Recent advances in the treatment of systemic lupus erythematosus

Survival for patients with systemic lupus erythematosus has much improved in the last 50 years. Faster diagnosis, renal dialysis and transplant, and better general care (including lowering of blood pressure and treating osteoporosis) have had important roles in this. We have optimized the use of corticosteroids and conventional immunosuppressive drugs, reducing the side effects and improving efficacy. However, the progression to end-stage renal disease has not changed. The advent of targeted therapies using biologic agents has held great promise but because of the design of the trials, the results are disappointing and these drugs are not yet widely accepted. More and better designed trials are needed.

KEYWORDS: biological ■ immunosuppressive ■ lupus nephritis ■ systemic lupus erythematosus ■ treatment

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Compared to the 1950s, when the survival for patients with systemic lupus erythematosus (SLE) was 50% at 5 years [1], the outlook for these patients has much improved; 5-year survival is now greater than 90%, including for lupus nephritis (LN) patients in whom remission is achieved [1]. Faster diagnosis, renal dialysis and transplant, and better control of comorbidities, such as high blood pressure and osteoporosis. have had important roles in this. However, the progression to end-stage renal disease has not changed as shown in one retrospective study in a single center over a 30-year period [2]. Still, this study by Croca *et al.* suggests we have optimized the use of corticosteroids and conventional immunosuppressive drugs for patients with aggressive nephritis [2].

Comorbidities

SLE affects virtually every organ/system in the body. The key to its successful treatment is the prevention of damage. It is also important to recognize that at least one-third of SLE patients have one or more comorbidities.

■ Osteoporosis

Osteoporosis is a common problem in SLE patients. They have a high risk of accelerated loss of bone mass and fractures [3]. The prevalence varies from 10 to 20%, including premenopausal patients [4], while the prevalence of osteoporosis in rheumatoid arthritis oscillates from 4 to 24% [5].The main causes are disease activity, immobility and, mainly, the use of glucocorticoids. Other risk causes include age, gender, familiarly osteoporosis, low BMI, fall risk, low vitamin D levels and lifestyle [6].

For these reasons, a regular assessment screening in these patients is required to facilitate the early diagnosis of osteoporosis. Dual x-ray absorptiometry is recognized by WHO as the reference method for measuring bone mineral density allowing accurate diagnosis of osteoporosis, fracture risk estimation and monitoring patients' treatment [7]. Dual x-ray absorptiometry should be carried out in women older than 65 years and in men with clinical manifestations of low bone mass (radiographic osteopenia, history of low trauma fractures and loss in height), as well as in postmenopausal women younger than 65 years or men with risk factors for fracture (advancing age, previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, cigarette smoking, alcohol consumption and secondary osteoporosis). The recommendations for screening of osteoporosis are not different in SLE patients [8].

There is a paucity of studies of osteoporosis treatment in SLE patients, but the effectiveness of this treatment in postmenopausal women in general is a strong argument to use it in those with low bone mineral density. Numerous studies have shown that osteoporosis treatment (alendronate, risedronate, strontium ranelate, raloxifene and zoledronic acid) decreases the fracture rate over treatment periods of 3–5 years (grade A), except teriparatide, for which the treatment period is 18 months [9]. Biphosphonates are the first choice because their effects are well known. If there is any contraindication other alternatives such as strontium ranelate, parathyroid hormone or denosumab are available [6].

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Atherosclerosis

In the last 35 years it has been recognized that cardiovascular (CV) disease is a major cause of death in SLE. CV disease is the result of atherosclerosis and thromboembolic events, and both are increased in SLE. Atherosclerosis is the most common etiology of cardiovascular disease and many studies have shown an increase in clinical and subclinical atherosclerosis in these patients. Classical CV risk factors contribute to this, notably smoking (approximately 20% of SLE patients continue to smoke), hypertension and dyslipidemia, the prevalence of which is increased in patients with SLE [4]. In addition, it has been demonstrated that the sustained inflammation in autoimmune diseases leads to accelerated atherosclerosis. Nephrotic syndrome and proteinuria can also contribute with an adverse lipid profile and higher prothrombotic risk [10]. Lupus patients should be screened for the presence of CV risk factors and CV disease [11].

