

New Drug Therapies for Systemic Lupus Erythematosus: A Systematic Review

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Abstract

From the literature research the belimumab studies were the only ones to meet the primary and some of the secondary endpoints. Introduction: Systemic Lupus Erythematosus (SLE) is a multiorganic autoimmune disease caused by an immune reaction against DNA. Despite continuous research progress, the mortality of SLE patients is still 2-4 times higher than the healthy populations and the standard drugs' adverse effects (especially corticosteroids) hamper the patients' quality of life. That is why there is an urgent need for new therapies. This paper reviews all phase III clinical trials of new SLE medication that were published since 2011 and analyses the drugs for their respective effects.

Methods: MEDLINE (PubMed), Livivo, The Cochrane Library and Embase were systematically searched for relevant publications. Only randomized, placebo-controlled and double blind studies that were published no earlier than 2011 were included. Exclusion criteria were analysis of one organ manifestation only (e.g. lupus nephritis), insufficient power or lack of full text availability. The studies were analyzed for their respective drug's efficiency and possible adverse effects.

Results: 7 studies were shortlisted Tabalumab showed significant improvement in biomarkers, but clinical effects were low and the primary endpoint was met in one treatment group only. None of the secondary endpoints were met. Atacicept showed some beneficial effects in the 150 mg treatment group, but these results must be viewed skeptically, as this arm was terminated prematurely due to the death of two patients. The 75 mg arm did not meet the primary endpoint. Epratuzumab treatment showed no significant effects.

Conclusion: Out of all analyzed drugs, belimumab shows the best efficiency and can therefore be recommended for SLE patients. Further research of tabalumab and atacicept is needed, with a special focus on the latter's potential side effects. Studies of epratuzumab have had disappointing results and that drug can therefore not be recommended.

Keywords: Databases; Systemic lupus erythematosus; Monoclonal antibody; B-cells

Introduction

Systemic Lupus Erythematosus (SLE) is a severe multi-organic relapsing autoimmune disease with a worldwide prevalence of 40/100,000 whose aetiology remains disputed. Women are affected 10 times more often than men, with an onset peak in the reproductive age [1].

Despite a lot of therapy improvements in the last years, the mortality of patients is still 2-4 times higher than in the healthy population and about 15% of SLE patients die during the first 15 years after their diagnosis [2]. Mortality and morbidity in SLE are mainly determined by renal manifestations, which appear in more than 40% of all patients, as well as neuropsychiatric disease. Important biomarkers for SLE are antinuclear antibodies (ANA), anti-double-stranded-DNA antibodies and low C3 and C4 complement levels.

Standard of care (SOC) for SLE consists of non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial medication (e.g. hydrochloroquin), and corticosteroids and, in severe cases,

immunosuppressant's like azathioprine, MTX or cyclosporine A. The side effects of the corticosteroid therapy (e.g. weight gain, hirsutism, cataract, diabetes mellitus, osteoporosis, and hypertension) and immunosuppressant's (infection, infertility) in particular can considerably impair an individual's quality of life [1].

Both the SOC side effects and the patient's increase mortality foster research for new SLE therapies. In 2011, belimumab, a fully humanized monoclonal antibody against BLyS, a B cell activating factor, was approved for mild SLE by the US Food and drug administration [1]. Other biological therapies for lupus are constantly developed and tested.

The purpose of this review is to give an overview of all the new SLE drugs that have undergone phase-III clinical trials since 2011 and to assess whether or not they can be recommended for lupus treatment.

Methods

Search in databases

In order to identify relevant trials, PubMed, Livivo, The Cochrane Library and Embase were searched from June 12 to June 27 2017.

PubMed research

In order to get an overview of all the drugs that are currently being tested, the search was started with rather general terms: "Lupus Erythematosus, Systemic/drug therapy"[Mesh], "Lupus Erythematosus, Systemic/therapy"[Mesh] and "Antibodies, Monoclonal, Humanized"[Mesh] were combined in several ways. The filters "Clinical Trial", "Clinical Trial, Phase III" and "last 5 years" were included as well. Search results and abstracts were browsed for new drugs currently undergoing clinical trials. The section "similar articles" in PubMed was checked as well. Also, the full text of one meta-analysis was skimmed for relevant drugs.

