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Emerging therapies in Systemic lupus erythematosus: From clinical trial to the real life.

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by multisystem involvement and a relapsing remitting course. SLE is a highly heterogeneous condition, with wide variations in both the presentation and severity of disease and the biological markers identified.

The use of biologics in SLE has lagged behind that of other rheumatological conditions such as rheumatoid arthritis, in part due to the diverse clinical manifestations of SLE, making it difficult to design appropriate trials for novel treatments. As such, broad immunosuppressive treatment regimens are still widely used in SLE. Nevertheless, in recent years, elucidation of some aspects of SLE pathogenesis have allowed the development of therapies targeted at molecular mediators of SLE. This review provides an update of biological available therapies and those currently under development.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by its relapsing remitting course and multisystem involvement.

The overall prevalence of SLE varies by ethnicity, age, geographical location and other factors. The prevalence in the United states has been quoted at between 14.6 and 50 per 100,000 persons [1]. More recently, a retrospective study covering most of the French population has demonstrated a prevalence of 40.6 per 100,000 persons [2].

Clinical manifestations include constitutional symptoms, such as fever and malaise, in addition to dermatological, musculoskeletal, renal, respiratory, cardiovascular, haematological and neurological involvement [3,4].

The mainstay of treatment for SLE still relies heavily on glucocorticoids, antimalarials and immunosuppressive agents [5]. These treatments have led to vast improvements in the prognosis of SLE, despite presenting their own unique challenges due to numerous adverse effects. Disease refractory to conventional therapies as well as the challenges posed by immunosuppressive and cytotoxic treatments has led to the need for development of more efficacious interventions with fewer associated risks.

The biological therapies represent a large group of emerging therapies for autoimmune diseases including SLE. However, both study design and identifying suitable and accurately measurable outcome criteria have presented significant barriers in the assessment of both efficacy and safety profiles in these promising new agents [6].

Here we discuss the current B-cell targeted therapies (Rituximab and Belimumab) already being used in the treatment of SLE, as well as the emerging treatments

thought to act on a variety of specific immunological targets shown to play a role in the pathogenesis of SLE.

B cell therapies already available

Rituximab

CD20 (or B-lymphocyte antigen CD20) is a protein widely expressed on B cell lymphocytes. Its function is as yet unknown. It is thought that it may play a role in calcium influx leading to the activation of B-cells. Rituximab is a chimeric monoclonal antibody against CD20 receptor. When rituximab binds CD20 it results in an asymmetric clustering of proteins on one side of the B-cell. This change in morphology leads to an increase in the successful kill rate by natural killer (NK) cells [7]. By this mechanism it is thought that rituximab results in a reduction in B-cell numbers and antibody titres. It is this purported mechanism of action that has, for years, underpinned the clinical use of rituximab in conditions where excess clonal proliferation of B-cells leads to an abundance of offending antibodies.

Evidence from a number of open-label, uncontrolled studies has supported the use of rituximab in SLE for more than one decade [6]. More recently the randomised controlled trials (RCTs) EXPLORER (the exploratory Phase II/III SLE evaluation of rituximab) [8] and LUNAR (lupus nephritis assessment with rituximab) [9] investigated the use of Rituximab in patients with SLE. The results of these two RCTs showed no superiority when compared with conventional treatments. This having been said, a thorough critical evaluation of the trials' design and observations is necessary before condemning the use of Rituximab in SLE altogether.

Firstly, It has been suggested that patients included in both trials (particularly EXPLORER) were likely to have less severe disease: in detail, in the EXPLORER

trial, previous cyclophosphamide (CYC) or high dose glucocorticoid therapy were among the exclusion criteria and in the LUNAR trial patients were included only if they experienced their first episode of lupus nephritis and were excluded if they had more than 50% glomerular sclerosis, interstitial fibrosis or an estimated glomerular filtration rate of $<25\text{ml/min/1.73m}^2$ [10].

Secondly, when looking at concomitant therapies used, both trials have been criticised for their use of high dose glucocorticoids (up to 1mg/kg) alongside Rituximab which many argue may have masked the true efficacy of B-cell depletion therapy in a short term follow-up period [11].

Thirdly, when comparing Rituximab to Belimumab (an inhibitor of B lymphocyte stimulator, shown to be effective in SLE by the BLISS-52 and BLISS-76 trials) the numbers of patients enrolled in the EXPLORER and LUNAR trials were smaller (257 and 144, respectively) when compared to the trials which demonstrated Belimumab's superior efficacy (867 in BLISS-52 and 819 in BLISS-76).

Finally, and most critically, aiming to prove the superiority of rituximab over current first-line immunosuppressive therapies in SLE does not reflect the use of rituximab in clinical practice, where rituximab is mainly considered in refractory cases to these therapies. Herewith, a brief summary of real-life experiences supporting the beneficial use of Rituximab in selected cases.

In Italy a multi-centre study looked at data from the off-label use of rituximab in the treatment of refractory lupus. They found a significant proportion of patients with a systemic complete response (CR) (defined as European Consensus Lupus Activity Measurement (ECLAM) score ≤ 1) or partial response (PR) (defined as $1 < \text{ECLAM} \leq 3$). Renal CR (RCR) and renal PR (RPR) were defined according to EULAR

recommendations for management of lupus nephritis. Following rituximab use, CR or PR were observed in 85.8% and CR in 45.5% of cases, after 12-month follow-up [12].

Ramos-Casals *et al.* reported 188 cases of refractory SLE treated with Rituximab in the literature. Of these 91% showed significant improvement in one or more systemic manifestations of SLE. When focusing on specific manifestation, it is worth noting that more than a hundred of the patients they reviewed had lupus nephritis and 91% of these achieved a response to treatment with rituximab [13]. Similarly, they found that non-renal manifestations of SLE showed improvement with rituximab. Notably they found that cardiopulmonary, haematological, articular and central nervous system manifestations of SLE showed a treatment response in 100%, 94%, 91% and 89% of patients respectively. [13]

Condon *et al.* followed 50 patients with biopsy proven (class III, IV or V) Lupus Nephritis treated with a regimen of three pulses of methylprednisolone (500mg) two rituximab infusions(1000mg), 14 days apart, given in combination with long term mycophenolate mofetil and in most cases without oral corticosteroids. Forty-five patients (90%) had either a complete or partial response to treatment and of those 45 only 2 patients required courses of oral steroids for a duration longer than 2 weeks for acute flares of systemic disease.[14] Given that steroid burden in patients with lupus is a serious problem, this study presents an early insight into the possible benefits of a treatment regime that could dramatically reduce total corticosteroid doses.

Davies *et al.* used rituximab to treat 18 patients with lupus nephritis refractory to conventional immunosuppressive therapy (including intravenous cyclophosphamide).

Over the follow-up period (minimum 1 year and in some cases longer) 13 out of 18 patients achieved a (complete or partial) response following treatment with rituximab. However, this study also identified a poor response in patients with rapidly progressive crescentic lupus nephritis with existing evidence of significant renal impairment. In these patients rituximab did not prevent progression to end-stage renal failure and dialysis [15].

Cobo-Ibáñez *et al* [16]. performed a systematic review of the efficacy and safety of rituximab in non-renal SLE. From a literature search they identified 26 studies (1 randomized controlled trial and its exploratory analysis, 2 open-label studies and 22 cohort studies, of which 15 were prospective), which in total analysed 1231 patients with SLE refractory to glucocorticoids and/or immunosuppressant drugs. They concluded from their analyses that rituximab could be considered a safe and effective short-term treatment in non-renal SLE, reducing disease activity, steroid doses and anti-ds-DNA levels and increasing complement levels. They did however identify significant relapses, with 11 studies reporting relapses in disease activity. The best responses to treatment were seen in articular involvement (complete or partial response ranging from 72% to 81.5% over 3-6 months) and thrombocytopaenia (of 6 cohort studies that evaluated short-term thrombocytopaenia, 3 showed 50–92% complete or partial response, and in the others the mean platelets level increase was significant). Regarding other non-renal manifestations the authors felt unable to draw meaningful conclusions due to lack of data.

In Korea a multicentre retrospective analysis of the use of rituximab in refractory SLE demonstrated a global response to treatment in 28 of 39 patients. This was

demonstrated by a significant reduction in SLEDAI scores over 6, 12 and 24 months after rituximab therapy. [17]

Very recently, a promising role of rituximab in an intensified protocol of induction therapy has been reported in patients for whom avoiding immunosuppressive maintenance therapy and sparing steroids are particularly appealing [18]. Such different approach, initially employed as a rescue therapy in refractory LN, has been proposed in order to minimize the long-term effects of both corticosteroids and the immunosuppressive agents used for remission maintenance. It was based on an intensified B-lymphocyte depletion consisting of “four (weekly) plus two (monthly) doses” of rituximab (375 mg/sm), associated with two i.v administrations of 10 mg/kg cyclophosphamide and three pulses of methylprednisolone, followed by oral prednisone tapered to 5 mg/day in 10 weeks, without further immunosuppressive maintenance therapy.