It seems, furthermore, that SLE treatment affects the development and progression of atherosclerosis. For example, hydroxychloroquine (HCQ) is associated with a reduction of steroid-induced hypercholesterolemia, with a decrease in subclinical atherosclerosis (aortic stiffness and carotid plaques), and with a reduction in the risk of all thrombovascular events. Mycophenolate mofetil (MMF), in addition to showing anti-atherogenic properties within the atherosclerotic plaque, was associated in a retrospective study with a reduction of CV mortality in a group of diabetic patients after renal transplant [12]; this effect has not yet been shown in lupus patients. A low dose of glucocorticoids may also have a protective effect in terms of plaque burden. A high dose of glucocorticoids (>10 mg/kg), on the other hand, accelerates atherosclerosis due to their known effects on blood pressure, blood glucose and atherogenic lipids. Azathioprine (AZA) use has been correlated with cardiac events [11]. In all of these associations, it is obviously difficult to distinguish the effect of the drug from the effect of disease activity. Since a clearly causal effect has not been established, patients' treatment should not be avoided.

Hypertension

SLE patients have an increased prevalence of hypertension (14–75%) [13]. It is associated with subclinical atherosclerosis, CV disease and with renal disease, which may be a major problem in approximately one-third of the patients [13]. As in atherosclerosis, the pathogenesis of hypertension is associated with classical risk factors and also with risk factors specific to the disease, particularly renal impairment, inflammation and corticosteroids [14].

International guidelines recommend control of CV risk factors. Blood pressure in these patients should be under 130/80 mmHg, as in other high-risk diseases (e.g., diabetes mellitus) preferably by using an angiotensin-converting enzyme inhibitor (if not pregnant) for their renoprotective effects, especially if the patient presents with proteinuria ≥0.5 mg/24h [11,15].

Advances in the use of nonsteroidals/immunosuppressives

Antimalarials have been used in rheumatic diseases for many years. HCQ's immunomodulating properties were discovered after it was used as malaria prophylaxis in the 1950s. This drug acts on different pathways and has multiple mechanisms of action, including blockage of low-affinity antigens (such as self-antigens), alteration of intracellular pH, decrease in macrophage-mediated cytokine production, inhibition of phospholipase A2 and C, decrease of estrogen production, inhibition of platelet aggregation and adhesion, induction of apoptosis, antiproliferative effects and it can dissolve circulating immune complexes [16]. Because the immune response against high-affinity antigens such as bacterial peptides is not impaired, the result is immunomodulation without immunosuppression [17]. HCQ prevents and alleviates articular and skin flares [17], protects from UV light and is associated with a milder disease. It improves sicca syndrome and facilitates the response to MMF in patients with renal involvement [18]. Among other benefits, HCQ can reduce total cholesterol, very low density lipoprotein cholesterol and triglyceride and increase high density lipoprotein cholesterol levels [19]. By helping to control glycaemia it may also decrease the risk of diabetes. There are reports of an association with a reduction of up to 50% of the frequency of coronary heart disease [20] and of the risk of development of carotid plaque [16,17], which makes it an especially good option for patients who are also treated with corticosteroids. It also has antithrombotic properties [19] and some potential antineoplastic effects have been described [21].

Most importantly, HCQ prevents damage [22–25]. In two studies in three ethnic groups, in the LUMINA cohort, HCQ use was associated with a longer time to integument damage over a mean disease duration of 5.9 ± 3.7 years (hazard ratio: 0.23; 95% CI: 0.12–0.47) [23] and with a reduced risk of damage accrual *de novo* over

a follow-up period of 5 years [24]; other groups demonstrated the same benefit.

A systemic review on the clinical efficacy and safety of antimalarial therapy notes that disease activity was reduced in all studies in approximately 50% of the patients [19].

Probably as a result of all this, it reduces mortality. Both in the study by Ruiz-Irastorza *et al.* with a mostly Caucasian cohort [26], and in the LUMINA cohort, with an multiethnic group [27], HCQ was shown to have a protective effect on survival.

It should be stated that, regarding the overall efficacy of antimalarials, confounders cannot be excluded because these drugs are frequently used in milder cases and frequently discontinued in patients with severe disease [19].

The toxicity of antimalarials is mild and not common, with an even lower incidence in HCQ compared with chloroquine. The most frequently affected organs are the skin and gastrointestinal system [19].

Recognition of the harms of corticosteroids

Corticosteroids, because of their anti-inflammatory and immunosuppressive properties, are widely used in SLE, as in many other autoimmune diseases. Their effects depend on diverse molecular mechanisms that include direct and indirect effects on gene expression, leading to alteration of the inflammatory process in different pathways [28]. Unfortunately, because of this gene expression alteration, some physiological pathways are also altered, resulting in many troubling side effects that vary in severity and frequency (TABLE 1).

