Joint Bone Spine 84 (2017) 267–274

Available online at ScienceDirect www.sciencedirect.com

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Review

Biotherapies in systemic lupus erythematosus: New targets

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ARTICLE INFO

Article history:
Accepted 10 June 2016
Available online 21 September 2016

Keywords:
Biotherapies
Systemic lupus erythematosus
Interferon
Glucocorticoids

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease with a polymorphic presentation. The variability in the clinical expression and severity of SLE makes new treatments both essential and challenging to develop. Several biotherapies targeting different pathophysiological pathways have been developed over the past 15 years. The results of Phase II trials were encouraging but rarely borne out by Phase III trials. Recent data, which are discussed in detail in this review, allowed belimumab – a monoclonal antibody against BLyS (B-lymphocyte stimulator) – to become the first biotherapy approved for use in SLE. Other molecules targeting B cells include the two anti-BLyS antibodies tabalumab and blisibimod; atacicept, which targets both BLyS and APRIL (a proliferation-inducing ligand); and the monoclonal antibody to CD22 epratuzumab. The rekindling of interest in the B-cell pathway has also driven new clinical research into rituximab, a monoclonal antibody targeting CD20 with evaluations of new strategies. A new and promising approach is the use of inhibitors of the type 1 interferon (IFN) pathway, of which the most promising is anifrolumab, a monoclonal antibody targeting the type 1 IFN receptor. In this review, we discuss study findings and their clinical relevance, present the most promising targets, and analyze possible explanations to negative results, such as inappropriate patient selection and treatment response criteria or the erratic use of high-dose glucocorticoid therapy.

Many biotherapies have been developed for systemic lupus erythematosus (SLE) in recent years. Although drugs aimed at numerous targets have been assessed, few produced a significant difference in the primary outcome measure. Belimumab is one of these exceptions but is rarely prescribed, as its clinical effect is considered modest (albeit significant) and its cost high [1].

This article is a review of biotherapies developed for SLE. It is based mainly on the Phase II and Phase III studies indexed in PubMed, the abstracts of EULAR and ACR meetings, and ongoing trials registered on clinicaltrials.gov. The data retrieved by the literature search are recapitulated in , Table S1 (See the supplementary material associated with this article online). Fig. 1 provides an overview of the treatment targets.

1. Bleak beginnings: a string of failures in the early 21st century

1.1. Is the B cell a wrong target?

Rituximab was initially developed as a treatment for B-cell malignancies. Rituximab is a chimeric human monoclonal antibody that selectively targets CD20+ B cells and causes their depletion. Possible benefits in autoimmune disorders were rapidly suggested, and two double-blind randomized trials were performed, EXPLORER in patients with SLE but no active renal or neurological disease [2] and LUNAR in patients with lupus nephritis [3] (Table 1). EXPLORER included 257 patients, most of whom had skin and joint involvement, with high disease activity (British Isles Lupus Assessment Group Index [BILAG] A score in at least one domain) or moderate disease activity (BILAG B score in at least two domains). The primary outcome was a composite clinical response score based on the BILAG. Patients were randomized to receive rituximab or placebo in addition to their usual treatment and to high-dose prednisone for the first 10 weeks [2]. In LUNAR, 144

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http://dx.doi.org/10.1016/j.jbspin.2016.07.004
1297-319X/

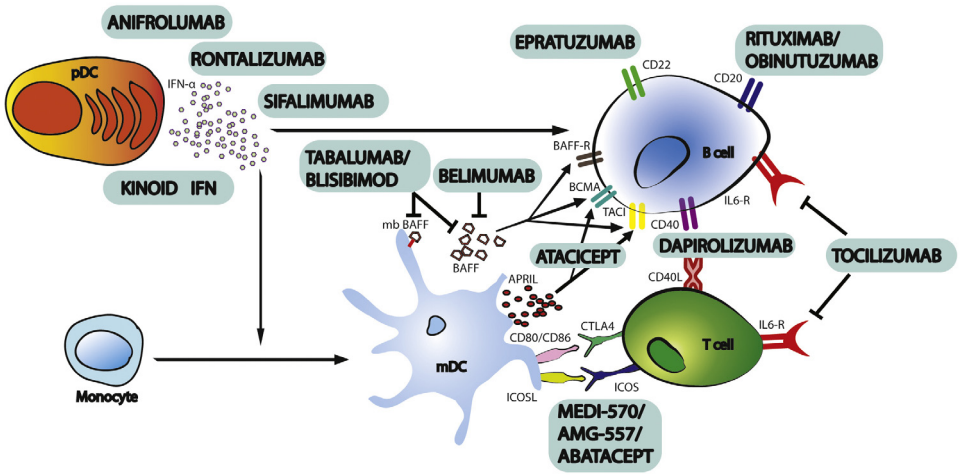

Fig. 1. Pathogenesis of systemic lupus erythematosus and treatment targets that have been or are being evaluated.

patients with class III or IV lupus nephritis were randomized to rituximab or placebo in addition to mycophenolate mofetil and prednisone. Complete or partial remission of the kidney disease was the primary outcome [3]. In neither trial was the primary outcome achieved.

Another drug targeting CD20, ocrelizumab, was assessed during the same period. Ocrelizumab is a fully humanized monoclonal antibody. Encouraging findings from a Phase II trial (BEGIN) [4] prompted a Phase III trial (BELONG) in patients with lupus nephritis [5]. This trial was discontinued prematurely because of severe infectious side effects, and the development of ocrelizumab for SLE was stopped.

1.2. Co-stimulation pathways: unexpected adverse events

Co-stimulation pathways contribute to activate autoreactive T cells. Among them, the CD40-CD40L and B7-CD28 pathways may hold promise as treatment targets in SLE. Two monoclonal antibodies to CD40L have been evaluated in SLE, ruplizumab and toralizumab. Ruplizumab [6] was evaluated in a Phase II study in patients with lupus nephritis. This drug reduced anti-double-stranded (anti-dsDNA), suggesting an immunomodulatory action. However, the study was stopped prematurely after 2 patients experienced myocardial infarction. Toralizumab was also associated with thromboembolic events, and the development of both molecules was stopped [7].

Abatacept is a fusion protein composed of an IgG1 Fc fragment and CTLA4. Abatacept binds to B7 with high affinity, thus blocking the B7–B28 co-stimulation pathway. A controlled double-blinded Phase IIb trial included 118 patients with SLE, no renal or neurological involvement, and a score A or B on at least one BILAG domain [8]. The primary outcome was the proportion of patients with a new flare, defined as a BILAG A or B score on an additional domain, during the treatment year. Abatacept was not superior over standard treatment (Table 2). However, a subgroup analysis showed that abatacept was effective in patients with predominant joint manifestations (proportion of patients with new flares during the treatment year, 57.1% with abatacept and 84.4 % with standard treatment). Two trials evaluated abatacept in lupus nephritis. In the Phase II ACCESS trial, patients received abatacept induction therapy as an adjunct to glucocorticoid therapy and low-dose cyclophosphamide (EURO lupus regimen), followed by maintenance azathioprine therapy [9]. In the other trial, abatacept was combined with a glucocorticoid and mycophenolate mofetil [10]. In neither trial was abatacept superior over the control treatment in lupus nephritis (Table 2). The efficacy outcomes used should, however, be considered when interpreting these findings. Thus, post hoc analyses showed that abatacept was more effective than the control

Table 1
Efficacy of biotherapies targeting CD20 and CD22 in systemic lupus erythematosus.

Name of the biotherapy	Treatment regimen Number (n) of patients per arm	Primary outcome
Rituximab (LUNAR) [3]	IV injection of 1000 mg on D1-D15-D168-D182 Placebo: $n = 72$ Rituximab: $n = 72$	No difference in complete or partial renal remission rate at W52 between the placebo arm and rituximab arm (45.8% versus 56.9%, respectively, for the global response; $P = 0.18$)
Rituximab (EXPLORER) [2]	IV injection of 1000 mg on D1-D15-D168-D182 Placebo: $n = 88$ Rituximab: $n = 169$	No difference in clinical response rate assessed using the BILAG at W52 between the placebo (28.4%) and rituximab (29.6%) ($P > 0.05$)
Ocrelizumab (BELONG) [5]	IV injection on D1 and D15, then W16, then every 16 weeks Placebo: $n = 125$ Ocrelizumab 400 mg: $n = 126$ Ocrelizumab 1000 mg: $n = 127$	No significant difference in global renal response at W48 between the placebo arm and the ocrelizumab 400 and 1000 mg arms (54.7, 66.7, and 67.1%, respectively)
Epratuzumab (EMBODY-1) [36]	12-week treatment cycles; 4 cycles Placebo: $n = 266$ 600 mg on W0, W1, W2, and W3 of each cycle: $n = 265$ 1200 mg on W0 and W2 of each cycle: $n = 262$	No difference in the BICLA response at W48 between the placebo (34.1%), epratuzumab 600 mg (37.5%), and epratuzumab 1200 mg (39.8%) ($P > 0.05$)
Epratuzumab (EMBODY-2) [36]	12-week treatment cycles; 4 cycles Placebo: $n = 263$ 600 mg on W0, W1, W2, and W3 of each cycle: $n = 266$ 1200 mg on W0 and W2 of each cycle: $n = 262$	No difference in the BICLA response at W48 between the placebo (33.5%), epratuzumab 600 mg (35.2%), and epratuzumab 1200 mg (34.1%) ($P > 0.05$)

IV: intravenous; SC: subcutaneous; D: day; W: week; BILAG: British Isles Lupus Assessment Group; SRI: Systemic lupus Responder Index; BICLA: BILAG-Based Composite Lupus Assessment.