Taken the above together, it is apparent that the conclusions arrived at by the EXPLORER and LUNAR trials differ from those presented by non-randomized studies and systematic reviews. There is a definite need for further large studies looking at the use of rituximab in patients with refractory SLE with both renal and non-renal manifestations. It seems however, that clinicians will continue to use rituximab in the treatment of refractory SLE.

Belimumab

B-lymphocyte stimulator (BLys) is a glycoprotein based cytokine and a member of the tumour necrosis factor (TNF) family, and is an important factor in controlling B cell survival and the generation of a normal immune response (Schneider et al 1999). Transgenic mice over expressing BLys has been shown to develop

autoimmune conditions analogous to SLE and Sjogren's syndrome in humans [19,20]. Indeed, levels of soluble BLys have been found to correlate to SLE disease activity in patients, both in terms of dsDNA levels and SELENA-SLEDAI scores [21].

As such, developing an antagonist to BLys seems a logical step in the search for novel SLE treatments.

Belimumab, a fully humanised monoclonal antibody inhibitor of BLys, gained regulatory approval in the US in 2011 and subsequently in Europe. As of writing, Belimumab remains the only licenced SLE biologic and US based studies carried in the last 2 years estimated that 5%-6% of patients are currently being treated with this medication [22][23]

Phase I and II trials for Belimumab were carried out in 2008 and 2009, with cohorts of 72 and 449 patients respectively. These trials showed that administration of Belimumab resulted in significantly reduced circulating CD20+ B cells levels after 4-8 weeks (Furie et al., 2008, Wallace et al., 2009), thus providing a level of evidence for its molecular efficacy in humans. These two trials also provided evidence for the safety of Belimumab with similar numbers of adverse events (such as serious infections) in the treatment group compared to the placebo group.

Potential confounders, which could have obscured an otherwise significant difference within a more specific group, included the heterogeneous patient population. The inclusion criteria was relatively broad, for example, while patients were required to have a history of positive circulating auto-antibodies, these antibodies did not have to be present at time of screening/initiation of therapy. The range of existing treatments for the trial cohort was also relatively diverse. In addition, Belimumab was used in combination with standard SLE therapies, changes

in these standard therapies during the study could have masked/extenuated the effect that Belimumab would have otherwise had.

Subcategory analysis showed that Belimumab was able to significantly reduce the number of disease flares during week 24-52, therefore suggesting that while suppression of B cell levels are achieved relatively early on in the treatment cycle, the clinical efficacy of Belimumab may take some time to take effect. Furthermore, subgroup analysis showed that seroactive patients (patients with clinically elevated circulating autoantibodies at the start of the trial, which was found to be correlated to BLyS levels) showed a significant greater reduction in SELENA-SLEDAI score compared to placebo. In addition, it was also noted that treatment with Belimumab reduced the required dose of corticosteroids in patients.

Two multi-centre Phase III trials for Belimumab were conducted in 2011 (Bliss 52 and 76), with over 1600 patients in total. Together, these two trials provided a good demographic coverage of the global SLE population (with the significant exception of Africa), with Bliss-52 being conducted in Asia, South America, and Eastern Europe and Bliss-76 carried out in the US and Europe [24,25]. Building on data from earlier studies, Belimumab was given with standard SLE therapy and compared with placebo plus standard SLE therapy. While a similar dose range of Belimumab was used (1 mg/kg and 10 mg/kg), higher disease activity was required in order to be included in these trials (a SELENA–SLEDAI score of ≥ 6 was needed compared to ≥ 4 in phase II trials) , and the endpoint at which primary efficacy was measured was set at week 52 instead of week 24

Both studies showed significant improvements in the SLE Responder Index (SRI) at the primary endpoint compared to placebo, with similar rates of adverse events. In

the BLISS52 trial, both 1 mg/kg and 10 mg/kg doses of Belimumab produced a significant SRI rates (51% and 58% respectively) compared to placebo (SRI: 44%), while in the BLISS76 trial a significant effects was only seen with the higher 10 mg/kg dose, where the SRI response of 42% compared to 33% in the placebo group. In both studies, the 10 mg/kg dose showed greater efficacy compared to the 1 mg/kg dose.

In addition to dampening disease activity, Belimumab was also shown to decrease the risk of SLE flares (van Vollenhoven et al., 2012). Further analysis of the trial data showed that patients with low complement levels, higher SELENA–SLEDAI scores (≥ 10), positive dsDNA titres or those treated corticosteroids exhibited greater response to Belimumab compared to patients who lacked these features [26]. As the presence of the above features is correlated with more active disease, it can be inferred that Belimumab exhibits the greatest efficacy in patients with more severe SLE.

In the BLISS 76 trial, SRI were also measured over a longer 76 week period. However, while SRI response rates was greater at this time point in the cohort treated with Belimumab compared to the placebo group, the improvement was not statistically significant [24]. The authors suggested that more liberal use of prednisolone in the placebo group coupled with a 7% dropout rate between weeks 52 and 76 could have prevented the results from reaching significance. Nevertheless, these results does raise questions regarding the efficacy of prolonged use of Belimumab in patients with SLE.

Taken the above together, some considerations are still needed. While in these studies, all patients received standard SLE therapy in addition to either placebo or

Belimumab, a restriction of new immunosuppressive therapies during the trials was placed on the initiation. In addition, there were limits placed on the doses of existing immunosuppressive, antimalarial and corticosteroid agents used in patients in both groups for the duration of the trial. While these limits and prohibitions does most likely serve to create a less biased comparison to the fixed dose regimes of Belimumab in the trial group, it does remove some of the dynamic, real world clinical responses to the evolution of disease in patients from the field of comparison. Use of IV Cyclophosphamide, historically regarded as a preferred treatment of severe SLE, was also an exclusion criteria in these studies [4]. Exclusion of such a major SLE treatment from comparison, whilst perhaps useful and necessary for the conduct of the trial, does also limit the potential application of the study's results.

In addition to cyclophosphamide, other major exclusion criteria in these studies were paediatric patients (age <18), and those with severe active central nervous system disease or/and severe active lupus nephritis, as such the usefulness of Belimumab in these patient populations cannot be extrapolated from these studies. A post hoc analysis of 267 patients with non-acute renal disease in these trials showed that Belimumab was more efficacious than placebo in terms of improving renal outcomes, however, statistical significance were not reached for many of the parameters measured. This inconclusive result is perhaps due to the relatively small numbers of renal patients involved and the fact that the BLISS trials excluded a significant proportion of patients with renal involvement [27].

Upcoming biological agents targeting B cells

Atacicept

As described earlier in this article, both APRIL and Blys are secreted cytokines, produced by a variety of cells involved in immune mediation such as monocytes, dendritic cells, macrophages, and T cells. These factors then bind to B cell surface receptors and resulting in B cell maturation into plasma cells and APRIL has also been shown to enhance antigen presentation by B cells through binding to the B-cell maturation antigen [28,29]. Blys and APRIL levels are increased in patients with autoimmune disorders including SLE [30–32].

Atacicept is a humanised recombinant protein, containing both human IgG and the extracellular portion of the B cell calcium-modulating ligand interactor (TACI), a receptor to which both Blys and APRIL bind in order to mediate their actions. Atacicept, with its binding site mimic, acts to bind Blys and APRIL, thereby blocking this signalling pathway [30,33][34].

However, there does exist conflicting evidence where serum levels of APRIL was shown to be inversely correlated to both dsDNA titres and clinical disease activity in at least one study [35]. While, this study does not claim any causative link between any decrease in APRIL and flare of SLE, it does raise the question of whether Blys is a better inhibitory target for controlling the disease.

In animal models of SLE, Atacicept was shown to reduce both B cell numbers and circulating Ig levels, and was able to delay the development of proteinuria and increase survival time in autoimmune-prone lupus mice [36,37].

Results of a phase 1a trial, conducted with healthy male volunteers and using subcutaneous injections showed that Atacicept was well tolerated across a relatively wide dose range [38]. Results from two phase 1b trials showed that Atacicept administration was effective in reducing both B cell numbers and Ig levels in patients with SELENA–SLEDAI scores between 1 to 10. Major exclusion criteria in the two

above studies study were patients already on immunosuppressive medications within 8 weeks of enrolment (i.e. azathioprine, methotrexate, mycophenolate, and cyclophosphamide), and patients on prednisolone doses greater than 20 mg. Furthermore, patients with significant neurological/CNS, liver, renal disease or congestive cardiac failure were also excluded [39,40]. These criteria limit any inferences regarding efficacy of Atacicept to SLE patients with mild or moderate disease without any significant major organ involvement.

In subsequent years, two phase II/III trials were conducted for Atacicept [30,41]. The results from these trials, while showing clinical efficacy at higher doses compared to placebo, revealed concerns about the propensity of SLE patient having a higher probability of developing serious infections while on Atacicept.

In the trial conducted by Isenberg et al, patients were randomised to receive placebo or Atacicept at 75 mg or 150 mg subcutaneously over a total of 52 weeks. At the 75 mg dose, the investigators failed to show a significant improvement in either SLE flare rates or time to first flare compared to placebo. Unfortunately, two cases of fatal respiratory tract infections led to the early termination of the 150 mg arm. In addition, non-fatal infections were more common in the treatment group than the placebo group. This outcome differs from the phase I trials where Atacicept appeared to be well tolerated. One explanation for this disparity could be that in the earlier trials Atacicept was either administered as a single dose or weekly for a maximum of 4 weeks, whereas in the phase II/III trial treatment was continued for 52 weeks resulting in an increased period of more pronounced immunosuppression [30,39,40].

However, despite the early termination, post-hoc analysis did show that at the 150 mg dose, Atacicept was able to significantly decrease both flare rates (odds ratio

0.48) and time to first flare (odds ratio 0.56). These results, while encouraging, need to be set against the risk for Atacicept to increase the chance of serious infections, especially in patients with only mild to moderate disease.

A study published in 2012 showed an association in levels of serum APRIL and proteinuria and histological severity/activity in patients with lupus nephritis. Additionally, both serum APRIL and intrarenal mRNA of APRIL levels were correlated with increased resistance to treatment [41]. On the back of this data, a phase II/III trial was conducted to evaluate the efficacy of Atacicept in combination with corticosteroids and MMF in patients with active lupus nephritis [41]. The study was terminated after enrolling just 6 patients, due to the occurrence of serious adverse events. A significant reduction in serum Ig levels in the treatment group compared to the placebo group was observed on day 1 of treatment, and Ig levels continued to decline throughout treatment, in three cases reaching the discontinuation limit of < 3g/l. Two of these patients developed pneumonia. Patients in the treatment group also developed more pronounced proteinuria compared to placebo. It is possible that the combination of medication led to a greater level of immunosuppression than the investigators anticipated.

The above studies raises serious concerns regarding the use of Atacicept in SLE patients and further studies are needed in order to assess its safety and pharmacodynamics before clinical efficacy can be evaluated. Evidence from trials on patients with rheumatoid arthritis also advises caution with a greater frequency of adverse events due to infections in the treatment cohort compared to those on placebo [42,43].

Blisibimod

Following from the success of Belimumab other Blys antagonists were developed. Blisibimod is a synthetic “peptibody” molecule where the stabilising effects of an Ig Fc fragment is used to reduce the rate of degradation of the pharmacologically active peptide [44]. It is able to bind both the membrane bound and soluble forms of Blys, which may allow it to achieve more potent level of target inhibition compared to Belimumab, which only binds soluble Blys [32].

A placebo controlled phase I trial, where patients with either stable or inactive SLE was carried out. Patients were given variable doses of Blisibimod in either a single injection or four weekly doses and the results compared to placebo. The percentage of adverse events between those treated with of Blisibimod and placebo were similar. Administration with of Blisibimod resulted in a significant reduction in the levels of naïve B cells, with a comparable increase in the number of memory B cells. However, by 160 days post administration the level of memory B cells had returned to baseline, while naïve B cell numbers continued to be suppressed. This led to a total reduction in B cell numbers of around 30% [32].

Building on the above data, a phase II trial was conducted on patients with moderate and severe SLE with a SELENA-SLEDAI score ≥ 6 and showed promising results [45]. Administration of Blisibimod resulted in significant reductions in dsDNA levels and B cell numbers coupled with increased C3 and C4 levels. At the highest doses, Blisibimod was able to significantly improve SLE Responder Index-5 response rates measured at week 20 post treatment ($p=0.02$). SRI response rates was the highest in patients with more severe disease (SELENA-SLEDAI ≥ 10) and receiving corticosteroid treatment at enrolment with 41.7% of patients achieving a ≥ 7 or $\geq 6=8$ point decrease in their SELENA-SLEDAI score. Furthermore, significant reductions in proteinuria was seen in patients with a protein creatinine ratio of 1-6 [46].

A phase III doubled blinded placebo controlled trial was initiated in 2013 by with an enrolment target of around 400 patients. Included patients were those with active SLE with a SELENA-SLEDAI score of ≥ 10 despite on-going stable corticosteroid therapy. Either Blisibimod or placebo was administered alongside standard therapy. The primary endpoint was set as the proportion of patients achieving SLE Responder Index at week 52. It was announced that the study had recently reached its enrolment target with the study completion date set at December 2015 [47].

Tabalumab

The monoclonal antibody Tabalumab has a similar mechanism of action as Blisibimod, acting as an antagonist to both the membrane bound and soluble versions of BLyS. As well as SLE, this medication has been trialled as a treatment for patients with rheumatoid arthritis with inadequate response to conventional treatments. The studies reported somewhat mixed results, with the most recent phase III trial failing to show clinical efficacy for Tabalumab. Nevertheless, the trials did show that Tabalumab was safe to use in RA patients [48–52].

More recently, two phase III trials have been conducted to assess the efficacy of Tabalumab [53,54]. In the ILLUMINATE-1 trial 1164 SLE patients with moderate to severe disease (SELENA-SLEDAI ≥ 6) were recruited. Standard of care therapy (SOC) was provided in addition to either Tabalumab (in the form of subcutaneous injections either two or four weeks') or placebo. The study showed that SOC plus Tabalumab was effective in significantly reducing B cell levels, serum Ig and levels dsDNA, while increasing C3 and C4 titres compared to SOC plus placebo. However, the primary endpoint: (percentage of patients achieving SRI-5 at week 52), was not met, with a similar proportion of patients achieving SRI-5 in the two treatment groups

(Fortnightly injections: 31.8%; 4 weekly injections: 35.2% and placebo: 29.3%), nor were the secondary endpoints met. Results from the ILLUMINATE-2 trial was more positive, the trial's 1124 patients had similar disease characteristics as those in the ILLUMINATE-1 trial. With ILLUMINATE-2, the primary endpoint (SRI-5 at 52 weeks) was met with the more frequent fortnightly treatments (Treatment: 38.4% and placebo: 27.7% $p=0.002$). The results from the once monthly treatments narrowly missed reaching significance (34.8%, $p=0.051$). In addition, secondary endpoints, such as reductions in time to next severe flare and sparing of corticosteroids were not met. It is noted that Tabalumab was more effective achieving the SRI-5 response in patients who were serologically active, and these patients showed greater improvement in SELENA-SLEDAI score, B cell, Ig and complement levels.

Data from these two large trials paint a mixed picture and it would appear that Tabalumab, while able to target both soluble and insoluble forms of BLys, is in fact less effective at controlling SLE disease activity compared to Belimumab. However, several potential confounders does exist in the study design, in the ILLUMINATE-1 study, investigators deemed any changes to patient's dose of steroids as failing the trial, even if the steroid dose was decreased. Also, it was pointed out by one of the primary investigators, that the target was perhaps set too high and the high levels of immunosuppression the patients in the study were already on could prevent the primary endpoint from being reached [55].

These points highlight the difficulty in designing a suitable large scale trial for the study of a multi-system disease such as SLE, where it is often very difficult to reduce or stop the existing treatments that the patients are on in order to make an entirely objective comparison. It would seem that careful trial design and careful patient

selection is key for studies such as the ones highlighted above to produce meaningful results.

Epratuzumab

Initially developed to treat non-Hodgkin's lymphoma, Epratuzumab is a fully humanised monoclonal antibody against the B cell surface receptor CD-22, (Wallace et al., 2013a). CD-22 is a glycol-protein membrane receptor which controls B cell activation and migration, it is also involved in B cell receptor (BCR) inactivation. CD-22 has been shown to be elevated in patients in patients with SLE and other autoimmune conditions [56].

In 2006, a small phase II open label trial was conducted on 14 patients with moderately active SLE (BILAG score 6 to 12), with 4 doses of Epratuzumab being given intravenously two weeks apart [57]. Patients were followed up at regular intervals for 6 months post treatment. Treatment with Epratuzumab was well tolerated and results showed an average decrease of 35% in B cell levels at week 18 (Epratuzumab has a half-life of 23.9 days) and no significant changes in T cells levels, immunoglobulins, or autoantibody levels were detected. All 14 patients showed a $\geq 50\%$ reduction in their BILAG scores at least one time point during the study, while 13 patients still experienced reductions in their BILAG at week 18 [57]. More, recently, the results of a small (a cohort of 20 patients with moderate-severe SLE despite standard therapy) 12 week, placebo controlled, phase 1-2 trial was published [58]. Epratuzumab was administered either weekly or fortnightly in a 4 week initial dosing period to achieve a cumulative dose (cd) of 200 mg to 2400 mg per patient. Epratuzumab was found to have an average half-life of 13 days, and its administration caused a decrease in both B cell numbers and average B cell CD-22

fluorescence intensity. Again, Epratuzumab was found to be well tolerated in SLE patients.

Building on the above studies, a randomised, double blinded, placebo controlled trial were conducted [59]. The EMBLEM trial recruited a total of 227 patients with moderate to severe SLE. Like the Tsuru et al study, patients received weekly/fortnightly Epratuzumab injections in a 4 week dosing period to achieve a cd of 200 mg to 3600 mg (5 treatment groups). Primary outcome was measured using a composite endpoint British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) (see addendum for score breakdown). It was reported that all treatment groups achieved a higher response rate compared to placebo, although the cumulative results failed to reach significance ($P=0.148$). Group specific analysis revealed that in the 2400 mg (cd) group, a significant treatment effect ($OR=2.9$ (1.2 to 7.1), nominal $p=0.02$).

The ALLEVIATE I and II trials recruited 90 patients in total and compared SOC plus Epratuzumab [60] (at 360 mg/m² n=42 or 720 mg/m² n=11) with SOC plus placebo (n=37). In both studies, Epratuzumab was administered in 12 week cycles for up to 48 weeks, giving a total of 10 doses. The primary endpoint was BILAG response at week 24 (all BILAG reduced by at least one grade e.g. from B to C/D and no new A and <2 new B scores). Recruitment started in 2005, however both trials were terminated early due to interruptions in the drug supply. As such the primary endpoint was assessed at 12, instead of 24 weeks. The available data from both RCTs were combined and analysed. It was found at week 12, responses were 44.1% for patients receiving the 360 mg/m² and 20% for the 720 mg/m² dose, while the response rate was 30% for the placebo group [61]. In terms of quality of life outcomes, both patient and physician global assessments of disease activity (PtGA

and PGA) showed greater improvements in the treatment arms compared to those receiving placebo and this was sustained through the trial but did not reach statistical significance. In addition, use of Epratuzumab was shown to be partially steroid sparing. At week 24, the mean cumulative corticosteroid doses for the groups on Epratuzumab was 1051 mg (360 mg/m² group p=0.034) and 1973 mg (for the 720 mg/m² group p=0.081) less than the placebo group respectively (Strand et al., 2014).

A theory has been put forward as to why the lower dose (360 mg/m²) of Epratuzumab showed more clinical efficacy than the higher dose (720 mg/m²). It has been reported that when serum concentrations of anti CD-22 antibodies are high, a process named trogocytosis, mediated by mononuclear cells, facilitates the removal of CD-22 molecules from the cell membranes, thereby allowing the cells to escape antibody targeting [62].

Twenty-nine patients who participated in the ALLEVIATE trials in the US were enrolled into a follow-on trial (SL0006) to study the efficacy and safety of long term administration of Epratuzumab. Patients were given Epratuzumab in 12 week cycles for a median of 120 weeks. However, it should be noted that due to the interruption in medication supply, there was a median delay of 165 days between the patients completing the ALLEVIATE trial and starting the SL0006 extension trial. Despite the delay, patients in the SL006 trial were able to maintain the improvement in their BILAG scores gained during treatment under ALLEVIATE [60].

Based on the promising data from the above Phase I and II trials, two phase III trials have been initiated (EMBODY I and II), both studies have been completed (June 2015), the results from these studies are still pending[63]. However in July 2015 it

was reported that although these trials did not identify any new safety concerns, they did fail to reach their primary endpoint for both dose of Epratuzumab [64].

Ocrelizumab

Like rituximab, Ocrelizumab is a monoclonal anti-CD20 antibody, and a B cell depleting agent. It binds a slightly different, but overlapping epitope as rituximab. In vitro experiments have shown that Ocrelizumab has greater ability to induce antibody-dependent cell-mediated cytotoxicity and reduced complement-dependent cytotoxicity compared to rituximab. If these effects hold true in vivo, it should lead to greater efficacy and reduced frequency and severity of adverse reactions [65].

With regards to rheumatological conditions, the safety and efficacy of Ocrelizumab were more extensively studied in rheumatoid arthritis patients than SLE. Elevated numbers of serious infections were reported in several trials, especially with higher doses of Ocrelizumab (500 mg) [66–68].

The BEGIN trial was initiated to study the safety and efficacy of Ocrelizumab in patient with non-renal SLE. This study was terminated early, due to the impression that Ocrelizumab was unlikely to be efficacious in active SLE [69].

The phase III (double blinded, placebo controlled randomised) BELONG trial studied patients with class III/IV lupus nephritis, with 381 patients recruited [70]. Patients were given either placebo, 400 mg or 1000 mg of Ocrelizumab, on day 1 and 15 of the trial, then every 16 weeks to maintain a state of B cell depletion. Administration of Ocrelizumab or placebo was accompanied by corticosteroid treatment plus either MMF or cyclophosphamide followed by azathioprine. The primary endpoint was the percentage of patients achieving total or partial remission from lupus nephritis at 48 week of treatment. BELONG was terminated early due to an significant higher

number of serious infections in the Ocrelizumab group (28.8 events per 100 patients for the 400 mg group and 25.1 events per 100 patients in the 1000 mg group) compared with placebo group (18.7 events per 100 patients). Of note, this imbalance only occurred in patients receiving Ocrelizumab and MMF, but not patients receiving Ocrelizumab with CYC followed by azathioprine, potentially suggesting that Ocrelizumab and MMF exerts a greater than expected synergistic immunosuppressive effect.

The response rates for patients treated with Ocrelizumab were greater than the group treated with placebo.

Biological agents targeting IL-6

Tocilizumab

Under the influence of IL-6, B lymphocytes differentiate into mature plasma cells and secrete antibodies. IL-6 levels have been shown to be raised in human and murine lupus, and murine studies have shown a link between IL-6 blockade and decreased levels of ds-DNA antibodies[71].

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). In an open-label phase I dosage escalation study Illei *et al.* administered tocilizumab (2mg/kg, 4mg/kg or 8mg/kg once a week, every other week) to 16 patients (one of whom was removed from the study for neutropenia), with mild-moderate disease activity scores, for 12 weeks. They were then monitored for an additional 8 weeks. They observed a ≥ 4 point reduction in SELENA scores in 8 of the 15 patients. In the 7 patient with arthritis at the outset of the study, all saw an improvement, in 4 of these patients their arthritis completely resolved. Anti-ds-DNA

antibody titres decreased by a median of 47% in the 4mg/kg and 8mg/kg dosage groups with a 7.8% decrease in IgG levels and a significant decrease in the frequency of circulating plasma cells. The study did however identify a transient drop in neutrophil counts (38% and 56% respectively in the 4mg/kg and 8mg/kg groups) which resolved after cessation of treatment.[72] Before tocilizumab could be part of the routine strategies in SLE, further studies are warranted.

Sirukumab

Sirukumab is a human monoclonal antibody that binds with high affinity to human IL-6. Szepietowski *et al.* administered 10mg/kg of Sirukumab or placebo to 15 patients (with a 2:1 ratio respectively) with SLE (with a SELENA-SELDAI scores of 5-12) in a randomized, double-blinded, dose escalation study. Adverse events occurred more often with sirukumab than placebo (90% vs 80%). Dose-independent reductions in white blood cell counts, neutrophil counts and platelet counts were observed with Sirukumab with minor elevations in total cholesterol also being observed. No clinically relevant changes in disease activity scores were identified between the sirukumab and placebo groups[73].

Biological agents targeting type I interferons

Type I interferons (IFN) are implicated in the pathogenesis of SLE [74–76]. It has been suggested that autoreactive T-cells which have escaped central tolerance promote the proliferation of autoreactive B cells and plasma cells and the formation of autoantibodies. One theory behind this is that dendritic cells proliferate, which promote the survival of autoreactive T-cells, may be upregulated by the over-

production of IFN- α in response to environmental factors such as viral infections, implicated in the pathogenesis of SLE and subsequent disease flares.

Sifalimumab

Sifalimumab is a human IgG1 monoclonal antibody to interferon- α . Phase 1 trials have demonstrated an acceptable safety profile and shown that Sifalimumab tended to reduce the number of disease flares [77–79]. A phase IIb randomized, double-blinded, placebo-controlled study followed 431 patients with moderate to severe SLE given monthly doses of 200, 600 or 1200mg of Sifalimumab or placebo for 1 year. Patients treated with Sifalimumab demonstrated reduced SLE disease activity over multiple clinical measures including joint involvement and fatigue scores. Surprisingly, neither high ds-DNA titres nor low complement levels were found to normalise over the course of the study [76].