The following drugs were shortlisted for further analysis: Rituximab, Belimumab, Epratuzumab, Sifalimumab, Ocrelizumab, Atacicept, Abatacept, Leflunomide, Blisibimod.

The next step was a targeted search for studies about each of these agents, built up as follows: ("Lupus Erythematosus, Systemic/therapy"[Mesh]) AND (name of the respective drug), for example: "Lupus Erythematosus, Systemic/drug therapy"[Mesh] AND tabalumab.

Other databases

After the research explained above was completed, Livivo, Embase (1980-2017) and the Cochrane Library were browsed for articles not listed in PubMed. The search strategy was similar to the one described above.

There was only one article [3] that could not be found in PubMed, but was in the Cochrane Library. However, this paper was excluded from the final analysis, as there was no full text available (Figure 1).

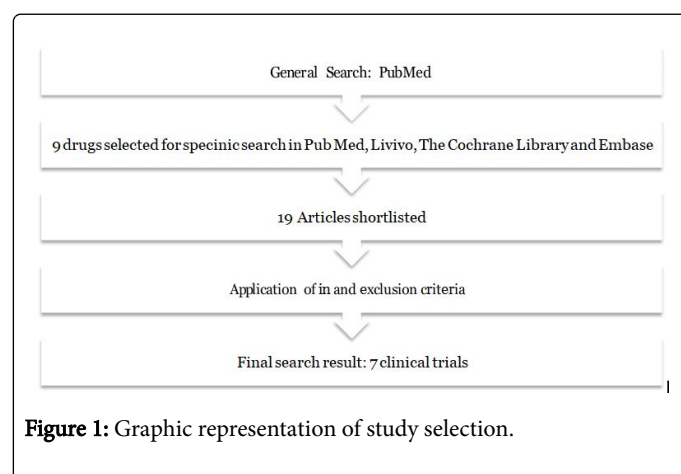


Figure 1: Graphic representation of study selection.

Inclusion and exclusion criteria

Only double-blinded, randomized, placebo-controlled phase III clinical trials about systemic lupus erythematosus that were published no sooner than 2011 were included.

Exclusion criteria were analysis of the effect on one organ manifestation only (i.e. lupus nephritis), insufficient blinding/randomization or lack of full text availability. Underpowered studies were excluded as well.

Analysis

The main focus of this review was the studies' achievement of their primary and secondary endpoints. Adverse effects were also taken into consideration. The quality of each trial was assessed with the Jadad et al. rating score [4]. All parts of the analysis were done in accordance to the "Statute of the Charite for securing good scientific practice" Finally, a recommendation for the use of these new drugs in lupus patients was made.

Results

In this context, 19 articles were shortlisted from the illustrated research, 7 of those [5-12] were chosen for analysis. The drugs whose effects were analysed in this review are tabalumab (6, 7), belimumab [7-9], atacicept [10] and epratuzumab [11].

One study was excluded because there was no full text available [3]. Others were not considered because they were open-labelled [13, 14], not powered and interrupted early due to a drug supply shortage [14], not double-blinded and without placebo control groups [15], only in phase II [16] or because they were published before 2011 [17]. Three other papers were found to be reviews of other studies and were consequently phased out [18-20]. The studies of ocrelizumab and abatacept [21, 22] were excluded as they only analysed the drug's effects in lupus nephritis and not in SLE.

In order to give a forecast of future developments, two papers about Lupuzor [23,24], a peptide that is currently undergoing a phase III clinical trial, were also included in this review, despite not meeting the inclusion criteria. These Lupuzor studies were analysed separately from the other trials and excluded from the finale recommendation.

Overview of the most relevant findings of each study

A summary of the studies' designs and primary endpoints can be found in table 1.

Drugs that are already approved for SLE treatment

Belimumab: The BLISS studies and the subcutaneous Belimumab study

Belimumab is a human immunoglobulin monoclonal antibody that binds and deactivates soluble B-lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF) [7].

B cells are known to play an important role in the pathogenesis of SLE and BAFF levels have been found to be increased in Lupus patients [1]. The two BLISS-studies [7,8] lead to the US Food and Drug administration's admission of belimumab for treatment of mild SLE [1]. While Belimumab was administered intravenously in the BLISS-studies, Stohl et al. examined the effects of subcutaneous belimumab [9]. In the BLISS-52 study 2 [7], both treatment groups met the primary endpoint of a significantly higher SRI-4 response rate [25] 1 vs. placebo. Moreover, time to the first flare, measured with the SLE Flare Index (SFI) [26] could be significantly reduced in both treatment groups.

Belimumab treatment also resulted in several corticosteroid sparing effects. On top of that, there was a significant fall in C3 and C4 levels as well as in anti-dsDNA 2 concentrations. Significantly more belimumab patients had their hypergammaglobulinaemia turned to normal and at

week 52, significantly more had turned from anti-dsDNA positive to negative (compared with placebo group) (Table 1).

Variables	ILLUMINATE-1 (7)	ILLUMINATE-2 (7)	ILLUMINATE-3 (9)	BLISS-52 (10)	BLISS-76 (11)	Subcutaneous belimumab(11)	April SLE (27)	EMBODY-1/2 (13)
Randomised?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Double blind		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Description of withdrawals and dropouts?		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method of randomization described and appropriate?		No	No	Yes	Yes	No	No	Yes
Method of blinding described and appropriate?		No	No	No	No	No	No	No
Sum score		3	3	4	4	3	3	4

Table 1: Assessment of trial quality with the Jadad et al. rating score (6), each positive answer transfers to 1 out of 5 possible points.

Although the BLISS-76 study design was similar to the BLISS-52's, the primary endpoint (SRI-4 response at week 52) was only met in the 10 mg/kg treatment group. On top of that, there were no more significant differences in SRI-4 responses between the treatment and placebo groups at week 76. However, a post-hoc analysis using higher SRI-thresholds showed significant success for the belimumab groups at week 76. Regarding biomarkers, the 10mg/kg treatment group showed significant increases in C3 and C4 as well as significantly more transitions from anti-dsDNA positive to negative at week 76 than the placebo group. The 1 mg/kg belimumab group experienced a significantly higher rate of C4 normalizations and a higher proportion of anti-dsDNA transitions compared with placebo both at weeks 52 and 76. Patients in this treatment groups also experienced less severe flares according to the SLE flare index. There were no relevant corticosteroid-sparing effects observed in either treatment group.

The subcutaneous belimumab study [9] had the same primary endpoint as the BLISS-studies and also succeeded in meeting it. Comparable with the ILLUMINATE-trials [5,6], there was a significantly higher proportion of SRI-5 to 8 responders³ in the belimumab group. Time to the first severe flare as measured with the modified SLE flare index was also significantly greater in the belimumab group. On top of that, belimumab patients were significantly less likely to experience a severe flare. As far as corticosteroid dosing effects are concerned, significantly less belimumab patients had their corticosteroid dose increased compared with placebo.

However, there were no significant differences between the treatment and the placebo group regarding the proportion of patients with a reduction in corticosteroid dose and neither in the average corticosteroid dose within the groups. Changes in C3, C4 and anti-dsDNA concentrations were not analyzed in this study.

Altogether, the vast majority of the belimumab studies primary endpoints were met.

A number of other favorable effects were shown as well. The outcomes of subcutaneous belimumab administration seem to be similar to the intravenous ones.

Drugs that have completed phase III clinical trials but are not on the market yet

Tabalumab the ILLUMINATE studies: Tabalumab is a human IgG4 monoclonal antibody binding and neutralizing both soluble and membrane-bound BAFF [5]. The ILLUMINATE studies were published in 2015 (online publication in 2016) and tested the efficiency of subcutaneous tabalumab in a sample of about 1,100 patients each. Although the design of both studies was similar, ILLUMINATE-2 met its primary endpoint in one of the treatment groups, while ILLUMINATE-1 failed to do so. Likewise, ILLUMINATE-2 showed a significantly higher percentage of SRI 4,6,7,9 and 10 responders in the Q2W4 group vs. placebo as well as significantly more SRI-9 and 10 responders in the Q4W5 group. Nevertheless, both ILLUMINATE-studies failed to meet their secondary endpoints, which were time to first severe flare on SELENA-SLEDAI flare [26] index, proportion of patients with a reduction in corticosteroid dose and change on the Brief Fatigue Inventory Score [27] at week 52.

