Targeting BAFF and APRIL in Systemic Lupus Erythemathosis

A comparison of trials of three BAFF/APRIL inhibitors

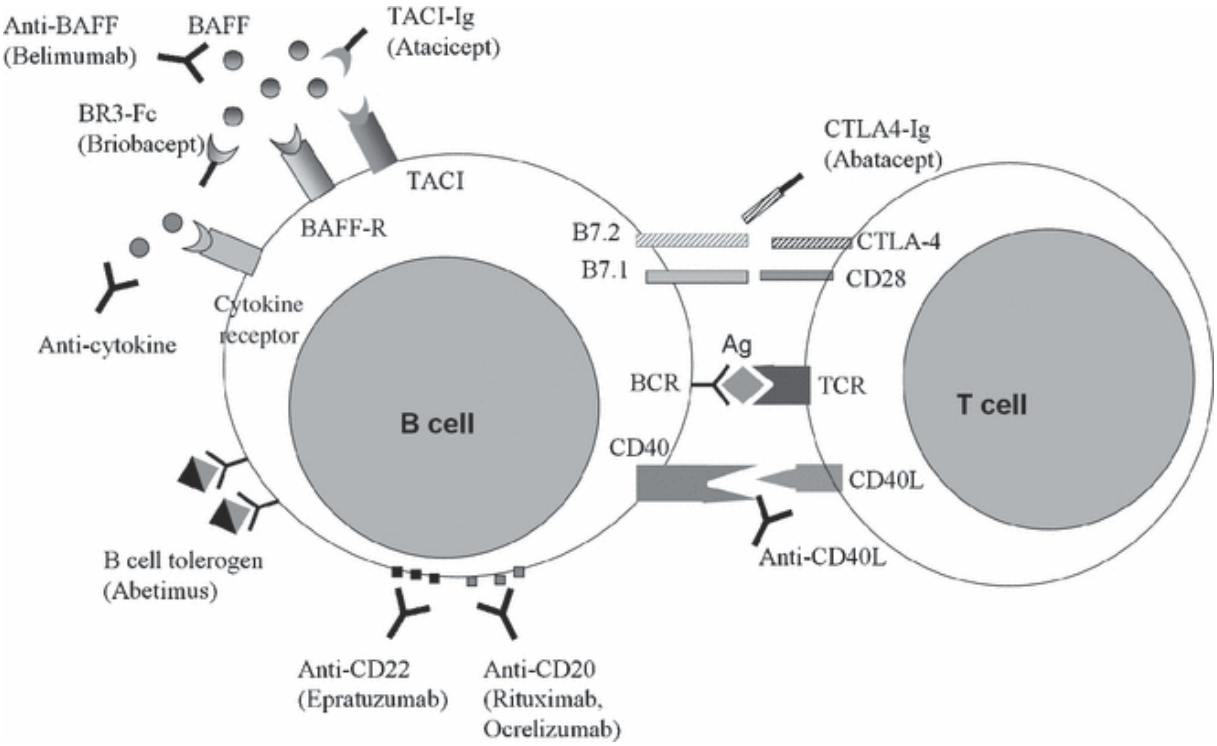

Figure 1: B-cell targeting therapies to treat systemic lupus erythemathosis (1)

Abstract:

Systemic Lupus Erythemathosis (SLE) is a complex autoimmune disease. Diagnosis and prognosis are difficult and have a lot of confounders. Progress of the disease is thus followed by a number of measures, such as damage indices like SELENA/SLEDAI and BILAG, B-cell numbers, immunoglobulin levels, in particular autoantibodies such as anti-dsDNA antibodies, and complement C3 and C4 levels. B-cell proliferation and activation are overstimulated in SLE, particularly through the BAFF/APRIL stimulated pathways. A number of BAFF/APRIL targeting biologicals have been approved for use in treatment of SLE or are currently in clinical trials. Three of these are highlighted here: Belimumab, Blisibimod and Atacicept.
Belimumab, a fully humanized anti-BAFF antibody, is already approved by the USFDA. In clinical studies it has been show to lower the damage index, B-cell numbers and immunoglobulin levels, it increases complement levels and may reduce the need for steroids.
Blisibimod, a synthetic peptibody, is in stage II trials. Like Belimumab, Blisbimod lowers the damage index and B-cell numbers, increases complement levels and may reduce the need for steroids.
Ataticept, a fusion protein, is in stage III trials. Atacicept also lowers the damage index, B-cell numbers and immunoglobulin levels, increases complement and may reduce the need for steroids.
The differences are relatively small and to determine the most promising of these treatments close attention has to be paid to the data from trials. So far, the fully human antibody Belimumab seems to retain the advantage over biologicals like Blisibimod and Atacicept.

Introduction:

Lupus:

Systemic Lupus Erythemathosis (SLE) is a complex and heterogeneous autoimmune disease. The pathology is so complex that it can be seen as a complex of immune diseases. The symptoms such as general malaise, fever, lethargy, renal and pulmonary problems as well as cardiac, nervous and hematopoietic manifestations are common. Because of the combination of symptoms patients have it is often hard to recognize lupus (2).

Prevalence of SLE is 20-150 per 100.000 persons. Women with lupus outnumber men by ten to one, and the disease is more prevalent in Africa and Asia than it is in Europe. The reason for the differences between these groups is unclear.

Diagnosis of SLE is difficult, and a large number of tests need to be done to ensure proper diagnosis. In addition to broad symptoms like rashes, arthritis, seizures, periods of lethargy and nephritis, the diagnosis has to be confirmed with laboratory tests.

As has been popularized in the American hit TV series House, the main manifestations of lupus are not unique to SLE, in fact SLE shares manifestations with more common afflictions such as depression, fibromyalgia, infection, and many connective tissue diseases. From a list of eleven symptoms, a patient needs to present at least four, before laboratory tests can add to the conclusions. Immunological measures for SLE includes high levels of Anti-Nuclear Antibodies (ANA), Anti double-stranded DNA antibodies (Anti-dsDNA), low C3 and C4 complement levels, anti-smith antibodies and antiphospholipid antibodies (3).

