest that the use of rituximab in SLE may be controversial, it is still extensively used "off label", especially in refractory cases to standard treatment. Belimumab has been the first biological agent approved by the Food and Drug agency (FDA) for the treatment of active SLE in addition to standard of care [1,2]. Despite the initial enthusiasm related to the approval of a tailored approach for SLE treatment, there are still uncertainties on the selection of the ideal patient that might benefit from this agent and the optimal duration of therapy [3,4].

In the last years, an increasing number of new biological therapies have been tested in SLE with heterogeneous results.

The current goal of development of novel biological agents for SLE is to identify therapies that are potentially more effective than conventional approaches and at the same time are able to reduce the risk of organ damage and therapy-induced side effects. This review summarizes available data on novel upcoming biological therapies for SLE, beyond rituximab and belimumab, focusing on recent results from clinical trials (Table 1).

1.1. B-cell targeted therapies

B cells can be selectively targeted for depletion either via direct B cell surface molecules such as CD19 and CD20 (rituximab and ocrelizumab) and CD22 (Epratuzumab) or by inhibition of B cell survival factors BLyS (belimumab) and APRIL (atacicept) [3].

It is out of the scope of this review to explore the clinical efficacy of rituximab in SLE since this has been extensively discussed elsewhere [5]. However, this topic is worthy of some considerations.

The use of rituximab in patients with SLE has been investigated in two randomized controlled trials, EXPLORER (the exploratory Phase II/III SLE evaluation of rituximab) [6] and LUNAR (lupus nephritis assessment with rituximab) [7] with negative results regarding superiority to conventional treatment. However, before concluding that rituximab is not effective in SLE, a critical evaluation of the design of the EXPLORER and LUNAR trials is required. Firstly, a high percentage of patients included were likely to have had mild to moderate SLE (especially in the EXPLORER trial) with no history of poor response to conventional therapies. This fact, in itself, may potentially justify why rituximab was not superior to the other therapies in this setting.

Secondly, considering concomitant therapies, we allowed very high doses of corticosteroids in both arms of these trials, leading to significant differences not being evident in a short-term follow-up. Thirdly, some authors have speculated a possible synergistic effect of rituximab in combination with immunosuppressive agents (cyclophosphamide or mycophenolate) [8] but this aspect was not analyzed in these RCTs. Fourthly, LUNAR and EXPLORE included different subsets of patients (mainly North and Central-South American patients) when compared to the majority of patients from uncontrolled studies (European). This observation about ethnicity might be considered as a variable therapeutic response to the different immunosuppressive agents [9].

Finally, and most importantly, aiming to prove the superiority of rituximab over current first-line therapies in SLE (corticosteroids, cyclophosphamide, and mycophenolate) does not reflect the use of rituximab in clinical practice, where rituximab is mainly considered in refractory cases to these therapies.

1.1.1. Ocrelizumab

Ocrelizumab is a humanized anti-CD20 monoclonal antibody. When compared to rituximab, ocrelizumab may have a safer profile in terms of immunogenicity and complement activation, theoretically leading to a reduced frequency of adverse infusion reactions and the development of drug neutralizing antibodies.

BEGIN and renal BELONG are two Phase III RCTs investigating the efficacy of ocrelizumab in non-renal SLE and renal SLE respectively [10]. Ocrelizumab was given at different doses (400 or 1000 mg intravenously) on day 1 and day 15.

A repeat single dosing was administered every 4 months. The BEGIN study was interrupted early when the decision was made that ocrelizumab was not likely to benefit patients with active SLE. In the BELONG study, a total of 381 patients were recruited to investigate the efficacy of ocrelizumab in patients with proliferative lupus nephritis (class III/IV) on top of high-dose glucocorticoids and either MMF or CYC (according to the Euro-lupus protocol). The trial was terminated early because of the higher rate of serious infections in patients receiving ocrelizumab compared to placebo (mainly in those receiving ocrelizumab and MMF). However, in patients who had passed the 32-week treatment point (223/381), the overall renal response in the ocrelizumab arm was (67%) not significantly higher than that of placebo (67% vs. 55%) [11].

1.2. Anti-CD22

1.2.1. Epratuzumab

Epratuzumab is a humanized monoclonal antibody targeting the CD22 surface receptor on mature B cells [12].

Two randomized placebo-controlled trials (ALLIVIATE 1 and ALLIVIATE 2, 14 and 90 recruited patients, respectively) investigating the use of epratuzumab in addition to the standard of care in SLE patients with moderate to severe activity reported a clinical improvement compared to placebo [13]. Epratuzumab was well tolerated without severe adverse events. However, these studies were terminated because of the disruption of drug supply [14].

Subsequently, ENBLEM, a more recent Phase IIb RCT (trial not powered for significance) including 227 SLE patients with moderate to severe disease activity (excluding severe neuropsychiatric and renal disease) showed that the proportion of responders was higher in all epratuzumab groups than in the placebo group. A post hoc analyses showed that a cumulative dose of 2400 mg of epratuzumab was associated with a significantly clinical improvement. The frequencies of AEs and SAEs, including infusion reactions, were not different across all groups of patients [15].

These promising results have led to two Phase III RCTs (EMBODY 1 and 2), aiming to investigate the clinical efficacy of epratuzumab in

Table 1
Novel biological therapies for systemic lupus erythematosus.

Mechanism	Agent
Targeting surface molecules on B cells	Ocrelizumab (fully humanized anti-CD20)
	Epratuzumab (fully humanized anti-CD22)
Targeting B cell growth and survival factors	Atacicept
	Blisibimod
	Tabalumab
Toleragen molecule	Abetimus sodium
Proteasome inhibition	Bortezomib
Targeting co-stimulatory molecules	AMG 557 (against B7RP-1, an inducible co-stimulator ligand)
Targeting T cells	Edratide
	Rigerimod
	Laquinimod
Targeting cytokines — IL 6	Tocilizumab
	Sirukumab
Targeting cytokines — type I interferons	Sifalimumab
	Rontalizumab

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