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Review

The 2018 pipeline of targeted therapies under clinical development for Systemic Lupus Erythematosus: a systematic review of trials

Renaud Felten[a], Elida Dervovic[b], François Chasset[c], Jacques-Eric Gottenberg[a], Jean Sibilia[d], Florence Scher[b], Laurent Arnaud[d,*]

[a] Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, RESO, Laboratoire d'Immunopathologie et de Chimie Thérapeutique, Institut de Biologie Moléculaire et Cellulaire (IBMC), CNRS UPR3572, France
[b] Service de Pharmacie-Stérilisation, Hôpitaux Universitaires de Strasbourg, France
[c] Sorbonne Université, Faculté de Médecine Sorbonne Université, AP-HP, Service de Dermatologie et Allergologie, Hôpital Tenon, F-75020 Paris, France
[d] Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, INSERM UMR_S1109, RESO, Université de Strasbourg, F-67000 Strasbourg, France

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ABSTRACT

Currently, Systemic Lupus Erythematosus (SLE) therapies range from antimalarials to glucocorticoids, in addition to immunosupressive agents or biologics such as rituximab or belimumab, when needed. Several unmet needs remain in the treatment SLE and more targeted drugs with improved safety profiles are expected. Based on recent advances in the understanding of the complex pathogenesis of SLE, several targeted treatments are currently assessed in clinical trials. In this study, we performed a systematic review of all targeted therapies under clinical development in SLE in 17 online registries of clinical trials. The search yielded a total of 1140 trials, from which we identified 74 targeted therapies for SLE. Those treatments target inflammatory cytokines, chemokines, or their receptors (n = 17), B cells or plasma cells (n = 17), intracellular signalling pathways (n = 10), T/B cells costimulation molecules (n = 8), interferons (n = 7), plasmacytoid dendritic cells (pDC) (n = 3), as well as various other targets (n = 12). Not all these candidate drugs will reach phase III, but the broad spectrum of drugs being investigated may satisfy the urgent need for improved lupus medications. The identification of biomarkers that would allow adequate prediction of response-to-therapy remains high, but when solved will allow a more rationale selection of the optimal pharmacological agent at the patient level.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a complex systemic autoimmune disease characterized by a wide spectrum of clinical, laboratory and immunological abnormalities and a variable course and outcome. Its overall incidence ranges from approximately 0.3 to 23.7 per 100,000 persons per year and its prevalence from 6.5 to 178.0 per 100,000 [1]. The pathogenesis of SLE is complex (Fig. 1) and not fully elucidated, but the disease has been recognized as the result of an interplay between immunological, genetic and environmental factors [2–4]. A characteristic feature of SLE is the production of autoantibodies to nuclear antigens [5], which form immune complexes and can deposit in various tissues and organs and activate the complement pathways. This leads to inflammation and tissue damage. Significant advances in our understanding of the molecular basis of innate immunity have led to identification of interferons (IFNs) and particularly IFN-α, as a central mediator in the pathogenesis of SLE [6]. However, only 50% to 75% of SLE patients express a high-interferon signature [7,8], and the broad spectrum of specific manifestations requires a customized approach to its management. Currently, SLE therapies range from antimalarials, which are recommended in all SLE patients, to nonsteroidal anti-inflammatory drugs, glucocorticoids, sometimes in addition to one or a combination of conventional immunosupressive agents, or more recently to biologics such as belimumab (which has been approved by FDA and EMA in 2011) or rituximab (off-label). However, several unmet needs remain for the treatment of SLE, and the medical community is avid for more targeted treatments along with improved safety profiles. In this context, many pharmaceutical companies have at least one candidate drug in the clinical development pipeline. The purpose of this systematic review is to provide the reader with an updated view of targeted therapies currently under clinical development in SLE.

* Corresponding author at: Service de Rhumatologie, Centre National de Référence des Maladies Autoimmunes et Systémiques Rares, Hôpital de Hautepierre, 1 Avenue Molière, BP 83049, 67098 Strasbourg, France.
E-mail address: Laurent.arnaud@chru-strasbourg.fr (L. Arnaud).