Progress of disease is followed using a number of indexes that score damage to organs, such as the SLICC/ACR damage index (SDI) (4), the SELENA/SLEDAI and British Isles Lupus Assessment Group (BILAG). These indexes measure progress of disease by scoring a number of symptoms, with each type of symptom weighted to indicate how important the symptom is for the prognosis. Examples of symptoms include a specific headache, evidence of proteinuria indicating renal damage , and evidence of chronic inflammation like rashes, arthritis and vasculitis (3). Measurements taken for the damage index include, among others, platelet count, complement count and leukocyte count in combination with assessment of pain, psychoses and sensory abnormalities.

These measurements for damage indexes measure damage already present. While types of damage can be indicative for prognosis, the measurements do not detect what is happening with the immune system in a direct way. Immunological measurement, such as the complement levels, can show activity of the disease.

Activity of SLE can be important for monitoring medication. Highly active disease sometimes requires suppression of acute inflammations. A burst of particularly active SLE is called a 'flare', though how exactly a flare is defined is still a matter of debate (5), though many adhere to a temporary increase of the SLEDAI score by four or more points.

Treatment:

In the short term patients with SLE can be treated with non-steroidal anti-inflammatory drugs (NSAIDs). These drugs only counter acute inflammation and have no long term immunosuppressive properties. NSAIDs need to be used only for short periods of time for reduction of symptoms, as prolonged use strongly increases risk of strokes, ulcers and renal failure (6).

Main therapy in treating SLE is relatively short courses of corticosteroids which are immunosuppressant but cause osteoporotic fractures, avascular necrosis and cataract formation when used in high doses (7). In addition to being immunosuppressive in the long term, they are anti-

inflammatory in the short term, making them efficient in heading off minor flares in serologically active disease.
Corticosteroid therapy can be supplemented with antimalarials such as hydroxychloroquine (6,8). Other antimalarials are used but they have strong side effects. Hydroxychloroquine is immunosuppressive and additionally is known to have cardioprotective properties.
In acute situations, corticosteroid use can be reduced or supplemented by lymphocytes inhibitors such as azathioprine and cyclophosphamide, both of which come with severe side effects.
Supplementary drugs and alternatives are aimed at reducing immediate anti-inflammatory drugs, and the risk anti-inflammatory drugs come with. So far all therapies come with their own risks and require low doses.

Pathogenesis
Over 200 genes are involved with the aetiology of SLE, and the disease is thought to be triggered by a combination of hereditary factors and environmental triggers such as UV exposure and exposure to certain drugs, such as penicillamine.
The nature of the genes involved in SLE and their contribution to pathogenesis of SLE is varied (9). Among the list are genes involved in nucleic acid sensing and interferon production, T-cell activation and B-cell activation. During normal inflammation, debris remains from apoptotic lymphocytes. In SLE patients this debris is insufficiently cleared. Faulty nucleic acid sensing may lead to exaggerated activation of the adaptive immune system, sometimes exacerbated by high interferon production. Activation of T and B-cells through antigen receptors is altered, leading to increased activation and longevity of active T and B-cells (10). T-cells are aberrantly activated when the intracellular domain of CD3 binds the spleen tyrosine kinase instead of the canonical CD3-ζ associated protein ZAP70 (11), leading to increased activation of B-cells, depleting the population of naïve B-cells and increasing the number of plasma cells (12).
The resulting glut of peripheral blood mononuclear cells goes into apoptosis, and the debris is insufficiently cleared (13). This debris, including nuclear components, as well as the contribution of B-cells in general, may trigger production of auto-antibodies. The auto-antibodies then activate the immune system to attack healthy tissue. As a further consequence, complement is depleted by continuous activation.
Tissue damage is mediated by combinations of auto-antibody-antigen immune complex deposition and apoptosis of tissue cells induced by cytokines. Large amounts of auto-antibodies and other inflammatory molecules cause plaques and chronic inflammation.

B-cells:
One of the major hallmarks in autoimmunity is presence of autoantibodies, such as antibodies directed against double stranded DNA. These antibodies are produced in mature B cells, thus mature B cells are a target for novel therapies to partially replace or supplement corticosteroid treatment.
During inflammation, inactive CD19+/CD20+ B-cells (immature, figure 2) are activated and express CD27 and IgD. These CD27+/IgD+ B-cells mature (Mature, figure 2) and one subset becomes IgD+/CD27+ memory B-cells, while other subsets switch class to IgD+/CD27- or IgD-/CG27- (plasma, figure 2) and secrete immunoglobulins (14).
In SLE, the population of B-cells that is affected most is CD19/CD20+ naïve B-cells. They are activated and subsequently undergo apoptosis and aberrantly undergo necroptosis, leaving debris in their wake (12,15).
Levels of immunoglobulins can be used as a measure of B-cell activity, but not as a measure of SLE disease activity.