Corticosteroids are administered in different ways (oral, intra-articular, intramuscular and intravenous) that can be adjusted to the organ involved and the severity of the situation, and the route of administration leads to different side effects. Side effects are mostly dose dependent and in a low-dose regimen (less than 7.5 mg daily) most side effects are considered rare. The steroid cumulative dose is associated with coronary artery disease, osteoporotic fractures, cataracts and glaucoma [29]. High-dose use, in endovenous administration (rather than the cumulative dose) is associated with avascular necrosis [29], venous thrombosis [30] and glucocorticoid-induced diabetes mellitus [31]. Of course some of these side effects are more likely to be a marker of severe disease [29].

The European League Against Rheumatism (EULAR) recommends clinical monitoring for a wide variety of side effects (TABLE 1). These side effects contribute significantly to the damage in SLE, in addition to the disease itself, as measured by the Systemic Lupus International Collaborating Clinic/ACR [29]. This is of great importance because damage is associated with greater mortality [29]. Furthermore, evidence concerning the ideal dose and duration of treatment with corticosteroids is still lacking [32]. Thus, it is evident that the best dose of corticosteroids is the lowest possible dose for the shortest possible period of time. Research into steroid sparing drugs is vital.

Optimizing the use of immunosuppressives

Renal

LN is present in up to 60% (although it is not always clinically overt) of all lupus patients and it is the most common life-threatening manifestation [33–35]. The management of LN has not advanced much in the last 10 years, although the use of immunosuppressives has been optimized to reduce their toxicity. The reported efficacy varies between trials and protocols, but complete remission is difficult to obtain and progression to end-stage renal disease is still high (4–9% [36,37], probably even higher in high-risk populations).

The induction phase is key to the management of these patients. It is evident that aggressive immunosuppressive therapy is necessary and that an early response to treatment predicts a good renal outcome [38,39]. The NIH trials in the 1980's suggested that the use of cyclophosphamide (CYC) was the gold standard for induction. In these studies, it was clearly demonstrated that CYC-containing regimens were superior to those with corticosteroids alone [37]. However, the frequent and serious toxicity (infection, ovarian failure, which depends on the cumulative dose, and possible bladder cancer) has lead to alternatives being investigated in the last decade.

In 2002, the Euro-Lupus Nephritis trial demonstrated the equivalent efficacy of a CYC low-dose regimen compared with the NIH high-dose regimen, with comparable probability of treatment failure in up to 10 years of follow-up [37,39]. This study was a multicenter prospective clinical trial with 90 lupus patients randomly assigned to a high- or low-dose CYC regimen (cumulative dose of 3 g in low-dose regimen) and AZA as a maintenance therapy. Although there were fewer side effects (fewer infections although not statistically significant and just one case of ovarian failure), these results are reasonably reassuring and most units now use this regimen in preference to the NIH regimen. It bears mentioning

Table 1. Corticosteroid side effects.

Clinical side effect	Relative frequency
Dyslipidemia	Common
Edema	Common
Hypertension	Occasional
Ischemic cardiovascular disease	Rare
Infections	Common
Peptic ulcer disease	Rare
Difficulty with sleeping	Common
Mood disturbances	Common
Psychosis	Common
Diabetes/glucose intolerance	Occasional
Body weight and fat redistribution	Common
Interference with hormone secretion	Common
Skin atrophy	Common
Acne, hirsutism, alopecia, easy bruising	Common
Osteoporosis	Common
Osteonecrosis	Occasional
Myopathy	Occasional
Cataract	Occasional
Glaucoma	Occasional

Adapted from [86].

that the NIH studies included more Hispanic and African–American patients, while the Euro-Lupus trial included mostly a Caucasian population, and hence its conclusions should not be extrapolated indiscriminately.

The Dutch Lupus Nephritis Study compared AZA and high-dose CYC as an induction therapy for LN, both arms together with steroids (CYC plus oral prednisone vs AZA combined with methylprednisolone). This was a small open-label study, with 87 patients, mostly Caucasians, that interestingly showed that both groups had similar renal function, end-stage renal disease probability and mortality in a follow-up period of almost 10 years [36,40], although the steroid effect is difficult to distinguish. It was also demonstrated that CYC is superior in preventing renal flares (10% in the CYC group vs 38% in the AZA group; p = 0.002; hazard ratio: 4.5) but without long-term consequences during the follow-up. This study confirmed that AZA, though inferior to CYC, is still an option, especially if fertility preservation is a concern.

MMF has been used since the early 2000s for refractory LN. The ALMS showed that MMF is not inferior to intravenous high-dose CYC in inducing renal remission at 6 months and was better than AZA at maintaining remission over 3 years [34,41].