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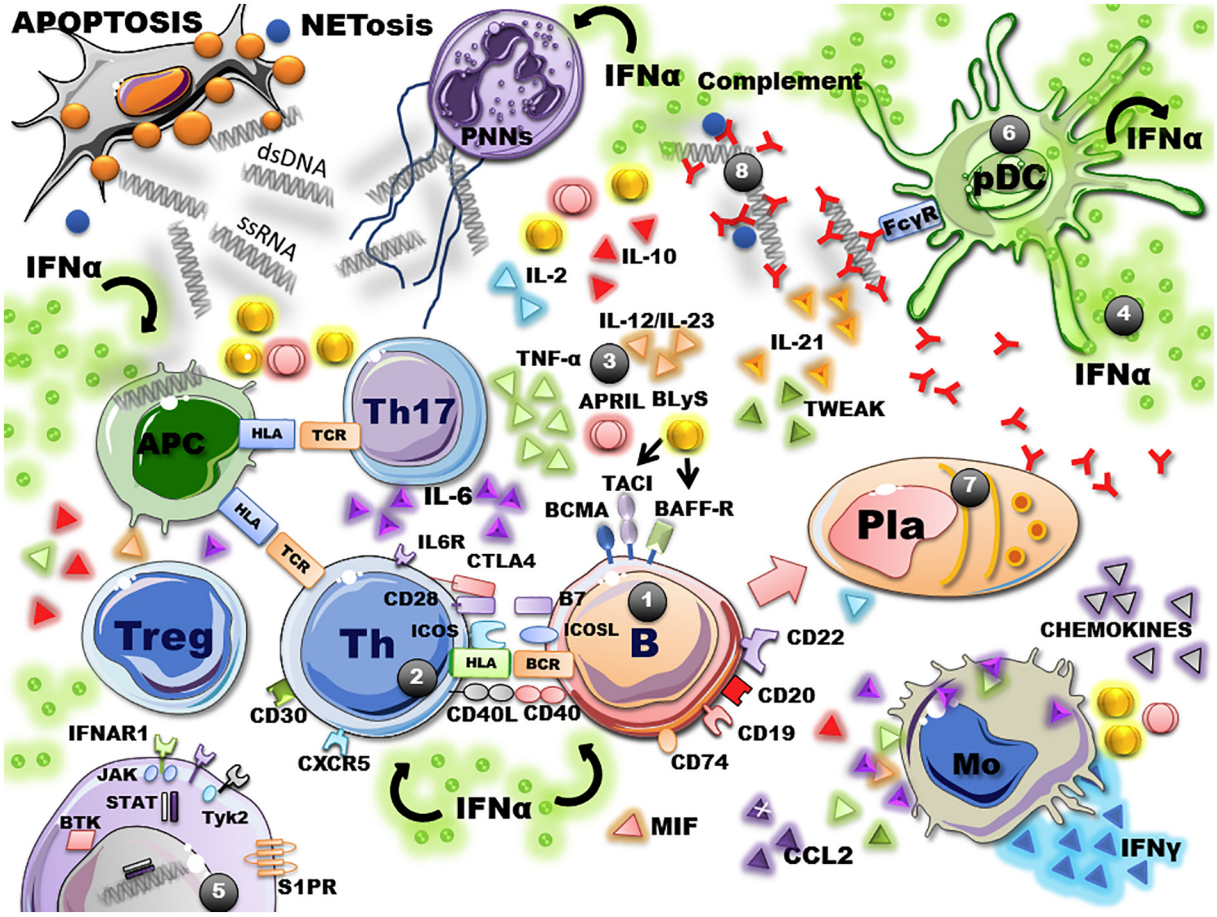

Fig. 1. The complex pathogenesis of SLE and targets of SLE treatments.
Targeting B cells (1), B/T cells costimulation molecules (2), cytokines, chemokines or their receptors (3), interferons (4), kinases of the intracellular machinery and S1P (5), pDCs (6), Plasma cells (7), or other mechanisms of action (8).

2. Methods

We performed a systematic review of all targeted therapies under clinical development in Systemic Lupus Erythematosus, in the main online registries of clinical trials. Targeted therapies were defined as drugs specifically designed to block certain molecules, receptors, or pathways involved in the development of autoimmune diseases. Clinical development stages were classified according to the current definitions for phases I, II, III & IV. Were excluded from this systematic review all pharmacological agents leading to a non-specific blockade of the immune system, such as classical immunosuppressive agents. Two authors (R.F. & F.S.) searched 17 national and international databases of clinical trials (Table 1) using the keyword “Lupus” (date of search: the 3rd of January 2018). Duplicates were excluded and each study was subsequently classified in consensus as whether it involved or not a targeted therapy for SLE, based on the descriptions provided in the registries or additional evidence gathered through the main internet search engines. Finally, targeted therapies for SLE were classified according to their mechanisms of action, and the current stage of drug development was extracted from the registries.

3. Results

Our search identified 1140 trials, from which were included 74 targeted therapies for SLE. The study selection process and reasons for exclusion are shown in Fig. 2. For each investigational drug, we considered only the study at the most advanced stage of clinical development.

The candidate drugs reached phase I (n = 20), I/II (n = 5), Phase II (n = 36), phase II/III (n = 2), phase III (n = 9) and phase IV (post-marketing development, n = 2). The corresponding trials were completed (n = 27), recruiting (n = 19), prematurely terminated (n = 17), active but not recruiting (n = 8), withdrawn (n = 3).

Treatment strategies under current clinical development for SLE target inflammatory cytokines, chemokines or their receptors (n = 17), B cells or plasma cells (n = 17), intracellular signalling pathways (n = 10), T/B cells costimulation (n = 8), interferons (n = 7), plasmacytoid dendritic cells (pDC) (n = 3), as well as various other targets identified in SLE (n = 12) (Fig. 1).

3.1. B cell therapies

B cells can be selectively targeted for depletion either via direct B cell molecules such as CD19, CD20, and CD22 or by inhibition of B cell survival factors: B lymphocyte stimulator (BLyS), a proliferation-inducing ligand (APRIL), or their receptors (TACI).

Fifteen molecules target B cells (Fig. 3 and Table 2) and have reached phase IV (n = 1), phase III (n = 6), phase II/III (n = 1), phase II (n = 3), phase I/II (n = 1) and phase I (n = 3).

The use of rituximab, a chimeric anti-CD20 antibody, in patients with SLE has been investigated in several phase III randomised controlled trials which are currently completed (LUNAR [9], EXPLORER [10]). Three other anti-CD20 antibodies are currently investigated in the SLE pipeline: TRU-015 (phase I terminated), obinutuzumab (phase II recruiting), and ocrelizumab (phase III completed [11]). Other agents include Epratuzumab, a humanized monoclonal IgG antibody that