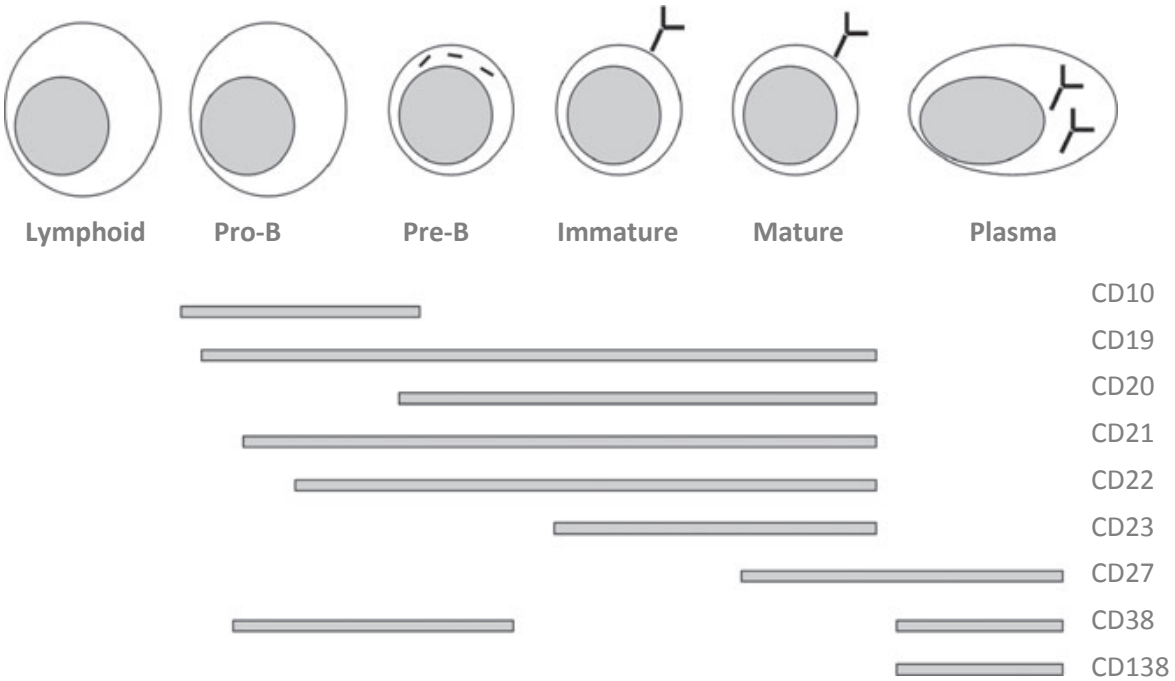

Figure 2: Maturation of B-cells with associated cell markers. Immature B-cells are recognized by expression of CD19 and CD20 and lack CD27. B-cells gain CD27 when maturing and becoming memory cells. Plasma cells have lost their CD27 (1).

Several promising new therapies aim to modulate the function of B-cells. Antibodies like Rituximab and Epratuzumab target receptors like CD20 and CD22 to affect B-cells. Targeting of CD20 results in activation of apoptotic pathways as well as attraction of effector T-cells which induce apoptosis (16). CD22 has a more complicated web of interactions and is involved in B-cell function and CD19 mediated B-cell survival (17).
Trials with rituximab targeting CD20 however showed little benefit to patients. Targeting of CD22 with epratuzumab showed more promise.
The most promising target for the treatment of SLE through manipulating B cells is the BAFF/APRIL axis. Rather than targeting total B-cell populations, activation of B-cells is target. B-cell Activating Factor (BAFF) and A PRoliferation Inducing Ligand (APRIL) are essential factors for B-cell survival and maturation (18). The BAFF/APRIL axis is part of a cascade of immune cell activation. BAFF is essential for maturation of B-cells, which then produce antibodies which will lead to T-cell activation (19). T-cells then produce BAFF to stimulate further B-Cell activation. Blocking BAFF and APRIL will stop this cascade (see figure 1).