Thus, in the first part of this trial it was demonstrated that MMF and CYC have similar efficacy in the induction phase. The renal response rate was 56.2% in the MMF group and 53% in the IV CYC group (p = 0.58).

Some previous small studies and meta-analyses suggested that MMF would be beneficial in even more patients than CYC [34] and actually, in this large and multiracial randomized open-label trial, MMF seems to have a more consistent efficacy between different racial or ethnic groups (see 'Differences in ethnic groups' section) [34]. They also have similar rates of adverse effects, although some side effects such as ovarian failure and increased malignancy risk were not evaluated because of a short follow-up. Furthermore, MMF has a more convenient oral administration. This trial confirmed that MMF is a reasonable first-line drug for the induction phase.

After the induction phase, it is essential to continue the immunosuppressive therapy in the maintenance phase so that remissions can be consolidated, relapses prevented and the progression to complete remission continued [41]. A much poorer outcome has been described in the absence of a maintenance therapy, with renal flares in 45% and progression to end-stage renal disease in 27% [40].

Contreras *et al.* reported better renal and systemic outcome with AZA or MMF as a maintenance therapy in comparison to CYC, in a small open-label randomized controlled trial with 59 patients, with a follow-up of 1–3 years [42]. Both MMF and AZA had a better event-free survival compared with CYC, with fewer side effects.

The MAINTAIN trial is of interest [43]. It compared the efficacy of MMF and AZA for the maintenance of remission in LN. The efficacy was similar, with similar time to renal or systemic flares, glucocorticoid withdrawal and to renal remission. The adverse events rate was also similar, with the exception of hematological cytopenias, which were more frequent in the AZA group.

There were some limitations in the MAINTAIN design, as it was mainly a European trial, with a small number of, mostly, Caucasian patients, not all of whom had a good initial response to the induction therapy, which led to the conclusion that more studies were necessary.

The second part of the ALMS trial also tested MMF as a maintenance therapy in a bigger multiracial randomized double-blind double-dummy

study [41]. The patients who had clinical response in the first part of the trial were then enrolled in the second, with a follow up of 36 months, which compared oral MMF (1 g two times a day) with oral AZA (2 mg per kg of body weight per day). As a maintenance therapy, MMF was significantly superior compared with AZA (p = 0.003) concerning time to treatment failure (defined as death, progression to end-stage renal disease, doubling the serum creatinine, renal flare or need for rescue therapy) and had almost half of the overall treatment failure rate (16.4% in the MMF group vs 32.4% in the AZA group). The group treated with MMF also showed higher levels of C3 and C4 and lower titers of anti-dsDNA antibodies. The incidence of adverse events was similar in both groups, but more patients treated with AZA had more serious side effects leading to withdrawal (39.6% in AZA group vs 25.2% in the MMF group; p = 0.02).

As in the induction phase, although AZA is not the first choice, it remains a viable drug to use, especially in pregnancy, unlike CYC and MMF [44].

In both trials, a high renal relapse rate was noted (19% in the MMF group and 25% in the AZA group in the MAINTAIN study; and12.9% in MMF group and 23.4% in the AZA group in the ALMS study), and the search for more drugs able to provide a more sustained remission continues.

Tacrolimus is another immunosuppressive drug that has been recently proposed as a good option for induction in LN. A meta-analysis including five randomized controlled trials with 225 patients showed that tacrolimus is superior to intravenous CYC in obtaining complete remission and decreasing urine protein, with a higher conversion rate to a negative anti-dsDNA antibody state [45]. There were significantly less gastrointestinal side effects and irregular menstruation and no significant difference in the other evaluated side effects. These data are suggestive that tacrolimus is an option for induction therapy, but more studies are necessary.

Nonrenal disease

For nonrenal lupus manifestations corticosteroids are usually the first choice [33], but there is some evidence that other drugs may have a beneficial effect, especially in refractory cases. Different drugs have been studied such as clofazimine, dehydroepiandrosterone and testosterone, methotrexate, leflunomide and rituximab, as well as the immunosuppressive drugs described above [33].

In 2007, Mok published a systematic review including 20 case series and open-labeled trials on the subject of MMF in nonrenal refractory manifestations of SLE [46]. It reported ten patients with refractory hematological manifestations that responded to the addition of MMF to their baseline treatment. It also reported 16 patients with refractory dermatological manifestations, of whom 69% responded well to the addition of MMF. Maintenance of MMF seemed to prevent relapses, which were documented when tapering MMF's dose.