Rontalizumab

Rontalizumab is a human IgG1 monoclonal antibody targeting all known isoforms of human IFN- α . Its safety and efficacy in SLE was first demonstrated by McBride *et al.* in a phase I study of 60 patients with SLE in a dose escalation study [80]. Subsequently a phase II study of 238 patients by Kalunian *et al.* showed no overall difference in response rates (evaluated by SRI/BILAG) between treatment and placebo at 24 weeks. However, an exploratory analysis showed a reduction in flare rates and steroid burden in some patients with a low baseline interferon signature metric (ISM)) in the rontalizumab arms [81].

IFN- α kinoid

IFN- α kinoid (IFN-K), a drug composed of inactivated IFN- α coupled to a carrier protein (keyhole limpet hemocyanin) has shown promising results in murine SLE studies [82]. Lauwerys *et al.* conducted a multi-centre, randomized, double-blind, placebo-controlled study of 28 mostly Caucasian women with mild to moderate SLE with a range in SLEDAI-2K scores between 4 and 10. Their results showed that IFN-K was well tolerated, induced anti-IFN antibodies, and down-regulated IFN-induced genes in patients overexpressing IFN-inducible genes at baseline. They also demonstrated that the anti-IFN antibody response induced by IFN-K was associated with the recovery of serum complement C3 levels[83].

Biological agents targeting T cell

Edratide

Edratide is a tolerogenic peptide based on the sequence of the first complementarity-determining (CDR1) regions of an anti-DNA monoclonal antibody (16/6 idotype). The drug has shown promising results in preliminary studies demonstrating the down regulation of cytokines, apoptosis and IFN- α gene expression [84][34]. A phase II trial of 340 SLE patients with SLEDAI-2K of 6–12 receiving either edratide or placebo showed an acceptable safety profile and the drug was overall well tolerated. The study failed to meet the primary endpoints of reduction in SLEDAI-2K and adjusted mean SLEDAI. However, the secondary endpoint of improved BILAG scores was met for the 0.5mg Edratide arm. A post hoc analyses also showed promising results [85].

Laquinimod

Laquinimod has been originally investigated in the treatment of relapsing–remitting multiple sclerosis [86]. Laquinimod downregulates the proinflammatory cytokines (IL-6, IL-12, IL-17, IL-23, and TNF- α) but increases the production of IL-10, exerting an immunomodulating effects on antigen presenting cells that direct T cells.

Jayne *et al.* conducted a 24 week phase IIa study where laquinimod or placebo (in combination with standard of care treatments) were given to 46 patients (2:1 ratio respectively) with active lupus nephritis. Preliminary results (REF only able to find abstract not fully published study) showed an improvement in renal function (as assessed by eGFR and proteinuria) as well as appearing to be well tolerated throughout the treatment groups [87].

Rigerimod/Lupuzor

Rigerimod, also known as Lupuzor, a novel 21-mer peptide agent currently undergoing phase III trials. This peptide is derived from a heavily phosphorylated region of the U1-70K snRNP protein, a nuclear riboprotein and a spliceosome component [88]. Auto-antibodies against this protein has been found in SLE and mixed connective tissue diseases [89,90]. The Lupuzor peptide contains an in-vivo phosphorylation site at position Ser140 (position 10 in the peptide itself), and is recognised by CD4⁺ T cells and binds IgG produced by classic murine models of SLE (MRL/lpr and (NZBxNZW) F1 mice) [91–93].

Although the exact mechanisms of action of Lupuzor is not completely understood , it doesn't seem to act as a immunosuppressant in the classical sense but rather as an immunomodulator, which modifies the sequence of cellular auto-immunological events that leads to SLE disease progression. The process of autophagy, which

modulates the disassembly and recycling of cellular components, has been shown to be an important pathway by which cellular antigens are presented to CD4⁺ T cells, which can then lead to the development of autoimmunity [94]. In mouse models administration of Lupuzor has been shown to reduce autoreactive T-cell priming by these antigens through reduction of the autophagic flux and reducing the stability of MHC II complexes [95–97]. Reassuringly, the effects of Lupuzor seems to be restricted to autoimmune processes and does not alter the ability to respond to viral infections in mouse models [96] which, if borne out in human patients, gives it a clear advantage compared to traditional “broad spectrum” immunosuppressive agents.

The safety and efficacy of Lupuzor was assessed in 2008 in an open label phase IIa trial involving 20 patients with moderately active SLE. This trial showed that the peptide was well tolerated and that three administrations of Lupuzor at 200 µg resulted in significant reductions in both auto-antibody levels and physician assessed disease activity [98]. This trial was followed by a double blinded placebo controlled phase IIb trial involving 149 patients who scored ≥6 on the SLEDAI-2K. This trials showed that an injection of Lupuzor (200 µg) every 4 weeks was efficacious in 61.9% of patients, measured by the SLE Responder Index (SRI) compared to 38.6% in the placebo group [99].

A phase III trial is currently underway in the US and Europe and going through patient recruitment and ethics approval. [100]

Biological Agents approved for other indication: the case of Abatacept

To launch a T cell dependent B cell response, T cells require two distinct signals. The first specific pathway involves the binding of the T cell receptor (TCR) to antigen in the context of major histocompatibility complex class II. The second involves non-

antigen specific pathways. Of these pathways the best described are the receptor ligand interactions between CD28 and CTLA4 (a molecule homologous to CD28 only expressed on activated T cells) on T cells with B7 molecules expressed on antigen presenting cells. If a T cell receives the first signal but not the second it will become anergic or undergo apoptosis.

Abatacept (a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4) binds B7 and in doing so halts the second pathway leading to unsuccessful T cell activation thereby preventing the B cell response [101].

In a phase IIb trial, Merrill et al. randomized 118 patients to receive abatacept and 57 to receive placebo in conjunction with 30mg prednisolone per day, to be tapered after 1 month. On entry to the trial patients should have BILAG A or B on at least one system. They found that after the start of the steroid taper, and over 12 months, there was no significant difference in (BILAG A/B) flare rates between the abatacept and placebo groups, 79.7 and 82.5% respectively[102]. However, post hoc analyses revealed that severe flares (BILAG A) were less frequent in the abatacept compared to the placebo group (40.7 vs 54.4%, with a treatment difference of -13.7 [95% CI -29.5, 2.1]) [103]

Furie et al. conducted a 12 month randomised, phase II/III, double-blinded study of 298 patients (with active class II or IV LN) treated with either abatacept (30mg/10kg or 10mg/10kg) or placebo on a background of MMF and corticosteroids. They used a composite end-point of 'time to confirmed complete response' demonstrated by maintenance of glomerular filtration rate, minimal proteinuria and inactive urinary

sediment over the 12 month treatment period. They showed no differences among treatment arms in the primary end-point [104].

Taken the above together, the use of Abatacept in SLE is still debatable and should be considered only in very selected case.

Expert commentary

Recent advances in SLE research have started to elucidate the complex pathogenesis underlying this autoimmune condition highlighting the critical role of auto-B cells in autoantibody formation, antigen presentation and T cell interaction. The approval of Belimumab by the FDA in 2011 was a significant milestone for the treatment of SLE. Promising preliminary results of ongoing studies such as those with epratuzumab and blisibimod further support the concept that targeting B-cell remains a promising approach in the treatment of SLE.

However, response to B cell target therapy is still variable across studies. Upcoming synthetic peptides and new oral immunomodulator agents might also be effective in SLE treatment. Considering the successful application of small molecule-mediated inhibition in treating malignancies in hematology, the idea of providing a specific, tailored to the patient's 'molecular identity' and possibly less toxic therapeutic agent in patients with SLE appears greatly attractive.

However, it is important to remember that the variability of the disease might impact on clinical response among SLE patients. The synergistic role of these new agents used with conventional drugs, the optimal dosages and duration of treatment have to be further investigated. With the availability of new agent growing, assessment tools have to be standardized and efficacy endpoints have to be appropriately defined. World-wide registry data collection and accurate post-marketing surveillance are also

crucial to evaluate the long-term safety, efficacy, and cost-effectiveness of these novel therapies.

5-year view

The heterogeneous clinical presentation of SLE may pose the question that agents targeting B cells are not the ideal tool for treating all patients. Indeed, different clinical manifestations may underline slightly different pathophysiology pathways making B cells depletion/modulation ineffective in some patients but effective in others. Comparing the safety and efficacy profile of biologics targeting different molecular pathways in different patient subpopulations as well as in different SLE manifestations would help determine which biologics are most suited for certain types of patients and clinical manifestations. This would result in a more tailored approach in term of both clinical care and cost effectiveness.

The principle of treating-to-target has been successfully applied in many rheumatic diseases, and above all in rheumatoid arthritis. The identification of tailored therapeutic goals and pursuing them in a systematic fashion has caused an improvement in the standard of care for patients with these conditions and useful guidance for healthcare practitioners and administrators. Very recently, a collaborative effort to identify possible therapeutic targets and design treat-to-target guidances in the management of SLE was attempted. To date, the treatment options for SLE consist of a relatively small number of agents in the therapeutic classes of glucocorticoids, anti-malarials, immunosuppressives and biologics. In the latter group, only Belimumab is approved for SLE, while Rituximab is used not infrequently 'off-label' in refractory cases.