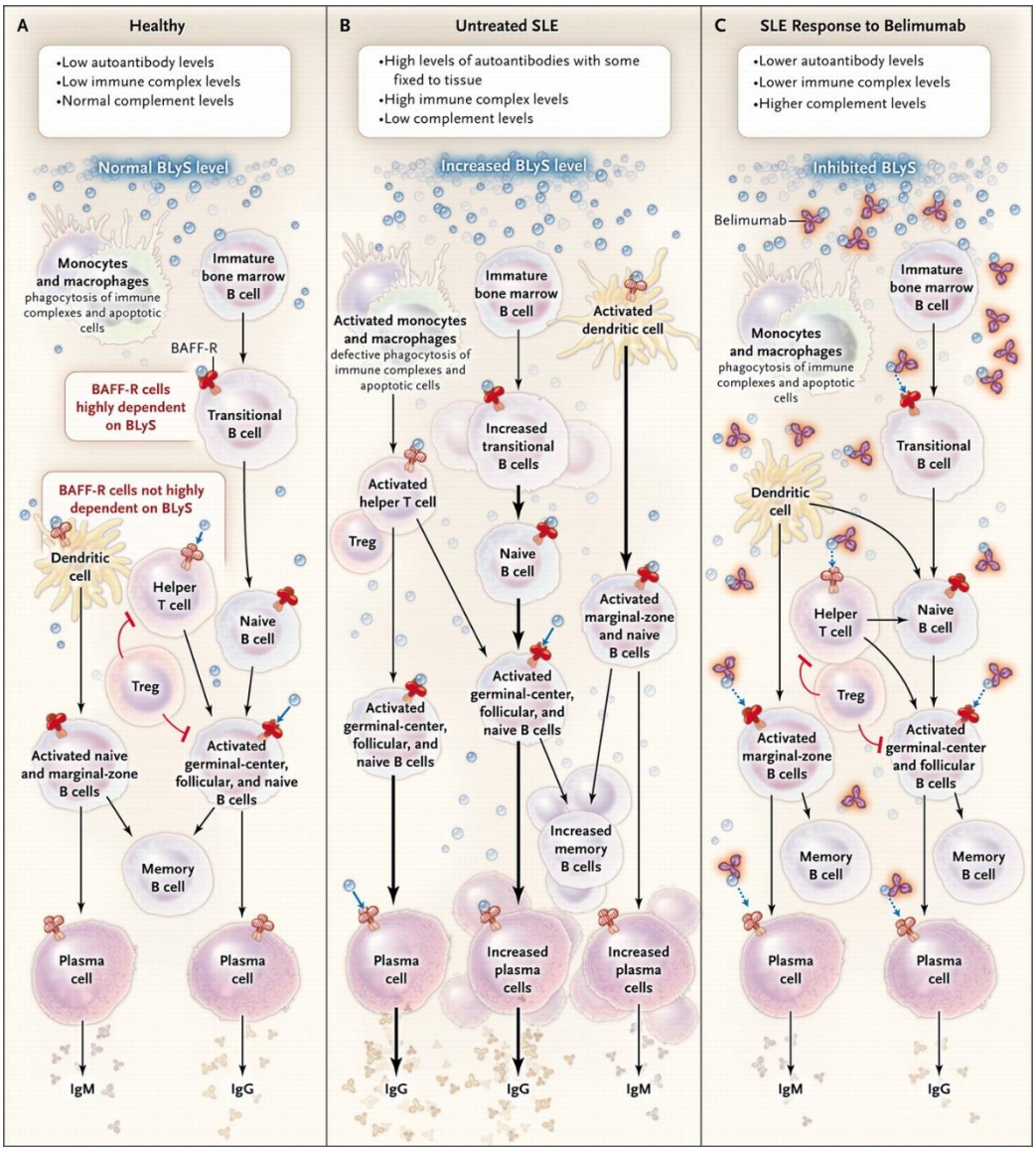

Figure 3: Blocking of BAFF in SLE. Dendritic cells , monocytes and macrophages are abnormally activated in SLE. BAFF blocking keeps T-helper cells from being activated and activating germinal centers and follicular B-cells (20).

BAFF/April inhibitors:

BAFF and APRIL affect maturation of B-cells from memory B-cells to active cytokine producing B-cells. Also known as BLyS, BAFF is a member of the TNF family of ligands (21). BAFF and APRIL have three receptors, BAFF-R, TACI and BCMA. Both soluble and membrane bound variants of BAFF exist, while APRIL only exist in soluble form. Interaction of BAFF and APRIL with their receptors overlap, which gives the system some redundancy (see figure 3). BAFF has the strongest connection with BAFF-R and has affinity for TACI with very low affinity for BCMA. APRIL only has affinity for BCMA and TACI.

Interaction of BAFF with BAFF-R is essential to survival of mature B-cells. This effect is thought to be tempered by interaction of APRIL with TACI, as deletion of TACI results in larger numbers of mature B-cells. BAFF interaction with BCMA is thought to be important for the survival of bone marrow plasma cells and plasmablasts. All three pathways work through NF-κB activation. In addition, BAFF-R promotes expression of the B-cell coreceptor complex, required for differentiation, and CD23. BCMA signalling leads to expression of surface proteins important for antigen presentation.

Blocking of BAFF will thus only affect survival of mature B-cells. Due to negative regulation of APRIL, blocking only APRIL will result in higher numbers of mature B-cells, while negatively influencing survival of plasma cells and plasmablasts. Blocking both pathways should result in lower levels of all three B-cell types.

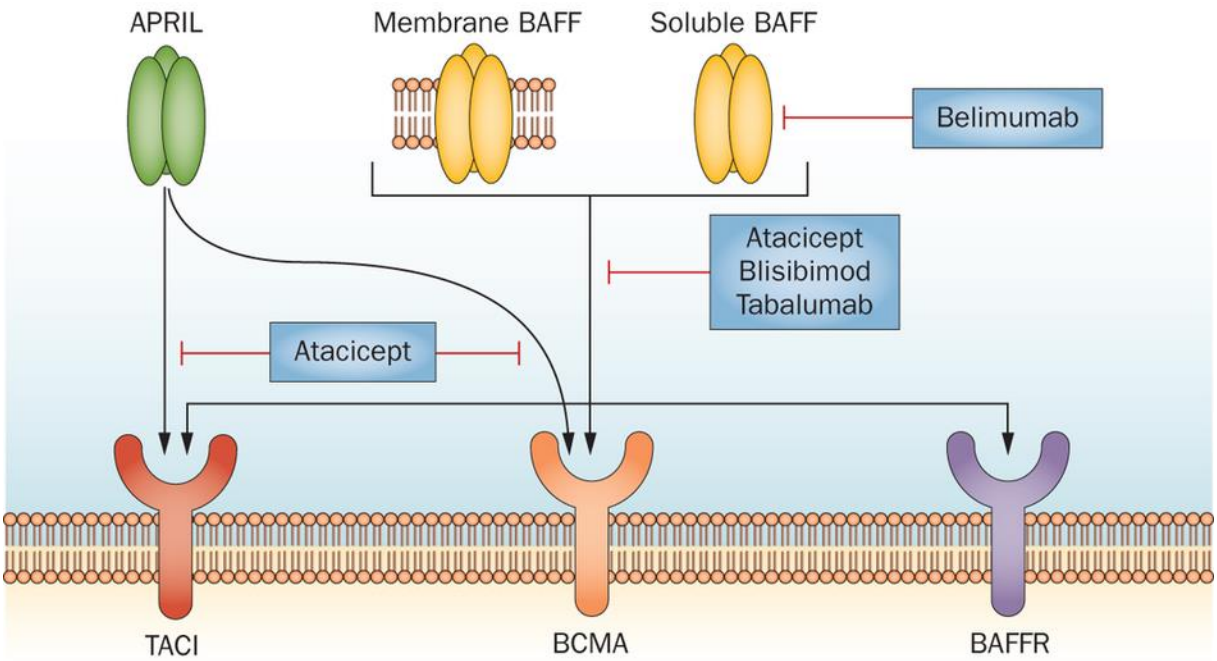

Figure 4: Targets of BAFF and APRIL. Belimumab targets soluble BAFF, which can bind to all three receptors, blisbimod targets both membrane an soluble BAFF, Atacicept targets both BAFF and APRIL, downregulating all signalling with TACI, BCMA and BAFF-R (22)

Several anti-BAFF/APRIL biologicals are currently on trials for use in SLE. Three are highlighted here: Belimumab, Blisibimod and Atacicept. Respectively, they target soluble BAFF, both soluble and membrane bound BAFF and both BAFF and APRIL. These biologicals are applied to reduce steroid use, to minimise the risks of toxicity, but not as full replacement. A common theme in trials is to taper steroid doses in order to establish a steroid reducing ability. The relatively small differences in targeting potential mean large differences in effect. In addition, each treatment may carry with it its own risks and putative side effects. Until now Belimumab has been approved by the USFDA so far, but approval of the other two is on the horizon. This naturally raises the question: which of the biologicals Belimumab, Blisibimod and Atacicept is most promising as a supplemental treatment for SLE?