Regarding effects in biomarkers, both studies showed significant decreases in anti-dsDNA levels and serum immunoglobulin's (both treatment groups vs. placebo) as well as an increase in C3 and C4 levels. In sum, it can be said that although tabalumab showed significant laboratory improvements, its clinical effects were low, as only one primary and none of the secondary endpoints were met.

Atacicept-the April-SLE trial: April, another B-cell activating factor [10]. There were two treatment groups in this study, one receiving 75mg atacicept subcutaneously, the other one 150 mg. Because of two deaths from pneumonia with pulmonary hemorrhage in the 150 mg arm, the enrolment in this group was stopped prematurely, so that only 62 out of 144 patients of the 150 mg arm completed the full 52 weeks of the study. The treatment in those patients that had not finished the study yet was stopped. Consequently, analyzing the outcome in the 150 mg arm is difficult. A potential completer (PC) population was generated post hoc, including all patients who were randomized at least 52 weeks before the 150 mg arm treatment was stopped. The analysis of this PC population suggested beneficial effects for 150 mg atacicept, as this treatment arm met the primary endpoint. A lower risk for a new BILAG A or B flare was observed in this group as well. There were also some corticosteroid sparing effects observed. Regarding the originals intention to treat population, defined as all

patients who received at least one dose of the study drug, neither the primary nor the vast majority of the secondary endpoints were met by the 75 mg arm. The only secondary endpoint met by this treatment group was the increase in C3 and C4 levels. Moreover, a decline in IgA and IgM and a reduction of anti-dsDNA antibodies were noticed. A post hoc analysis of the 150 mg arm revealed some improvements as well, although it must be remembered that this arm was terminated early, so that this result is unpowered.

In sum, there were no relevant improvements in the 75 mg arm. Beneficial results in the 150 mg arm should be analyzed with care.

Epratuzumab-the EM body trials: Epratuzumab is a humanized monoclonal IgG antibody against CD22 on B-cells, therefore it interferes with the B cell receptor signaling complex [11].

Both EM body- trials were designed identically, the only difference being the location of the study sites (see table 1). Neither the primary

nor the secondary endpoints were met by either study. Also, no beneficial effect of the treatment was seen in the subgroup analysis. A post-hoc analysis in which the rules for concomitant medication were less stringent was not successful either. However, there was a reduction in peripheral B cell levels and a decrease in IgM levels in epratuzumab patients, but no p values are given. Generally, it can be said that in these studies, epratuzumab showed no significant beneficial effects.

Adverse effects

All drugs were generally well tolerated and incidences of serious adverse events were low. However, two death from pneumonia occurred in the 150 mg atacicept group, resulting in the premature termination of this study arm. Slightly higher depression rates (verum vs. placebo) were reported in ILLUMINATE-2 and BLISS-76.

A summary of the respective side effects can be found in (table 2).

ILLUMINATE-1	Adverse events were similar in tabalumab and placebo group
ILLUMINATE-2	Q2W group: More patients with injections-site reactions than placebo
	Higher depression rates in the Q2W and Q4W groups compared with placebo (n=18, 21, 6, respectively)
	Increased rate of treatment-emergent suicidal ideation
BLISS-52	Three anaphylactic belimumab reaction, two of them severe
BLISS-76	Higher percentages of depression in belimumab groups (6-7%) than in placebo (4%)
	Higher rates of malignancies in the belimumab groups
	More infusion and hypersensitivity reaction in the belimumab groups
	Headaches, nasopharyngitis and insomnia were observed more frequently in the belimumab groups
	Higher rates of bronchitis and pyrexia in the 10 mg/kg belimumab group compared with placebo
Subcutaneous Belimumab	More injection site reactions in the belimumab group, but no serious or severe ones
	3 deaths from infections in the belimumab group vs. one vascular and one from SLE--related thrombocytopenia in placebo
APRIL-SLE	In general, there were more adverse events in the atacicept groups than in the placebo group
	Two patients in the 150 mg treatment group died of pneumonia --> termination of this treatment arm
	10% of the atacicept-treated patients lost their protective pneumococcal and tetanus vaccination titres (3,3% in placebo)
	Higher infection rates in the atacicept groups
EMBODY-1	More cases of gastrointestinal disorders and nausea (both treatment groups)
	Increase in nervous system disorders (both groups)
	Higher proportion of musculoskeletal, connective tissue and vascular disorders in the 1200 mg group
EMBODY-2	Increase in metabolism and nutrition disorders (both groups)
	Raise in vascular disorders (600 mg)

Table 2: Summary of each drug's adverse effects, only effects that were more frequent in the treatment groups than in the placebo group mentioned.