The common goal of all of these agents is the control of disease activity and the reduction flares rate, leading to a net minimization of long-term damage accrual in SLE patients. Indeed, in the era of the omics, it is crucial that important adjunctive therapies such as hydroxychloroquine and optimization of cardiovascular risk factors should not be forgotten in SLE management.

Several new agents of significant interest are at different stage of development for the treatment of SLE, raising hopes that will soon be possible to aim for therapeutic targets with greater confidence that they can be succeeded.

Key issues

- Belimumab is the first agent licensed for use in SLE in more than fifty years.
- Despite the poor outcome of two RTCs, the use of Rituximab in refractory/life-threatening SLE is supported by open label and uncontrolled studies.
- Cautious evaluation of the risk/benefit balance of upcoming molecules in SLE is essential.
- Treat-to-target approach includes early management of lupus nephritis, minimizing exposure to corticosteroids, prevention of long-term damage accrual and improving quality of life in SLE patients
- A better understanding of the pathogenic pathways along with their lupus-relevant molecular aberrations may allow for more targeted and rational interventions

REFERENCES

1. Jiménez S, Cervera R, Font J, Ingelmo M. The epidemiology of systemic lupus erythematosus. *Clin. Rev. Allergy Immunol.* [Internet]. 25(1), 3–12 (2003). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12794256>.
2. Arnaud L, Fagot J-P, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: a 2010 nation-wide population-based study. *Autoimmun. Rev.* [Internet]. 13(11), 1082–9 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25172239>.
3. Kamal A, Khamashta M. The efficacy of novel B cell biologics as the future of SLE treatment: a review. *Autoimmun. Rev.* [Internet]. 13(11), 1094–101 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25149393>.
4. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N. Engl. J. Med.* [Internet]. 358(9), 929–39 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18305268>.
5. Chan VS-F, Tsang HH-L, Tam RC-Y, Lu L, Lau C-S. B-cell-targeted therapies in systemic lupus erythematosus. *Cell. Mol. Immunol.* [Internet]. 10(2), 133–42 (2013). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4003049&tool=pmc&rendertype=abstract>.
6. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J. Clin. Pathol.* [Internet]. 56(7), 481–90 (2003). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1769989&tool=pmc&rendertype=abstract>.

7. Rudnicka D, Oszmiana A, Finch DK, *et al.* Rituximab causes a polarization of B cells that augments its therapeutic function in NK-cell-mediated antibody-dependent cellular cytotoxicity. *Blood* [Internet]. 121(23), 4694–4702 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23613524>.
8. Merrill J, Buyon J, Furie R, *et al.* Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). *Lupus* [Internet]. 20(7), 709–16 (2011). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21478286>.
9. Rovin BH, Furie R, Latinis K, *et al.* Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum.* [Internet]. 64(4), 1215–26 (2012). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22231479>.
10. Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus* [Internet]. 22(14), 1489–503 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24135078>.
11. Fattah Z, Isenberg DA. Recent developments in the treatment of patients with systemic lupus erythematosus: focusing on biologic therapies. *Expert Opin. Biol. Ther.* [Internet]. 14(3), 311–26 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24387632>.
12. Iaccarino L, Bartoloni E, Carli L, *et al.* Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. *Clin. Exp. Rheumatol.* [Internet]. 33(4), 449–56. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26053285>.

13. Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: A systematic review of off-label use in 188 cases. *Lupus* [Internet]. 18(9), 767–76 (2009). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19578100>.
14. Condon MB, Ashby D, Pepper RJ, *et al.* Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann. Rheum. Dis.* [Internet]. 72(8), 1280–6 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23740227>.
15. Davies RJ, Sangle SR, Jordan NP, *et al.* Rituximab in the treatment of resistant lupus nephritis: therapy failure in rapidly progressive crescentic lupus nephritis. *Lupus* [Internet]. 22(6), 574–82 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23632989>.
16. Cobo-Ibáñez T, Loza-Santamaría E, Pego-Reigosa JM, *et al.* Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: a systematic review. *Semin. Arthritis Rheum.* [Internet]. 44(2), 175–85 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24830791>.
17. Bang S-Y, Lee CK, Kang YM, *et al.* Multicenter retrospective analysis of the effectiveness and safety of rituximab in korean patients with refractory systemic lupus erythematosus. *Autoimmune Dis.* [Internet]. 2012, 565039 (2012). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3523406&tool=pmc&rendertype=abstract>.
18. Roccatello D, Sciascia S, Baldovino S, *et al.* A 4-year observation in lupus

- nephritis patients treated with an intensified B-lymphocyte depletion without immunosuppressive maintenance treatment-Clinical response compared to literature and immunological re-assessment. *Autoimmun. Rev.* [Internet]. (2015). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26244817>.
19. Groom J, Kalled SL, Cutler AH, *et al.* Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. *J. Clin. Invest.* [Internet]. 109(1), 59–68 (2002). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=150825&tool=pmc.ncbi&rendertype=abstract>.
 20. Mackay F, Woodcock SA, Lawton P, *et al.* Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J. Exp. Med.* [Internet]. 190(11), 1697–710 (1999). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2195729&tool=pmc.ncbi&rendertype=abstract>.
 21. Petri M, Stohl W, Chatham W, *et al.* Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum.* [Internet]. 58(8), 2453–9 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18668552>.
 22. Askanase AD, Yazdany J, Molta CT. Post-marketing experiences with belimumab in the treatment of SLE patients. *Rheum. Dis. Clin. North Am.* [Internet]. 40(3), 507–17, viii (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25034159>.
 23. Yazdany J, Trupin L, Schmajuk G, Katz PP, Yelin EH. Quality of care in systemic lupus erythematosus: the association between process and outcome

- measures in the Lupus Outcomes Study. *BMJ Qual. Saf.* [Internet]. 23(8), 659–66 (2014). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4117346&tool=pmc&rendertype=abstract>.
24. Furie R, Petri M, Zamani O, *et al.* A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* [Internet]. 63(12), 3918–30 (2011). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/22127708>.
25. Navarra S V, Guzmán RM, Gallacher AE, *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet (London, England)* [Internet]. 377(9767), 721–31 (2011). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/21296403>.
26. van Vollenhoven RF, Petri MA, Cervera R, *et al.* Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann. Rheum. Dis.* [Internet]. 71(8), 1343–9 (2012). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3396451&tool=pmc&rendertype=abstract>.
27. Dooley MA, Houssiau F, Aranow C, *et al.* Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. *Lupus* [Internet]. 22(1), 63–72 (2013). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/23263865>.
28. Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F. The

- BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity. *Cytokine Growth Factor Rev.* [Internet]. 24(3), 203–15 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23684423>.
29. Yang M, Hase H, Legarda-Addison D, Varughese L, Seed B, Ting AT. B cell maturation antigen, the receptor for a proliferation-inducing ligand and B cell-activating factor of the TNF family, induces antigen presentation in B cells. *J. Immunol.* [Internet]. 175(5), 2814–24 (2005). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16116167>.
30. Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). *Ann. Rheum. Dis.* [Internet]. 74(11), 2006–15 (2015). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4680140&tool=pmc&rendertype=abstract>.
31. Richez C, Truchetet M-E, Schaefferbeke T, Bannwarth B. Atacicept as an investigated therapy for rheumatoid arthritis. *Expert Opin. Investig. Drugs* [Internet]. 23(9), 1285–94 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25078871>.
32. Stohl W, Merrill JT, Looney RJ, et al. Treatment of systemic lupus erythematosus patients with the BAFF antagonist “peptibody” blisibimod (AMG 623/A-623): results from randomized, double-blind phase 1a and phase 1b trials. *Arthritis Res. Ther.* [Internet]. 17, 215 (2015). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4545922&tool=pmc&rendertype=abstract>.