Belimumab:

Belimumab is a human IgG1λ antibody targeting soluble BAFF/BLyS and it is the only biological currently approved for use in SLE treatment. Belimumab targets soluble BAFF thereby inhibiting contact with its receptors, BAFF-R, TACI and BCMA (23) and disrupting B-cell survival and maturation. In treatments with Belimumab B-cell numbers are significantly decreased. While improvement of SELENA/SLEDAI after Belimumab treatment were long debated (24), ANA and anti-dsDNA antibodies were reduced. It is considered that Belimumab treatment is most effective in active disease (25). Aside from rare cases of an allergic reaction, no side effects of the treatment were noted.
Two major phase III clinical trial have been held for Belimumab, the BLISS-52 and BLISS-76 trials, lasting 52 weeks and 76 weeks respectively. As both trials were conducted by the same group, the

data can be, and already were combined by Furie et al. Belimumab was administered intravenously, in doses of 1 mg/kg or 10 mg/kg on a four week basis (26).
The 10 mg/kg but not the 1 mg/kg had a response of at least a four point reduction in the SELENA/SLEDAI score compared to baseline after 52 weeks, though a small reduction of the SELENA/SLEDAI score was noted for both groups compared to baseline and placebo. After 76 weeks, the 10 mg/kg group managed even an over 10 point reduction in SLEDAI score. This score was not slanted towards improvement effects to one organ or system; improvements were noted similarly to all organs (27).
Anti-dsDNA levels were reduced and complement C3 and C4 were increased while after 52 weeks 10 mg/kg Belimumab decreased IgA, IgG and IgM (see table 1).
The risk of severe flares was reduced greatly, by 34% in the 1 mg/kg and 23% in the 10 mg/kg group. One subset of B-cells, activated CD27+ cells, which includes nearly all activated B-cells, was particularly suppressed.
As explicitly stated by Chatham Et al. in 2012, Belimumab carries no risk of higher infection rates, and antibodies gained from vaccination are not affected.
High BAFF levels have been associated with high activity of SLE (28). Roth et al. 2015 compared groups within the BLISS-52 and BLISS-76 trials based on high and low levels of BAFF. Higher levels of BAFF are associated with higher flare risk, but patients with higher BAFF levels also responded more strongly to Belimumab treatment.
Though the BLISS52 and BLISS-76 trials indicated a decrease in steroid use, the data were not significant (see figure 5).
Dooley et al. (2015) focused on the effects on renal problems. Mycophenolate mofetil, or MMF is commonly used as a supplementary drug to treat lupus nephritis. According to Dooley, Belimumab offers additional benefits on top of the effects of MMF.

Blisibimod:
The peptibody Blisibimod, a composite peptide, is an antagonist for both soluble and membrane bound BAFF, inhibiting interaction with all receptors for BAFF, thereby inhibiting B-cell survival and maturation in a similar manner as Belimumab. The role of membrane bound BAFF in B-cell activation may be very minor, if it has any role in B-cell activation at all, indicating that the difference with Belimumab in target may not be measurable at all. Blisibimod is composed of four high-affinity BAFF binding domains fused to the Fc domain of a human IgG (26,29).
Few major trials for use of Blisibimod in SLE therapy have been performed so far. Here we selected a stage I trial by Stohl et al. (22) and the PEARL-SC stage II trial . Stage I and II trials are small and exclude the most vulnerable patients. The Stohl trial selected only subjects with mild disease, receiving 0.1 mg/kg -3.0 mg/kg subcutaneous or 1.0 mg/kg – 6.0 mg/kg intravenous on a weekly basis (30) (see figure 5). The PEARL-SC trial, for which the most severe cases were excluded, administered 100 mg Blisibimod per week, 200 mg Blisibimod per week or 200 mg Blisibimod per month (29). Stohl et al. thus administered a much higher dose in their highest dose category than the PEARL-SC trial.
In the Stohl trial, changes in damage indices were not noted, instead the trial focused on safety, tolerance and biomarkers. PEARL-SC met their goal of SLEDAI reduction of at least five points in the group receiving 200 mg Blisibimod per week. The subgroup with the highest response rate was also the subgroup with most active disease.
The Stohl trial, in addition to a general decline in B cell population, marked one subset that was particularly depleted, namely the IgD+/CD27- naïve B cells, in favour of mature IgD-/CD27+ memory B cells. Additionally, CD38 was increased in favour of CD19. The PEARL-SC trial merely showed a general decrease in B-cells. In both trials with Blisibimod treatment B-cell numbers are lowered,

while natural killer and T cells numbers remain stable (30). Similar to the studies with Belimumab, the groups which most benefitted from the treatment were the patient groups with the most active disease (see figure 5). The base treatment with corticosteroids remained indispensable.
The PEARL-SC trial showed a marked increase in C3, and C4 complement levels, as well as a sharp decrease in anti-dsDNA antibodies in all dosage groups. These results indicate effectiveness in all doses, and not just above a certain threshold (seetable 1).
Both trials were only stage I and II trials, meaning small trials mainly aimed at assessing risk and tolerance of the drug, which is invaluable when designing robust stage III trials with larger patient numbers. The Stohl trial lasted sixteen weeks, which limits the trial's scope. In two cases, severe kidney related problems were reported in the Stohl trial with Blisibimod, which could not be excluded as being related to the study drug. While such low numbers may not seem meaningful, it is important to appreciate that the kidneys are a risk area during phase III trials.

