Author's response to reviews

Title: Novel therapeutic agents in clinical development for SLE

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Author's response to reviews: see over
Reviewer 1 comments:

Reviewer's report:

This is a well-written review article dealing with novel therapeutic agents which are currently in clinical development for SLE. I have no major comments.

Minor Essential Revisions

1. Belimumab has not been approved by some local administrations, including NICE and the German drug administration. This deserves some discussion.

Although belimumab received regulatory approval from the United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA), its use in some countries has been restricted until approval by national drug evaluation organisations. The German Institute for Quality and Efficiency in Health Care (IQWiG) has recommended evaluation of belimumab for additional benefit over optimised immune-suppression rather than over standard therapy prior to full approval [www.iqwig.de].

In 2012 The National Institute for Health and Clinical Excellence (NICE) provided a draft national guidance on the use of belimumab for systemic lupus erythematosus in the United Kingdom. NICE did not recommend belimumab within its licensed indication as add-on therapy to standard immune-suppressive drugs in adult patients with active auto-antibody positive SLE. In making this decision, NICE considered the clinical trial evidence, clinical specialist and patient opinions. NICE concluded that the use of belimumab was not sufficiently cost-effective to the National Health Service (NHS) in relation to its reported clinical effectiveness. A final decision will be expected after the appeals process has been concluded [www.nice.org.uk].
2. Some preliminary results on IFN-alpha blockade in SLE were published in the ACR 2012 meeting. The authors could discuss them.

The efficacy and safety of rontalizumab, a recombinant humanized monoclonal antibody to IFN-α was recently assessed in a randomized, double-blind, placebo-controlled phase II trial in adults with moderate to severe non-renal SLE. In the initial part of the study, SLE patients received either 750 mg intravenously of rontalizumab or placebo for four weeks. In the second part of the study, SLE patients received either 300 mg subcutaneously of rontalizumab or placebo for two weeks. Overall, response rates at 24 weeks as measured by BILAG and Systemic Lupus Erythematosus Responder Index (SRI) were similar between rontalizumab and placebo. However, in patients taking > 10 mg/kg of steroids daily, rontalizumab was more effective in reducing lupus disease activity than placebo. Patients were further analysed as per their interferon gene expression signature, which showed that rontalizumab was more effective in those with a more elevated interferon signature.

Efficacy and Safety of Rontalizumab (Anti-Interferon Alpha) in SLE Subjects With Restricted Immunosuppressant Use: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 2 Study.


3. Jak kinases and other small molecules/kinase inhibitors are also evaluated as
therapeutic targets in SLE. The authors should report on their current status in clinical development in lupus or other autoimmune diseases.

Janus kinase (JAK) and spleen tyrosine kinase (Syk) inhibitors

**Tofacitinib (JAK inhibitor)**

Tofacitinib is a Janus Kinase (JAK) selective inhibitor which has been approved as the first oral biologic for the management of rheumatoid arthritis. JAKs are essential for signal transduction of cytokines and contribute to inflammatory responses [van der Heijde D, *Arthritis Rheum* 2013, **65**(3):559-570].

Targeting JAKs in SLE would be a logical therapeutic option which can be studied further starting with trials to determine the safety, pharmacodynamics and efficacy of these drugs in SLE.

**Fostamatinib (Syk inhibitor)**

Spleen tyrosine kinase (Syk) is implicated in the B cell immunopathogenesis of SLE and is a potential therapeutic target. Syk inhibitors have been shown to prevent the onset of skin and renal disease in lupus-prone mice. In addition Syk inhibitors reduce inflammatory arthritis. