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Review article

Success and failure of biological treatment in systemic lupus erythematosus: A critical analysis

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ABSTRACT

Patients affected with systemic lupus erythematosus (SLE) still display increased mortality and decreased quality of life in respect to general population. The major determinant of poor long term prognosis is organ damage, which is predictive of more damage and death. Damage is in turn triggered by uncontrolled disease activity and especially by the long-standing corticosteroid use which often accompanies SLE patients over their disease course, owing both to the need of reaching disease remission and to the habit of keeping patients on a small steroid dose for an indefinite period of time. Hence, the need for new drugs and therapeutic strategies aiming at minimizing damage accrual through a better control of disease activity and a steroid-sparing potential is paramount. So far, however, the therapeutic strategy in SLE requires a multitarget approach which is not devoid of widespread immunesuppression. In fact, several studies have been carried out in recent years targeting both the adaptive and the innate immune system, the majority of which did not achieve their primary endpoint, being often divergent from successful clinical experience and thereby committing physician to off-label use of targeted therapies in face of refractory SLE manifestations. The study designs and the chosen endpoints were often blamed for inadequacy, being at least in part responsible for study failures. In this review, we go over major clinical trials conducted in SLE by analyzing any critical aspects related to study design, predefined endpoints and biological activity of novel compounds that may have hampered study outcome, despite the great effort of providing less toxic drugs within a targeted, pathogenic-based approach.

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1. Introduction

Many progresses have been made in treatment of patients with systemic lupus erythematosus (SLE), pursuing better survival and better short term prognosis compared to the past [1]. However, long-term prognosis still remains poor especially for patients experiencing major organ involvement and no improvement has been documented as compared to the last 10 years [2,3], suggesting therapies have reached their plateau between disease healing and treatment-related organ damage.

Corticosteroids have been and still represent the mainstay of SLE treatment. They have been among the few approved drugs for sixty years and have proved as life-saving drugs, yet they are associated with organ damage, namely preterm osteoporosis, diabetes, cardiovascular disease and accelerated organ failure [4].

Accordingly, several efforts have been made to make SLE therapy evolve, but the barrage of traditional immunosuppressive drugs has not been overcome yet [5].

Currently, the only approved biologic drug for SLE is belimumab, in face of a great number of randomized controlled trials (RCTs) on other biologics having failed.

Several questions have been raised on why did almost all RCTs in SLE fail; were the drugs truly ineffective or was the trial design to be defective? Indeed, a number of *post-hoc* analysis showed how clinical trials could have succeeded by using slightly different outcome measures and subgroup analysis revealed a greater effect size in different subgroups that was not connoted in the global results [6]. Hence, it may be claimed that RCTs are not the most suitable tool in providing information on comparative drug effectiveness or safety in the general population.

In this review, we go over novel drugs being tested in SLE and on the value of experience in a landscape of strict evidence-based medicine.

2. Unmet needs in SLE

Unmet needs may be defined as unsolved clinical issues affecting disease course and patients prognosis.

In fact, SLE patients display a 4.6 fold increased mortality compared with age-matched population, decreased work productivity, mood disorders and deteriorated organ function [7]. Several evidences have highlighted organ damage as a major determinant of poor long-term prognosis [8,9], which is in turn triggered by persistent disease activity and above all by persistent immunosuppression and particularly corticosteroid abuse in SLE [4,10].

The vicious cycle made of badly controlled disease requiring more aggressive therapy leads to damage which in turn leads to more damage and death. Moreover, sometimes damage may not be easily distinguished from disease activity by clinical judgement, therefore contributing to long-lasting immunosuppressive therapy and especially corticosteroid treatment, even when facing an exhausted disease.

Hence, preventing damage and pursuing a stable disease control i.e. a stable remission emerged as the main target in SLE treatment [11], however until now the rate of durable remission in different cohorts has been disappointing [12–14], with a considerable percentage of patients experiencing uncontrolled disease activity and an annual flare rate ranging from 0.19 to 1.20 patient/year according to different cohorts [12–14].

Interestingly, no shared definition of remission is available in SLE, likely because the concept itself is not well characterized in clinical practice.

In light of novel acquisitions on SLE pathogenesis as well as of the profound awareness on how deleterious an improper use of medications may be over time, it is mandatory to help for new drugs and treatment strategies pursuing durable disease control and minimization of damage accrual in order to improve patient prognosis.

3. Hurdles in setting up RCTs in SLE

A great deal of RCTs have been performed in SLE [15–39] (Table 1) among which the rate of failures greatly overcame that of success at least until recently [40].

The major shortcomings faced in setting up a RCT in SLE rely in recruitment of a representative patient population, due to low disease prevalence and protean clinical features. Indeed, though not being classified as a rare disease, SLE has an annual incidence ranging from 2 to 3.8/100.000 patients in European countries [41] which makes it hard to recruit a suitable number of patients, running the risk of study underpowering.

Moreover, SLE displays a great variety of clinical manifestations ranging from mild symptoms to life threatening organ involvement, which share common immunological pathways but are not completely pathogenically overlapping [42].

Furthermore, disease activity patterns in SLE deserve attention since they have been shown to affect disease course, time to remission and flare rate [14,43,44]. We have outlined four main patterns of disease activity in our lupus cohort, among which three included a clinically active disease and were experienced by two thirds of our patients during a 7-year follow-up [43].

Hence, any trial design generally focusing on disease activity in SLE is biased by a clinical and immunological diversity that may challenge the study outcome as well as the adequacy of patients recruited.

In fact, RCTs by definition enroll a homogenous patient population that is unlikely to mirror disease complexity and to provide reliable information on comparative drug effectiveness or safety in the general population. This is true even in those trials narrowed to organ-specific manifestations e.g. lupus nephritis (LN), since within one organ involvement there are multifaceted clinical features and pathogenic mechanisms that may influence patient prognosis and response to treatment [45].

RCTs enrolling naïve patients and/or patients with a mild disease in whom a new drug is tested as an add-on therapy have to face a high rate of response to placebo, which is indeed the standard of care (Table 2).

Actually, patients with severe manifestations and/or with previous cyclophosphamide treatment are often excluded from RCTs, thus shaping a study population which is most likely to respond to