Atacicept:
Atacicept is a fusion protein which is not only an antagonist for soluble BAFF, but not membrane bound BAFF but also for APRIL, by adding the Fc part of IgG to a BAFF receptor, TACI. This dual function has effects that differ from Blisibimod and Belimumab. Atacicept inhibits B-cell maturation and survival as Belimumab would, while it should also inhibit T-cell activation by blocking a pathway leading to cytokine production (21).
Several phase III trials have been attempted to assess Atacicept as a component to treat SLE. The first was planned with subcutaneous injection of 150 mg at least weekly for 48 weeks (31). However, the protocol for this trial also included high doses of corticosteroid before initiation of Atacicept. The trial was terminated after several patients suffered severe infections due to immunoglobulin depletion, thought by the authors to be likely caused by corticosteroid treatment. Only six patients were enrolled in the program by that point, and the longest participation was for 33 weeks. While the early termination and low number of participants, four on Atacicept and two placebo, may not yield statistically significant data, enough data was collected to indicate effectiveness. A reduction in both B-cell numbers, anti-dsDNA antibody levels, and immunoglobulin levels could be observed as well as modest increases in C4 levels, but not levels of C3 (see table 1).
This trial was soon followed by a trial with two subcutaneous injections of Atacicept, with 150 mg or 75 mg, twice weekly for the first fourweeks, then set a week apart for 48 weeks (32). Success was measured as an improvement in the BILAG score, which was reached in the 150mg group. This group also showed significant delay in time to first flare.
IgG levels were reduced, as in the previous trial, by corticosteroid treatment prior to treatment with Atacicept. The data showed further IgG decrease after initiation of Atacicept, as was also seen for IgA and IgM.
Anti-dsDNA antibodies were reduced in Atacicept treatment by 31% and 38% in the 75 mg and 150 mg arms respectively, while a 14% reduction in anti-dsDNA was observed in the placebogroup (see figure 5).
Although a delay in flares has been shown (32), safety concerns about Atacicept have not been solved. In the Isenberg Et al. trial, two fatal infections occurred in the 150 mg group, which could not be excluded to be indirectly caused by Atacicept, or the combination of Atacicept and corticosteroid treatment. These infections, combined with infections in the discontinued trial, show how treating SLE relies on a delicate balance between fighting auto-immunity and preserving the adaptive immune system. The 150 mg dosage group stopped recruiting new subjects as a consequence of the infections.

The possible suppression of T-cells by Atacicept may be cause for concern (33) though the trials may be skewed by randomizing patients into the Atacicept group which would receive high doses of corticosteroids shortly before the trial.

	Belimumab	Blisibimod	Atacicept
Dose	1 or 10mg/kg Intravenous	1, 2 or 3 mg/kg subcutaneous, 1, 3 or 6 mg/kg intravenous	150 mg
BILAG	NA	Improved	Improved
SLEDAI	Reduced 4-10	Reduced 5 (PEARL-SC)	NA
B-cells	Up to 55% reduction	Up to 40% reduction	NA
Immunoglobulins	Anti-DsDNA -45% IgA -4.5% IgG -9.7% IgM -20.9%	Anti-DsDNA: No change (Stohl) -25% (PEARL-SC)	Anti DsDNA -38%
Complement	C3 +21% C4 +45%	C3 up to +20% C4 up to +15%	C3 +0% C4 +15%
Steroid sparing	Insignificant data	No change (Stohl) 12% of patients reduced steroids to <7.5 mg/day (PEARL-SC)	NA

Table 1: Comparison of data. The data from the trials is varied, although a number of factors can be compared. Anti-dsDNA is measured in all trials as well as complement levels. Other comparisons between two treatments can also be discussed.

Discussion:

Issues with comparison:

It is hard to compare Belimumab, blisbimod and Atacicept based on these trials. Not all trials used SLEDAI to score their response index, method of administration of the drug and dosage differed widely between treatments and though there is of course a lot of overlap measurements have not focussed on the same parameters.

Despite this variety between trials, a lot of overlap exists, which can be compared. Where trials for all three do not overlap in measurements, two may overlap and provide an angle of comparison.

The three treatments were administered in different doses and through different methods throughout the trials. The three compounds have a similar function, to bind BAFF and thus eliminate it, although belimumab is twice as heavy as the other two. Thus it would make sense for belimumab to have a higher dose in weight. From the trials, however, we see that belimumab requires similar weight to have an effect (~150 mg per dose) as atacicept and blisibimod.

The difference between Belimumab and the other B-cell targeting drugs Atacicept and Blisibimod is that the latter are can be injected subcutaneously while Belimumab is injected intravenously. The difference between subcutaneous and intravenous is one of both the practice of intravenous taking a lot of time and man hours while subcutaneous injection requires less time and equipment to administer. The biological barriers faced by subcutaneous injection are however greater (34). While the drug introduction method may be a practical issue, it may have some consequences for the targeting of the drug and of course the method has a consequence for dosage.

Damage indices:
Trials for three biological, Belimumab, Blisibimod and Atacicept claim that the treatments reduce damage index scores (26,30-32). Regular high doses of Belimumab were the only treatment to reduce the SELENA/SLEDAI score by at least ten points. Blisibimod treatment scored nearly as good with weekly high doses. The trial for Atacicept did not use SLEDAI scores for their response index but BILAG scores, which trials for Belimumab and Blisibimod used in addition to SLEDAI score. Belimumab hit their best score in 69% of subjects with the highest dose, Blisibimod hit their best score in 78% of subjects with the highest dose and Atacicept scored similarly with 71% of subject with the highest dose, giving a similar image for all three treatments.
The BILAG score is one measure to measure flares, but it is not informative about timing. While the Belimumab trials did not score the timing until first flare, both the Blisibimod and Atacicept trial showed a delay until the first flare for their highest dosage, suffering flares after five to two times as long respectively.

Biomarkers:
B-cell populations:
B-cell populations in SLE grow far beyond normal. One subpopulation, the IgD-/CD27- naïve B-cell population of active B-cells that normally makes up barely 5% of the total B-cell population (35) in SLE threatens to become the dominant population (36).
All B-cell depleting treatments of course have a negative impact on B-cell population. The Belimumab trial claims a 55% of CD20+ naïve B-cells in Belimumab, while this figure is around 30%-40% in Blisibimod trials. The Atacicept trial did not show B-cell counts, focusing on other parameters. Most interesting is the effect on subpopulations, where the CD27- subpopulations, including the IgD-/CD27- subpopulation are most effected. Both Belimumab and Blisibimod had the strongest effect on naïve B-cells, and less effect on plasma cells and memory B-cells. On one hand this means that the naïve population, which is already strained, is further repressed, on the other, the IgD-/CD27- population may be a problematic subpopulation that is now controlled.

Immunoglobulins:
Belimumab and Atacicept trials measured levels of immunoglobulins IgG, IgA and IgM, which is an important measure for the effect on B-cells, and which are elevated in SLE. The trial for Belimumab showed clear percentage changes while the Atacicept methods confounded immunoglobulin levels with high corticosteroid doses shortly before the trial started. However, both trials indicated a significant reduction in immunoglobulins, even if the data were not conclusive.

Anti-dsDNA:
In SLE a significant increase in anti-dsDNA is defined as at least a four-fold increase to acceptable levels (37). Belimumab showed a 45% decrease in anti-dsDNA levels in the BLISS trials for the highest dose level. The Stohl trial of Blisibimod showed a less than 25% decrease in anti-dsDNA levels. The highest dosage of Atacicept proved to reduce anti-dsDNA levels by 38%. Combined with the lower dosages needed for Belimumab, Belimumab seems to have a clear advantage over Blisibimod and Atacicept. None of these three drugs drive anti-dsDNA levels below acceptable levels but the effect is significant.

Complement levels:
Complement levels in SLE are depressed to below 900 mg/L of blood from normal levels of 750-1350 mg/L for C3 and below 160 mg/L from normal levels of 130-750 mg/L. While complement levels

below 900 mg/L and below 160 mg/L may still be within an acceptable range, it is considered a risk factor in SLE.
In the Belimumab BLISS trials, a 21% increase in C3 and a 45% increase in C4 was achieved (26), which is hard to compare with the Blisibimod PEARL-SC study which merely noted the increase in C3 and C4 as 'significant', and showed a 50 mg/L increase in C3 and a 20 mg/L increase in C4 (29). More comparable are the Atacicept results, which claim a 15% increase in C3 levels and a 49% increase in C4 levels (32). Isenberg Et al. also noted these increases mean increased by up to 138 mg/L for C3 levels and by 66 mg/L for C4 levels, making Belimumab and Atacicept comparable where Blisibimod appears to lag behind. Only the increases in C3 cannot be considered normalisation.

Steroid sparing:
For each of the biologicals, one of the secondary goals was to reduce corticosteroid use to 7.5 mg/day or less, to mitigate side effects of corticosteroids. This reduction in steroid use was achieved in the Belimumab BLISS trials in nearly 20% of the Belimumab group, but as the placebo group managed this reduction in 13% of subjects, the results did not stand on their own. Comparing these results to Blsibimod results, again only a modest advantage can be observed for Blisibimod of 12% of the Blisibimod group versus 9.5% for the placebo group. In the Atacicept trial, steroid use was kept low from the start, and increase of steroid use were measured instead. No good comparison with Atacicept can be made for steroid sparing effects, though none of the treatments may result in significant reduction of steroid use.

Conclusion:

To proclaim one of the biologicals Belimumab, Blisibimod or Atacicept most promising, they were compared point by point. The three biologicals have a similar level of effect on damage indices, realising no worsening of the disease in around 70% of the subjects with the highest doses. Belimumab and Blisibimod both seem to target the naïve CD20+CD27- subpopulation of B-cells, though the effect on the most problematic subpopulation of B-cells, the CD27-/IgD- population is also significant. While none of the trials could provide conclusive data on overexpression of immunoglobulins, significant reductions in anti-dsDNA were achieved by all three biologicals, with Blisibimod as the weaker drug. For the normalisation of complement, it is notable that while C4 is normalized by all three biologicals, C3 is still reduced. Lastly none of the biologicals seem to significantly reduce steroid use.
From the above, Belimumab comes out as the most promising. It has to be taken into account that Belimumab has had a longer period of testing than Blisibimod and Atacicept, but also research into the latter two can refer to the development of Belimumab.

To discuss why these differences exist, one point of further comparison is the structure of the three compounds.
Both Blisibimod and Atacicept are fusion proteins, removing non-essential parts from the structure in their design, as evidenced by their size, 63 KDa and 71 KDa respectively, compared to Belimuab which is 150 KDa. Both fusion proteins have smaller BAFF and APRIL binding domains attached to Fc domains while Belimumab is a full-sized fully humanized antibody.
Also of interest is the difference between clinical outcome and biological markers. While most markers show a significant change along with a significant improvement in clinical outcome, the marker C3 lags behind, possibly indicating a lesser importance for low levels of C3.

The inconclusive results in steroid paring effect of the biologicals reinforce the importance of maintaining steroids as the mainstay of SLE treatment, and research into steroid sparing drugs remains important.
While Blisibimod and Atacicept show promise, more research and development of their structure may lead to better results. Additionally, more research has to be done to assess the risks of Atacicept. Thus, in conclusion, Belimumab remains so far the most promising biological to target the BAFF/APRIL axis in B-cell signalling.