Outview: Lupuzor/peptide 140

Lupuzor is a new drug consisting of P140 peptide administered in 5,4% mannitol. Its effect mechanism is completely different from that

of the drugs described above, as Lupuzor interacts with T cell activity. On the one hand, P140 seems to act as an altered peptide ligand of CD 4 T cells' receptors, resulting in a change of autoreactive T cell phenotypes as well as in cytokine secretion. On the other hand, the

peptide might also interfere with the autophagic flux, a recycling of intracellular components by the lysosome. This mechanism is thought to enable the delivery of cytoplasmic and nuclear antigens to MHC II molecules, a process that might result in autoimmunity (Table 3-part 1, part 2, part 3). Apparently, Lupuzor can both reduce this autophagic process as well as decrease the stability of MCH II molecules. That is why it is suggested that treatment with P140 leads to a weaker activation of self-reactive T-cells. Without those T-cells, auto reactive B

cells cannot differentiate to plasma cells, which would result in a decrease of autoantibody levels [23,24].

Therefore, Lupuzor selectively reduces auto reactive immune cells, which is a completely new approach, as all other treatments for autoimmune diseases (e.g. corticosteroids and immunosuppressant's) inhibit the immune system as a whole. Consequently, infections are a common and possibly life threatening side effect of these drugs.

Main information	Inclusion criteria	Drug doses administered	Primary endpoint	Met?
ILLUMINATE-1(7) Tabalumab Isenberg.D.A. et al. ITT=1138 52 weeks Eli Lilly and company	Age 18 yrs 4/11 ACR SLE criteria ANA titre $\geq 1:80$ SELENA-SLEDAI ≥ 6 -33	Tabalumab 120 mg SC every 2 weeks+SOC (n=381, Q2W group) Tabalumab 120 mg SC every 4 weeks+SOC (n=378, Q4W group) Placebo+SOC (n=379)	SRI-5 response at week 52	No
ILLUMINATE-2 (8) Tabalumab Merrill J.T. et al. ITT=1124 52 weeks Eli Lilly and company	See ILLUMINATE-1	Tabalumab 120 mg SC every 2 weeks+SOC (n=372, Q2W group) Tabalumab 120 mg SC every 4 weeks+SOC (n=376, G4W group) Placebo+SOC (n=376)	See ILLU MINATE-1	Yes. by the Q2W group
BLISS-52 (9) Belimumab Navarra S.V. et al. (9) ITT=865 52 weeks Human Genome Sciences, GlaxoSmithKline, BioScience	Age 18 yrs ACR SLE criteria SELENA-SLEDAI 6 ANA-titre $\geq 1:80$ or anti-ds DNA antibodies (≥ 30 IU/ml) Stable treatment regimen with fixed doses of prednisone, NSAID, antimalarial or immunosuppressive drugs ≥ 30 days before study start	I.v. infusion of either belimumab 1 mg/kg+SOC (n=288), Belimumab 10 mg/kg +SOC (n=290) or Placebo+SOC (n=287) on days 0,14 and 28, afterwards every 28 days until week 48	SRI-4 response rate at week 52	Yes
Part 1				
Main information	Inclusion criteria	Drug doses administered	Primary endpoint	Met?
BLISS-76 (10) Belimumab Furie R et al. ITT=819 76 weeks Human genome sciences, Glaxo Smith Kline	Age ≥ 18 yrs ACR SLE criteria SELENA-SLEDAI ≥ 6 2 positive ANA (titre $\geq 1: 80$) or anti-dsDNA (≥ 30 IU/ml) test results Stable treatment regimen for ≥ 30 days before first study dose	see BLISS 52 m=271,273,275 respectively	SRI-4 response rate at week 52	Yes but only in 10mg/kg group
Subcutaneous Belimumab (11) Stohl W et al. (11) ITT=836	Age ≥ 18 years ACR SLE criteria ANA or anti-dsDNA positive	Belimumab 200 mg SC+SOC (N=556) Placebo+SOC (n=280) Weekly application, no loading dose	SRI-4 response rate at week 52	Yes