33. Morais SA, Vilas-Boas A, Isenberg DA. B-cell survival factors in autoimmune rheumatic disorders. *Ther. Adv. Musculoskelet. Dis.* [Internet]. 7(4), 122–51 (2015). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4530383&tool=pmc-entrez&rendertype=abstract>.
34. Fairfax K, Mackay IR, Mackay F. BAFF/BLyS inhibitors: A new prospect for treatment of systemic lupus erythematosus. *IUBMB Life* [Internet]. 64(7), 595–602 (2012). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22641424>.
35. Stohl W. Therapeutic targeting of the BAFF/APRIL axis in systemic lupus erythematosus. *Expert Opin. Ther. Targets* [Internet]. 18(4), 473–89 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24521424>.
36. Carbonatto M, Yu P, Bertolino M, *et al.* Nonclinical safety, pharmacokinetics, and pharmacodynamics of atacicept. *Toxicol. Sci.* [Internet]. 105(1), 200–10 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18522929>.
37. Gross JA, Johnston J, Mudri S, *et al.* TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. *Nature* [Internet]. 404(6781), 995–9 (2000). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/10801128>.
38. Munafo A, Priestley A, Nestorov I, Visich J, Rogge M. Safety, pharmacokinetics and pharmacodynamics of atacicept in healthy volunteers. *Eur. J. Clin. Pharmacol.* [Internet]. 63(7), 647–56 (2007). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/17473917>.
39. Dall’Era M, Chakravarty E, Wallace D, *et al.* Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus

- erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. *Arthritis Rheum.* [Internet]. 56(12), 4142–50 (2007). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18050206>.
40. Pena-Rossi C, Nasonov E, Stanislav M, *et al.* An exploratory dose-escalating study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous atacicept in patients with systemic lupus erythematosus. *Lupus* [Internet]. 18(6), 547–55 (2009). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3835146&tool=pmc&rendertype=abstract>.
 41. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res. Ther.* [Internet]. 14(1), R33 (2012). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3392829&tool=pmc&rendertype=abstract>.
 42. Genovese MC, Kinnman N, de La Bourdonnaye G, Pena Rossi C, Tak PP. Atacicept in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor antagonist therapy: results of a phase II, randomized, placebo-controlled, dose-finding trial. *Arthritis Rheum.* [Internet]. 63(7), 1793–803 (2011). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21452293>.
 43. van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. *Arthritis Rheum.* [Internet]. 63(7), 1782–92 (2011). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21452294>.

44. Sutherland S. Peptibodies: the new cool technology. *Drug Discov. Today* [Internet]. 9(16), 683 (2004). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/15341775>.
45. Furie R, Toder K, Zapantis E. Lessons Learned From the Clinical Trials of Novel Biologics and Small Molecules in Lupus Nephritis. *Semin. Nephrol.* [Internet]. 35(5), 509–20 (2015). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/26573553>.
46. Furie RA, Leon G, Thomas M, *et al.* A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. *Ann. Rheum. Dis.* [Internet]. 74(9), 1667–75 (2015). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/24748629>.
47. ANTHERA-PHARMACEUTICALS. A Study of the Efficacy and Safety of Subcutaneous Blisibimod in Subjects With Systemic Lupus Erythematosus. *Natl. Libr. Med. (US), Bethesda (Feb 29 2000)* [Available from
<http://clinicaltrials.gov/ct2/show/NCT01395745>]. (2000).
48. Genovese MC, Lee E, Satterwhite J, *et al.* A phase 2 dose-ranging study of subcutaneous tabalumab for the treatment of patients with active rheumatoid arthritis and an inadequate response to methotrexate. *Ann. Rheum. Dis.* [Internet]. 72(9), 1453–60 (2013). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/23599435>.
49. Genovese MC, Bojin S, Biagini IM, *et al.* Tabalumab in rheumatoid arthritis patients with an inadequate response to methotrexate and naive to biologic therapy: a phase II, randomized, placebo-controlled trial. *Arthritis Rheum.*

[Internet]. 65(4), 880–9 (2013). Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/23359344>.

50. Genovese MC, Fleischmann RM, Greenwald M, *et al.* Tabalumab, an anti-BAFF monoclonal antibody, in patients with active rheumatoid arthritis with an inadequate response to TNF inhibitors. *Ann. Rheum. Dis.* [Internet]. 72(9), 1461–8 (2013). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/23268367>.
51. Greenwald M, Szczepanski L, Kennedy A, *et al.* A 52-week, open-label study evaluating the safety and efficacy of tabalumab, an anti-B-cell-activating factor monoclonal antibody, for rheumatoid arthritis. *Arthritis Res. Ther.* [Internet]. 16(4), 415 (2014). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4177512&tool=pmc&rendertype=abstract>.
52. Schiff M, Combe B, Dörner T, *et al.* Efficacy and safety of tabalumab, an anti-BAFF monoclonal antibody, in patients with moderate-to-severe rheumatoid arthritis and inadequate response to TNF inhibitors: results of a randomised, double-blind, placebo-controlled, phase 3 study. *RMD open* [Internet]. 1(1), e000037 (2015). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4623366&tool=pmc&rendertype=abstract>.
53. Isenberg DA, Petri M, Kalunian K, *et al.* Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann. Rheum. Dis.* [Internet]. (2015). Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/26338095>.

54. Merrill JT, van Vollenhoven RF, Buyon JP, *et al.* Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann. Rheum. Dis.* [Internet]. (2015). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26293163>.
55. Isenberg D. Further thoughts about the Illuminate studies of tabalumab in SLE. *Ann. Rheum. Dis.* [Internet]. (2015). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26530320>.
56. Al Rayes H, Touma Z. Profile of epratuzumab and its potential in the treatment of systemic lupus erythematosus. *Drug Des. Devel. Ther.* [Internet]. 8, 2303–10 (2014). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4242126&tool=pmc&rendertype=abstract>.
57. Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. *Arthritis Res. Ther.* [Internet]. 8(3), R74 (2006). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1526638&tool=pmc&rendertype=abstract>.
58. Tsuru T, Tanaka Y, Kishimoto M, *et al.* Safety, pharmacokinetics, and pharmacodynamics of epratuzumab in Japanese patients with moderate-to-severe systemic lupus erythematosus: Results from a phase 1/2 randomized

- study. *Mod. Rheumatol.* [Internet]. 26(1), 87–93 (2016). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26382733>.
59. Wallace DJ, Kalunian K, Petri MA, *et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann. Rheum. Dis.* [Internet]. 73(1), 183–90 (2014). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3888603&tool=pmc&rendertype=abstract>.
60. Strand V, Petri M, Kalunian K, *et al.* Epratuzumab for patients with moderate to severe flaring SLE: health-related quality of life outcomes and corticosteroid use in the randomized controlled ALLEVIATE trials and extension study SL0006. *Rheumatology (Oxford)*. [Internet]. 53(3), 502–11 (2014). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3930886&tool=pmc&rendertype=abstract>.
61. Wallace DJ, Gordon C, Strand V, *et al.* Efficacy and safety of epratuzumab in patients with moderate/severe flaring systemic lupus erythematosus: results from two randomized, double-blind, placebo-controlled, multicentre studies (ALLEVIATE) and follow-up. *Rheumatology (Oxford)*. [Internet]. 52(7), 1313–22 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23542611>.
62. Rossi EA, Goldenberg DM, Michel R, Rossi DL, Wallace DJ, Chang C-H. Trogocytosis of multiple B-cell surface markers by CD22 targeting with epratuzumab. *Blood* [Internet]. 122(17), 3020–9 (2013). Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/23821660>.

63. PHARMA U. No Title. *Study Epratuzumab Versus Placebo Subj. With Moderate to Sev. Gen. Syst. Lupus Erythematosus (EMBODY 1)*. (2010).
64. UCB announces Phase 3 clinical trial program for epratuzumab in Systemic Lupus Erythematosus did not meet primary endpoint.
<http://www.ucb.com/presscenter/News/article/UCB-announces-Phase-3-clinical-trial-program-for-epratuzumab-in-Systemic-Lupus-Erythema>. (2015).
65. Genovese MC, Kaine JL, Lowenstein MB, *et al*. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum*. [Internet]. 58(9), 2652–61 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18759293>.
66. Rigby W, Tony H-P, Oelke K, *et al*. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. *Arthritis Rheum*. [Internet]. 64(2), 350–9 (2012). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21905001>.
67. Tak PP, Mease PJ, Genovese MC, *et al*. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to at least one tumor necrosis factor inhibitor: results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. *Arthritis Rheum*. [Internet]. 64(2), 360–70 (2012). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22389919>.
68. Emery P, Rigby W, Tak PP, *et al*. Safety with ocrelizumab in rheumatoid

- arthritis: results from the ocrelizumab phase III program. *PLoS One* [Internet]. 9(2), e87379 (2014). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3911947&tool=pmc&rendertype=abstract>.
69. Leone A, Sciascia S, Kamal A, Khamashta M. Biologicals for the treatment of systemic lupus erythematosus: current status and emerging therapies. *Expert Rev. Clin. Immunol.* [Internet]. 11(1), 109–16 (2015). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/25511179>.
70. Mysler EF, Spindler AJ, Guzman R, *et al.* Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum.* [Internet]. 65(9), 2368–79 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23740801>.
71. Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. *Lupus* [Internet]. 13(5), 339–43 (2004). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2014821&tool=pmc&rendertype=abstract>.
72. Illei GG, Shirota Y, Yarboro CH, *et al.* Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum.* [Internet]. 62(2), 542–52 (2010). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3057537&tool=pmc&rendertype=abstract>.
73. Szepietowski JC, Nilganuwong S, Wozniacka A, *et al.* Phase I, randomized, double-blind, placebo-controlled, multiple intravenous, dose-ascending study

- of sirukumab in cutaneous or systemic lupus erythematosus. *Arthritis Rheum.* [Internet]. 65(10), 2661–71 (2013). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/23896980>.
74. Crow MK. Interferon-alpha: a therapeutic target in systemic lupus erythematosus. *Rheum. Dis. Clin. North Am.* [Internet]. 36(1), 173–86, x (2010). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2843146&tool=pmc&rendertype=abstract>.
75. Pascual V, Farkas L, Banchereau J. Systemic lupus erythematosus: all roads lead to type I interferons. *Curr. Opin. Immunol.* [Internet]. 18(6), 676–82 (2006). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17011763>.
76. Mathian A, Hie M, Cohen-Aubart F, Amoura Z. Targeting interferons in systemic lupus erythematosus: current and future prospects. *Drugs* [Internet]. 75(8), 835–46 (2015). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/25940912>.
77. Merrill JT, Wallace DJ, Petri M, *et al.* Safety profile and clinical activity of sifalimumab, a fully human anti-interferon α monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study. *Ann. Rheum. Dis.* [Internet]. 70(11), 1905–13 (2011). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/21798883>.
78. Petri M, Wallace DJ, Spindler A, *et al.* Sifalimumab, a human anti-interferon- α monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. *Arthritis Rheum.* [Internet]. 65(4), 1011–21 (2013). Available from:

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3654174&tool=pmc&rendertype=abstract>.

79. Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon- α monoclonal antibody, in systemic lupus erythematosus. *Clin. Pharmacokinet.* [Internet]. 52(11), 1017–27 (2013). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3824374&tool=pmc&rendertype=abstract>.
80. McBride JM, Jiang J, Abbas AR, *et al.* Safety and pharmacodynamics of rontalizumab in patients with systemic lupus erythematosus: results of a phase I, placebo-controlled, double-blind, dose-escalation study. *Arthritis Rheum.* [Internet]. 64(11), 3666–76 (2012). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/22833362>.
81. Kalunian KC, Merrill JT, Maciuga R, *et al.* A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon- α) in patients with systemic lupus erythematosus (ROSE). *Ann. Rheum. Dis.* [Internet]. 75(1), 196–202 (2016). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26038091>.
82. Zagury D, Le Buanec H, Mathian A, *et al.* IFN α kinoid vaccine-induced neutralizing antibodies prevent clinical manifestations in a lupus flare murine model. *Proc. Natl. Acad. Sci. U. S. A.* [Internet]. 106(13), 5294–9 (2009). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2654395&tool=pmc&rendertype=abstract>.
83. Lauwerys BR, Hachulla E, Spertini F, *et al.* Down-regulation of interferon

- signature in systemic lupus erythematosus patients by active immunization with interferon α -kinoid. *Arthritis Rheum.* [Internet]. 65(2), 447–56 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23203821>.
84. Sciascia S, Talavera-Garcia E, Roccatello D, Baldovino S, Mengatti E, Cuadrado MJ. Upcoming biological therapies in systemic lupus erythematosus. *Int. Immunopharmacol.* [Internet]. 27(2), 189–93 (2015). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26028152>.
 85. Urowitz MB, Isenberg DA, Wallace DJ. Safety and efficacy of hCDR1 (Edratide) in patients with active systemic lupus erythematosus: results of phase II study. *Lupus Sci. Med.* [Internet]. 2(1), e000104 (2015). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4538379&tool=pmc&entrez&rendertype=abstract>.
 86. Brück W, Zamvil SS. Laquinimod, a once-daily oral drug in development for the treatment of relapsing-remitting multiple sclerosis. *Expert Rev. Clin. Pharmacol.* [Internet]. 5(3), 245–56 (2012). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22697588>.
 87. LB0003 A Randomized Controlled Study of Laquinimod in Active Lupus Nephritis Patients in Combination with Standard of Care - Lancaster University (Alma) [Internet]. Available from: http://onsearch.lancs.ac.uk/primo_library/libweb/action/display.do;jsessionid=87BFEECAA8378E2E9710A109920FF1487?tabs=detailsTab&ct=display&fn=search&doc=TN_bmj10.1136%2fannrheumdis-2013-eular.528&indx=3&reclds=TN_bmj10.1136%2fannrheumdis-2013-

eular.528&recldxs=2&elementId=2&renderMode=poppedOut&displayMode=ful
l&frbrVersion=4&mode=Basic&vid=LUL_VU1&tab=articles&vl(81797464UI0)=c
reator&vl(86261973UI1)=all_items&dscnt=0&vl(freeText0)=Appel%2C
G.&scp.scps=primo_central_multiple_fe&dsmtp=1452112689.

88. Spritz RA, Strunk K, Surowy CS, Hoch SO, Barton DE, Francke U. The human U1-70K snRNP protein: cDNA cloning, chromosomal localization, expression, alternative splicing and RNA-binding. *Nucleic Acids Res.* [Internet]. 15(24), 10373–91 (1987). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=339950&tool=pmcentrez&rendertype=abstract>.
89. Haddon DJ, Jarrell JA, Diep VK, *et al.* Mapping epitopes of U1-70K autoantibodies at single-amino acid resolution. *Autoimmunity* [Internet]. 48(8), 513–23 (2015). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/26333287>.
90. Kattah NH, Kattah MG, Utz PJ. The U1-snRNP complex: structural properties relating to autoimmune pathogenesis in rheumatic diseases. *Immunol. Rev.* [Internet]. 233(1), 126–45 (2010). Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3074261&tool=pmcentrez&rendertype=abstract>.
91. Monneaux F, Lozano JM, Patarroyo ME, Briand J-P, Muller S. T cell recognition and therapeutic effect of a phosphorylated synthetic peptide of the 70K snRNP protein administered in MR/lpr mice. *Eur. J. Immunol.* [Internet]. 33(2), 287–96 (2003). Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/12548559>.

92. Dieker J, Cisterna B, Monneaux F, *et al.* Apoptosis-linked changes in the phosphorylation status and subcellular localization of the spliceosomal autoantigen U1-70K. *Cell Death Differ.* [Internet]. 15(4), 793–804 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18202700>.
93. Pathak S, Mohan C. Cellular and molecular pathogenesis of systemic lupus erythematosus: lessons from animal models. *Arthritis Res. Ther.* [Internet]. 13(5), 241 (2011). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3308079&tool=pmc&entrez&rendertype=abstract>.
94. Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. *Nat. Rev. Immunol.* [Internet]. 13(10), 722–37 (2013). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24064518>.
95. Page N, Gros F, Schall N, Briand J-P, Muller S. A therapeutic peptide in lupus alters autophagic processes and stability of MHCII molecules in MRL/lpr B cells. *Autophagy* [Internet]. 7(5), 539–40 (2011). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21282971>.
96. Page N, Gros F, Schall N, *et al.* HSC70 blockade by the therapeutic peptide P140 affects autophagic processes and endogenous MHCII presentation in murine lupus. *Ann. Rheum. Dis.* [Internet]. 70(5), 837–43 (2011). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3070272&tool=pmc&entrez&rendertype=abstract>.
97. Monneaux F, Muller S. Peptide-based immunotherapy of systemic lupus erythematosus. *Autoimmun. Rev.* [Internet]. 3(1), 16–24 (2004). Available

from: <http://www.ncbi.nlm.nih.gov/pubmed/14871645>.

98. Muller S, Monneaux F, Schall N, *et al.* Spliceosomal peptide P140 for immunotherapy of systemic lupus erythematosus: results of an early phase II clinical trial. *Arthritis Rheum.* [Internet]. 58(12), 3873–83 (2008). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19035498>.
99. Zimmer R, Scherbarth HR, Rillo OL, Gomez-Reino JJ, Muller S. Lupuzor/P140 peptide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled phase IIb clinical trial. *Ann. Rheum. Dis.* [Internet]. 72(11), 1830–5 (2013). Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3812851&tool=pmc&rendertype=abstract>.
100. A 52-Week, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a 200-mcg Dose of IPP-201101 Plus Standard of Care in Patients With Systemic Lupus Erythematosus (LUPUZOR). *www.clinicaltrials.gov.* (2015).
101. Dall’Era M, Davis J. CTLA4Ig: a novel inhibitor of costimulation. *Lupus* [Internet]. 13(5), 372–6 (2004). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15230295>.
102. Merrill JT, Burgos-Vargas R, Westhovens R, *et al.* The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* [Internet]. 62(10), 3077–87 (2010). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20533545>.

103. Hoi A, Littlejohn G. Is there still a role for abatacept in the treatment of lupus? *Expert Opin. Biol. Ther.* [Internet]. 14(9), 1345–50 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25005704>.
104. Furie R, Nicholls K, Cheng T-T, *et al.* Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. *Arthritis Rheumatol.* (Hoboken, N.J.) [Internet]. 66(2), 379–89 (2014). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24504810>.