(1) Mok MY. The immunological basis of B-cell therapy in systemic lupus erythematosus. Int J Rheum Dis 2010 Feb 1;13(1):3-11.

(2) Kamal A, Khamashta M. The efficacy of novel B cell biologics as the future of SLE treatment: a review. Autoimmun Rev 2014 Nov;13(11):1094-1101.

(3) Lam GK, Petri M. Assessment of systemic lupus erythematosus. Clin Exp Rheumatol 2005 Sep-Oct;23(5 Suppl 39):S120-32.

(4) Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996 Mar;39(3):363-369.

(5) Petri MA, van Vollenhoven RF, Buyon J, Levy RA, Navarra SV, Cervera R, et al. Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III belimumab trials. Arthritis Rheum 2013 Aug;65(8):2143-2153.

(6) Amissah-Arthur MB, Gordon C. Contemporary treatment of systemic lupus erythematosus: an update for clinicians. Ther Adv Chronic Dis 2010 Jul;1(4):163-175.

(7) Toloza SM, Roseman JM, Alarcon GS, McGwin G,Jr, Uribe AG, Fessler BJ, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXII. Predictors of time to the occurrence of initial damage. Arthritis Rheum 2004 Oct;50(10):3177-3186.

(8) Lee SJ, Silverman E, Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis. Nat Rev Nephrol 2011 Oct 18;7(12):718-729.

(9) Crispin JC, Liossis SN, Kis-Toth K, Lieberman LA, Kyttaris VC, Juang YT, et al. Pathogenesis of human systemic lupus erythematosus: recent advances. Trends Mol Med 2010 Feb;16(2):47-57.

(10) Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011 Dec 1;365(22):2110-2121.

(11) Crispin JC, Kyttaris VC, Juang YT, Tsokos GC. How signaling and gene transcription aberrations dictate the systemic lupus erythematosus T cell phenotype. Trends Immunol 2008 Mar;29(3):110-115.

(12) Odendahl M, Jacobi A, Hansen A, Feist E, Hiepe F, Burmester GR, et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. J Immunol 2000 Nov 15;165(10):5970-5979.

(13) Perniok A, Wedekind F, Herrmann M, Specker C, Schneider M. High levels of circulating early apoptic peripheral blood mononuclear cells in systemic lupus erythematosus. Lupus 1998;7(2):113-118.

(14) Kaminski DA, Wei C, Qian Y, Rosenberg AF, Sanz I. Advances in human B cell phenotypic profiling. Front Immunol 2012 Oct 10;3:302.

(15) Fan H, Liu F, Dong G, Ren D, Xu Y, Dou J, et al. Activation-induced necroptosis contributes to B-cell lymphopenia in active systemic lupus erythematosus. Cell Death Dis 2014 Sep 11;5:e1416.

(16) Oflazoglu E, Audoly LP. Evolution of anti-CD20 monoclonal antibody therapeutics in oncology. MAbs 2010 Jan-Feb;2(1):14-19.

(17) Tedder TF, Poe JC, Haas KM. CD22: a multifunctional receptor that regulates B lymphocyte survival and signal transduction. Adv Immunol 2005;88:1-50.

(18) Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol 2009 Jul;9(7):491-502.

(19) 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 2013 Jun;24(3):203-215.

(20) Hahn BH. Belimumab for systemic lupus erythematosus. N Engl J Med 2013 Apr 18;368(16):1528-1535.

(21) Bossen C, Schneider P. BAFF, APRIL and their receptors: structure, function and signaling. Semin Immunol 2006 Oct;18(5):263-275.

(22) Stohl W. Therapeutic targeting of the BAFF/APRIL axis in systemic lupus erythematosus. Expert Opin Ther Targets 2014 Apr;18(4):473-489.

(23) Jordan NP, D'Cruz DP. Efficacy, pharmacokinetic and pharmacodynamic profile of belimumab for systemic lupus erythematosus. Expert Opin Drug Metab Toxicol 2015;11(10):1635-1645.

(24) Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum 2009 Sep 15;61(9):1168-1178.

(25) van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012 Aug;71(8):1343-1349.

(26) Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, 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 2011 Dec;63(12):3918-3930.

(27) Manzi S. Lupus update: perspective and clinical pearls. Cleve Clin J Med 2009 Feb;76(2):137-142.

(28) Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. Arthritis Rheum 2001 Jun;44(6):1313-1319.

(29) Furie RA, Leon G, Thomas M, Petri MA, Chu AD, Hislop C, 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 2015 Sep;74(9):1667-1675.

(30) Stohl W, Merrill JT, Looney RJ, Buyon J, Wallace DJ, Weisman MH, 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 2015 Aug 20;17:215-015-0741-z.

(31) Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J, Ramos E, et al. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. Arthritis Res Ther 2012 Feb 7;14(1):R33.

(32) 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 2015 Nov;74(11):2006-2015.

(33) Wang X, Xiao H, Wei Y, Liu X, Han G, Chen G, et al. Blockade of B-cell activating factor with TACI-IgG effectively reduced Th1 and Th17 cells but not memory T cells in experimental allergic encephalomyelitis mice. Cent Eur J Immunol 2015;40(2):142-148.

(34) Supersaxo A, Hein WR, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. Pharm Res 1990 Feb;7(2):167-169.

(35) Morbach H, Eichhorn EM, Liese JG, Girschick HJ. Reference values for B cell subpopulations from infancy to adulthood. Clin Exp Immunol 2010 Nov;162(2):271-279.

(36) Milner EC, Anolik J, Cappione A, Sanz I. Human innate B cells: a link between host defense and autoimmunity? Springer Semin Immunopathol 2005 Mar;26(4):433-452.

(37) ter Borg EJ, Horst G, Hummel EJ, Limburg PC, Kallenberg CG. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus. A long-term, prospective study. Arthritis Rheum 1990 May;33(5):634-643.