In the ALMS trial a wide range of SLE manifestations was assessed [34] using the British Isles Lupus Assessment Group (BILAG) index and a secondary end point of measuring whole body disease activity and immunologic parameters was established [33]. Although the conclusions cannot be extrapolated to the group of nonrenal lupus patients, it was notable that both MMF and CYC were effective (with similar efficacy) in controlling nonrenal manifestations after the induction treatment. The disease activity was accessed by both the BILAG index and the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which includes a definition of flare. A total of 60% of the patients with active disease achieved remission and 70% had a reduction in disease activity after 24 weeks, with similar efficacy in each of the organs/systems. Flares were prevented (only two patients had a flare, with neurological symptoms). The immunologic response was also obvious, as the levels of complement had increased and titers of anti-dsDNA antibodies reduced.

In the second phase of the ALMS trial comparing MMF with AZA as a maintenance therapy, the rate of extra-renal flares was also low: 6.9% in the MMF group and 6.3% in the AZA group, and the time to major extra-renal flare did not differ between the two groups [41].

Ciclosporin is another possible option as a steroid-sparing drug for severe lupus. Griffiths *et al.* showed that a low-dose regimen (<5 mg/kg/day) has similar efficacy compared with AZA, in a group of patients with normal renal function (but 29% had renal involvement) [47]. The expected side effects of ciclosporin were present, such as hypertension and renal impairment, but they were mild and reversible on reducing the dose of ciclosporin.

For neuropsychiatric SLE there are limited data and few trials, and the overall prognosis seems favorable. Pego-Reigosa *et al.* reported

on 485 SLE patients who had been followed for periods of more than 20 years and reported a 2.3% prevalence of lupus psychosis (average follow-up period was 14 years) [48]. A total of 60% of these patients had a resolution of the symptoms after the first year and 70% achieved complete remission after a mean follow-up of 155 months. These patients were treated with methylprednisolone, oral prednisolone, intravenous cyclophosphamide, azathioprine and plasma exchange, and all the patients received antipsychotic agents.

A clinical trial with 32 patients with neuropsychiatric manifestations compared methylprednisolone alone versus methylprednisolone combined with CYC [49]. The overall response was 75%, but the CYC had a higher response rate ($p < 0.03$), suggesting that CYC might be superior than corticosteroids.

EULAR recommends corticosteroids alone or in combination with CYC or AZA, and other drugs have been used in refractory cases [50].

Is the 'day of the biologics' coming?

Given the ongoing need to improve the outcome for SLE patients, the advent of targeted therapies using biologic agents has held great promise. Disappointingly, they have not been established as a recognized treatment of SLE as they have for rheumatoid arthritis. However, there are signs of a greater acceptance of their role in the treatment of at least some SLE patients.

Belimumab

Belimumab is a human monoclonal IgG 1 that specifically binds to soluble form of the protein human B lymphocyte stimulator (BLyS) [51].

It was approved on March 2011 by the US FDA for autoantibody-positive (antinuclear antibody [ANA] ≥1:80 and/or anti-dsDNA ≥30 IU/ml) adult SLE patients with refractory skin and joint disease, but is not approved for other aspects of lupus including central nervous or renal disease [52].

The most important studies of belimumab, BLISS-76 and BLISS-52, were both Phase III efficacy and safety studies [53,54]. They showed that belimumab was effective in reducing disease activity (measured by SELENA/SLEDAI) and preventing flares (using BILAG), with no worsening in Physician Global Assessment. At week 52 the 10 mg/kg belimumab group had more responders (43.2 vs 33.5% in the placebo group, $p = 0.017$); at week 76 the response was also greater in the belimumab arm but with no statiscal significance.

It was particularly effective in mucocutaneous, musculoskeletal and vascular manifestations, and had a steroid sparing effect [54].

Belimumab was also immunologically effective, lowering anti-dsDNA antibody levels and raising C3 and C4 levels.

A *post hoc* analysis identified a subset of autoantibody-positive (ANA titer ≥1:80 and/or anti-dsDNA antibody level ≥30 IU/ml) patients with a low C3 (71.5% of the original cohort) in whom belimumab was particularly effective [54].

The doses of belimumab used in these trials were 1 or 10 mg/kg and CD20 cells were significantly reduced at week 24 with both doses [54–56]. The 6-year extension data has demonstrated durability and an increase in the percentage of responders [52].

Importantly, belimumab did not show more adverse events than placebo.

The studies are similar, but there were some difference between the two. In BLISS-76 the exclusion criteria were more strict and the patients were excluded if they had been treated with B-cell depletion in the past, CYC in the last 6 months or any of the following in the last 3 months: intravenous immunoglobulin, plasmapheresis, anakinra, TNF inhibitors or prednisone higher than 100 mg/day. In both, they had also standard care treatment. In BLISS-76, the efficacy was consistent after week 52 (compared with week 24 in BLISS-52) [54–56].