52 weeks Human genome sciences, Glaxo Smith Kline	SELENA-SLEDAI ≥ 8			
April-SLE (12) Atacicept Isenberg DA et al. (12) ITT=455 52 weeks+24 weeks follow-up EMD serono	Only patients with essentially inactive disease, elaborate pre-treatment Age ≥ 16 yrs (≥ 18 in Switzerland, Australia, Lithuania, Lebanon, Poland, Bulgaria and site 120 Australia) Active SLE (Category A and B on BILAG index (31) excluding a single B in haematology) ACR SLE criteria ANA ≥ 1 : 80 or dsDNA ≥ 30 IU/L	Atacicept 75 mg SC+SOC Atacicept 15 mg SC+SOC Placebo+SOC Administration 2x a week for 4 weeks and 1x a week for 48 weeks	%of patients with ≥ 1 flare of BILAG A or B (31)	No
Part 2				
Main Information	Inclusion Criteria	Drug doses administered	Primary endpoint	Met?
Embody-1 (13) Epratuzumab Clowse MEB et al. (13) ITT=793 48 weeks+4weeks follow-up UCB pharma	Age ≥ 18 years \geq ACR SLE criteria BILAG 2004 (34) grade A ≥ 1 or grade B ≥ 2 of musculoskeletal, mucocutaneous or cardiorespiratory body systems SLEDAI 2 K score ≥ 6 (35) ANA ≥ 1 : 80 and anti-dsDNA	Epratuzumab 600 mg every week Epratuzumab 1200 mg i.v every 40 days Placebo 4 treatment cycles of 12 weeks duration each, drug was delivered in the first 4 weeks, respectively	% BICLA (36) responders at week 48	No
Embody-2 (Epratuzumab) Clowse MEB et al. (13) ITT=793 48 weeks+4weeks follow-up UCB pharma	See EMBODY-1	See EMBODY-1	See EMBODY-1	No
Part 3				

Table 3: Summary of study designs and main results.

Lupuzor is currently undergoing a phase III clinical trial. A phase IIb randomized, double-blind and placebo-controlled trial published in 2012 met its primary endpoint of a reduction in the SRI score with the 200 μ g/4 weeks Lupuzor treatment group. That is why Lupuzor is a promising new agent for SLE.

Discussion

Limitations of this review

Although four big databases were searched, it is possible that some relevant papers could not be included in this review if they were not published online during the time of research. Due to insufficient expertise of the author, no critical analysis of the trials' statistic tests could be performed. Furthermore, no statement can be made about the drugs' efficiency with lupus nephritis and central nervous system manifestations; as such patients were excluded from all trials. Likewise, children and teenagers were not included in the trials, so a recommendation for this group is impossible as well. On top of that, evidence for male patients is very low, as $\geq 90\%$ of all patients were female across the trials. This is, however, due to the fact that lupus is much more common in women than in men.

Critical analysis of the main results

Out of all the substances analyzed in this review, belimumab is the only one to meet both the primary and also some of the secondary endpoints in three different clinical trials [8-10]. All other agents failed to meet their primary and secondary endpoints (despite the Q2W group in ILLUMINATE-2) [28]. This is probably the reason why belimumab is also the only drug out of those reviewed here that was administered for SLE treatment. However, only 43-61% of belimumab-treated patients met the primary endpoint of an SRI response across the studies and the improvement over the placebo group was only about 10-15% [7-9]. Therefore, it is doubtful if the positive effects of belimumab are clinically relevant. Likewise, the German "Institute for Quality and Efficiency in Health Care" or "IQWiG" has assessed the BLISS-studies' results as moot on the ground that SOC medication was restricted in the trials. The IQWiG argues that due to this restriction, only the safety and general effectiveness of the drug can be assessed, but that no statement can be made about belimumab's additional benefits over SOC [29]. The subcutaneous belimumab trial [9] provided no information at all about the management of SOC medication, which makes a statement about the additional effects of SC belimumab difficult as well. On top of that, belimumab did not show

significant disease improvement until week 16, so a patient would have to be very compliant and have a lot of perseverance, too.