Rituximab

Rituximab is a chimeric murine/human monoclonal antibody IgG1 κ inmunoglobulin against the CD20 antigen that is found on the surface of B lymphocytes [57].

In many open-label studies, rituximab has shown very good clinical results in patients with many lupus features including fatigue, skin, arthritis, serositis and renal disease. At the same time, it has been shown to be safe and well tolerated [58,59].

The EXPLORER study was the first randomized controlled Phase II/III trial of B-cell depletion in patients with active extra-renal SLE receiving immunosuppressive drugs and corticosteroids, designed to demonstrate the benefit of adding rituximab to standard treatment [60]. Rituximab was not superior to placebo in preventing or delaying flares. Although there was some evidence of delaying A flares (BILAG), no firm conclusion can be drawn from these data.

In a *post hoc* analysis of EXPLORER, Tew *et al.* found that B-cell depletion normalizes anti-DNA antibodies and complement levels

in anti-dsDNA positive patients [61]. Similarly, serum levels of anticardiolipin antibodies were also decreased and in a small number of patients with thrombocytopenia at baseline, the platelet numbers were normalized.

The LUNAR study is a Phase III randomized double-blinded placebo-controlled trial of SLE patients with class III and IV LN treated with MMF and corticosteroids, who were randomized to receive rituximab or placebo. The results showed that rituximab plus MMF was not superior to MMF alone [62].

The EXPLORER and LUNAR trials confirmed that rituximab is safe and well tolerated and *post hoc* analyses suggested that it delays the time to moderate or severe flares when patients are in remission [63]. The overall failure of these studies to achieve their primary end points may well be owing to their design. Thus, the exclusion of patients with severe and refractory disease and the maintenance of ongoing background immunosuppressive therapy (notably the high dose of corticosteroids) are likely to have contributed to the overall disappointing results.

More encouragingly, Lighstone and coworkers have established a regimen (Rituxilup) for LN at the time of diagnosis using rituximab and a low dose of MMF, which aims to avoid oral corticosteroids (although the regimen includes methylprednisolone in the induction phase). Condon *et al.* reported the results of the first 50 consecutive patients treated with the Rituxilup protocol in a multicenter open-label randomized controlled trial [64]. A total of 90% of these patients achieved complete or partial remission in 37 weeks (72% achieved complete remission and 18% partial remission). Six of the 50 patients in the cohort had systemic flares and only two of those patients showing an initial response needed 2 weeks oral steroifs to control a flare.

In support of this approach, Ezeonyeji *et al.* also reported the safety and effectiveness of an early administration of rituximab [65]. In this study, eight newly diagnosed SLE patients were treated with rituximab (1 g) plus intravenous methylprednisolone (125 mg) on days 1 and 14, and CYC (750 mg) on day 2, followed by AZA and HCQ, but no oral corticosteroids. Their outcome was compared with three carefully matched controls (SLE patients treated conventionally). It was evident that the rituximab regimen was clinically and immunologically effective, with much lower steroid cumulative doses at 6 months.

Epratuzumab

Epratuzumab is a recombinant humanized monoclonal IgG antibody against CD22 antigen that binds to the extracelular domain of CD22, modulating B cells in SLE [66]. The result is a moderate antibody-dependent cellular cytotoxicity without complement-dependent cytotoxicity [67] (which may explain the absence of infusion reactions in humans) [66].

UCB-Immunomedics (Brussels, Belgium) showed good results in the EMBLEM study comparing epratuzumab with placebo in patients with SLE. In this study with 227 patients with moderate to severe activity, epratuzumab obtained a superiority of 24.9% [68].

In the ALLEVIATE studies, epratuzumab demonstrated steroid-sparing properties and improvements in health quality of life, with confirmed safety [69].

The EMBODY studies, two pivotal, Phase II, 48-week trials with 2000 patients are in progress [66].

Atacicept

Atacicept is a human recombinant protein that inhibits B-cell-stimulating factors APRIL and BLyS.

A Phase I study showed good tolerance but there is some concern about the increased risk of infection [70]. Isenberg *et al.* evaluated the efficacy and safety of atacicept in preventing flares in SLE in a randomized, double-blind, placebo-controlled, multicenter study [71]. After achieving low disease activity with a course of corticosteroids, 461 patients were randomized to receive placebo or atacicept. No statistically significant difference was observed in flares in the ataticept 75-mg group (compared with placebo). Intriguingly, the atacicept 150-mg group was statistically superior in delaying flares but this arm was terminated early owing to two fatal pulmonary infections.

Another Phase II/III trial in LN patients reported hypogammaglobulinemia and increased risk of infections, although this is almost certainly linked to a notable reduction in immunoglobulin levels following MMF before the atacicept was given [72].

Anti-IFN-α

Since 1979, when increased levels of IFN-α were found in SLE patients' sera [73], that there has been increasing research supporting the importance anti-IFN-α in the pathogenesis of SLE.

IFN-α is a type of IFN-I that is encoded on chromosome 9p and is the most important IFN

in SLE [74]. It is mostly produced by the plasmacytoid dendritic cells, in a pathway dependent of TLR-7 and -9 [75].

Several genes implicated in the IFN-I pathway are risk genes for SLE and also the nucleic acid immune complexes trigger the cascade production of IFN in plasmacytoid dendritic cells [74].

Accordingly, some clinical trials have been initiated in SLE, using monoclonal antibodies against IFN-α and its receptor (IFNAR) or using an immune therapy to induce polyclonal anti-IFN-α antibodies.

Rontalizumab

This is a humanized antibody IgG1 against all IFN-α subtypes. The results of a Phase I trial have been reported recently, which aimed to evaluate the efficacy and safety of the drug in 238 patients with moderate-to-severely active extrarenal lupus. Patients were randomized to rontalizumab or placebo. There was no overall response observed in BILAG and SLE Response Index at 24 weeks, but in the specific group of patients with low IFN-I levels there was a significant response compared with placebo and a sparing-steroid effect was observed. The patients with low IFN were similar in terms of disease activity and had lower rates of anti-dsDNA and anti-RNA binding protein (anti-RBP antibodies). Maybe a higher dose of rontalizumab is necessary for the IFN higher level group [76].

Sifalimumab

This is an antibody IgG1k anti- IFN-α. Its safety has been demonstrated and it is effective in lowering the IFN levels, but the results of its effect on disease activity is contradictory [77].

ASG-009

This is an antibody anti-IFN-α that has shown good tolerance and a dose-dependent response [74].

Finally, other alternatives to block IFN-I are to block its receptor (IFNAR) or induce a polyclonal anti- IFN-α response (with IFN-α kinoid), but data about this option are limited [74].

Other considerations

Differences in ethnic groups

Several studies have shown a higher risk of LN and a worse prognosis in African–American and Hispanic lupus patients [78–79].

The ALMS trial provided some information about ethnicity. Although MMF and CYC showed similar overall efficacy, it was interesting to see that more patients in the high-risk group responded to MMF, which had a more consistently effective response in all racial groups, while CYC is less effective in African or Hispanic patients [80]. In the maintenance phase, MMF was also superior independently of race [41]. Pharmacokinetic studies did not show differences in metabolism in different races [81] and the risk of infection was also similar [82].

The EXPLORER study suggests that the patients from American, African and Hispanic groups, can benefit from the addition of rituximab ($p = 0.0408$) [60].

These results showed that ethnicity, race and geographical location are important because they can affect patients' response to different treatment.

Biologics Register

Many countries have started to collect data on patients that are treated with biologic therapy in national large-scale registers, to learn more about the 'real life' experience with these drugs.

In the UK, the BILAG BR is ongoing. It is a prospective observational cohort study of SLE patients treated with biologic drugs. One of the goals of this register is to know whether the patients with this treatment have an increased risk of infection and hospitalization, compared with conventional therapy. The other purpose of the BILAG BR is to determine the long-term efficacy of biological therapies in the treatment of SLE.

Recent guidelines: EULAR & ACR

For the initial treatment of LN class III, IV and V, EULAR [15] and ACR [83] recommend MMF (3 g per day) or CYC as the first choice treatment, together with intravenous pulses of methylprednisolone or high doses of glucocorticoids (0.5 mg/kg/day). EULAR and ACR's guidelines recommend the low-dose CYC regimen (3 g/3 months) as the preferred one. The high-dose regimen (0.5–1 g/m^2 intravenous per month for 6 months) is reserved for patients with worse clinical or histological features (EULAR) or may be the first option in a non-Caucasian population (ACR).

For subsequent treatment, MMF is unanimously the first choice because of its proven superiority.

The recommended treatment for class I and II LN with podocytopathy is low-dose of prednisone (0.25–0.5 mg/kg/day), with the addition of AZA (1–2 mg/kg/day) as a steroid-sparing agent.