In the BLISS-76 study, higher rates of malignancies and depression were reported in the belimumab treatment group. In the BLISS-52 study, information about depression rates is missing without an explanation why this is the case. The question is whether it is worth risking these adverse events for such a small clinical benefit.

Regarding the other drugs analyzed in this trial, it should be discussed which of them is the most promising for further research.

Although only one of the ILLUMINATE studies' treatment groups could meet a primary endpoints and none of the secondary endpoints were met, assessments with higher SRI- thresholds (e.g. SRI-6,7,8) showed significant improvement in the treatment groups, suggesting that setting a more challenging primary endpoint might enhance the differences between placebo and treatment groups. On top of that, tabalumab showed significant changes in biomarkers. It remains unclear why these could not be transferred in clinic results. Another point of criticism is that the ILLUMINATE trials were sponsored by Eli Lilly, a company with a bad reputation for keeping their drug's side effects secret.

The April-SLE trial must be analyzed with care. Firstly, patients had to undergo an elaborate pre-treatment programme with prednisone before being randomized. Only patients with an inactive disease after this corticosteroid treatment were eligible for the trial. Consequently, any beneficial effects of atacicept can only be transferred to a very limited patient population. Furthermore, the 150 mg treatment arm was terminated prematurely due to two patient deaths in this group. Although a post-hoc analysis suggested success for this atacicept dose, this analysis is underpowered and can therefore not be used for a recommendation [30].

Furthermore, there was a tendency of a higher AE rate in the treatment groups, which, together with the two fatal outcomes, raises concern about the safety of atacicept. Another point that criticism is that only one score, BILAG, was used to assess the agent's effects, while all other studies used the systemic lupus erythematosus Responder Index, which summarizes three different scores. Considering the diversity of SLE's organ manifestations, a single score is insufficient for assessing the disease's activity.

The EM body-trials had a poor outcome: No primary or secondary endpoint was met and no other significant improvement was observed as well. A number of sensitivity analyses and a post-hoc analysis using an alternate score for assessing disease activity also failed to detect any difference between placebo and treatment groups. Although the primary endpoint of this study was more stringent than the other trial's one, a beneficial effect of epratuzumab remains doubtful.

The phase IIb Lupuzor trial showed promising effects, although these might be affected by bias: An interim analysis with about two thirds of the original study population was done for safety reasons before the study was finished and the result of this analysis was open for access. The interim analysis showed significant improvements in the SLEDAI-2K score for the Lupuzor patients. Consequently, a possible beneficial effect of Lupuzor was already known before the original study was completed, which might have had an impact on the study's final results [24]. The results of the clinical phase III study that is currently running are to be awaited and might provide more information about Lupuzor's efficiency,

Regarding this review's results, the question raises why Lupus has such poor results in clinical trials. One of the most obvious problems is that Lupus is a multiorgan disease with many different faces. Therefore, the analysis of a possible disease activity improvement is very challenging. This can be seen in the multitude of scores used in the trials. This index diversity also hampers the studies' analysis, as different score might result in different outcomes. Furthermore, the analysis is complicated by the manifold ways of SOC regulations. The tabalumab studies are a perfect example for this: In ILLUMINATE-1, no change in immunosuppressant's or antimalarial at all was permitted, while in ILLUMINATE-2, a reduction of these drugs was allowed. Apparently, these different provisions have influenced the trial's result, as a post-hoc analysis of ILLUMINATE-1 using the same regulations as the ILLUMINATE-2 resulted in one treatment groups' meeting of the primary endpoint. This demonstrates the powerful influence of SOC medication on a study's outcome.

In sum, guidelines for the design of SLE trials would be quite desirable, as they would simplify a cross-comparison between different studies.

Conclusion

If a ranking of the analyzed drugs was required, epratuzumab would be on the last place due to its low efficiency. Tabalumab would claim the third place, as significant improvements in biomarkers were shown. Since atacicept showed some promising results, it would rank just before tabalumab, but there is definitively more research needed, with special attention to adverse effects. The belimumab trials had the best results and also the highest Jadad-scale. Therefore, belimumab is the only biologic drug that can be recommended for SLE patients.

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