In the case of refractory disease (failure to improve in 3–4 months, not achieving partial response in 6–12 months or remission in 2 years), a switch is recommended to a different immunosuppressive drug that can be mycophenolic acid, MMF, CYC or rituximab, added to the previous treatment or as monotherapy.

Biopsies should be undertaken in all patients with clinical evidence of active, new-onset and untreated LN.

Both guidelines mention the importance of HCQ and ACR suggests prescribing this drug to all lupus patients with nephritis.

Clinical trial design

Clinical trials design in SLE is fundamental but complex. The difficulty is evident because lupus is a relatively uncommon condition, very heterogeneous, whose activity is difficult to assess, with a relapsing–remitting clinical course, and has few standardized biomarkers [81]. It is clear the clinical trial design in most SLE studies has been suboptimal. Wofsy *et al.* analyzed this matter when reflecting on a trial of abatacept in LN [84]. They concluded that the definition of primary outcome is essential for the ability of the trial to detect therapeutic benefits and a correct and unanimous definition of complete remission in SLE is needed to define the main outcomes in a clinical trial.

Therefore, EULAR has developed recommendations [85] for conducting clinical trials. The main points to consider are:

- Define primary (e.g., level of disease activity assessed with a standardized index, causes of death and adverse events) and secondary end points (such as health status and quality of life) with care;
- Follow CONSORT guidelines and Good Clinical Practice guidelines. It is necessary to define the hypothesis, the type of trial, methods and duration, and plan the statistical analyses. It is also essential to define the efficacy of the drug, remission, response and treatment failure;
- Eligibility criteria (disease definition, its duration since the diagnosis and demographic characteristics) should be defined to allow comparisons between studies and subgroup evaluation if needed;
- Characterize concomitant medications (immunosuppressive drugs, corticosteroids

Executive summary

Comorbidities

- Monitor high blood pressure, atherosclerosis and osteoporosis risk factors and treat early.

Advances in the use of nonsteroidals/immunosuppressives

- Hydroxychloroquine reduces damage and mortality and has antiatherogenic and antithrombotic properties, reducing cardiovascular disease, and has low toxicity.
- Hydroxychloroquine can be used in virtually all patients.

Recognition of the harms of corticosteroids

- Corticosteroids are a major cause of damage, which is associated with greater mortality.
- We should try to minimize the use of long-term oral corticosteroids.

Optimizing the use of immunosuppressives

- The Euro-Lupus regimen (lower dose intravenous cyclophosphamide) is better than the NIH regimen, at least for the Caucasian population.
- Mycophenolate mofetil is as good as intravenous cyclophosphamide for the induction and maintenance therapy of lupus nephritis.
- Azathioprine is a good option, especially if fertility preservation is a concern.
- It is important to treat active disease quickly and aggressively, avoiding damage (which is associated with worse prognosis).

Is the 'day of the biologics' coming?

- Belimumab is approved by the US FDA for skin and joint disease.
- Rituximab's efficacy has not been demonstrated in controlled clinical trials, probably owing to clinical trial design.
- Other biologics are being developed.

Other considerations

- Mycophenolate mofetil has a more consistently effective response in all racial groups compared with cyclophosphamide.
- Biologics Registers enable understanding of the 'real life' experience of these drugs.
- EULAR and ACR have published recent guidelines for lupus nephritis.
- Clinical trial design in systemic lupus erythematosus is complex but fundamental and EULAR has developed recommendations for conducting clinical trials.

and other drugs). It is necessary to define the drugs allowed in the clinical trial, the dose range and the duration of the treatment.

Conclusion

The outlook for SLE patients is now much better than 50 years ago, but there is still a need for improvement. We have probably gone as far as we can with conventional treatment – that is, corticosteroids, immunosuppressive drugs, HCQ, antihypertensive drugs and anti-osteoporosis drugs. We are now using more steroid-sparing drugs and less toxic doses of immunosuppressive drugs, improving the efficacy of treatment and diminishing the side effects, and also dealing earlier and better with damage and associated diseases.

The use of biologics is becoming more acceptable and might change the course of SLE, but the results of the trials have been disappointing.

Future perspective

Although a decade behind the use of biologic drugs in the treatment of rheumatoid arthritis, there is a realistic expectation that the next decade will see the widespread acceptance of the use of these drugs in the treatment of SLE. It will require the optimization of clinical trials to demonstrate benefit; the recognition that a variety of particular targeted approaches will be needed to 'capture' the diversity of clinical features in SLE and a willingness on the part of individual countries/players to cover the cost of the biologic approaches. With these caveats we eagerly anticipate a genuine 'new age of therapy' for patients with SLE, in particular for those who fail to respond adequately to conventional immunosuppression.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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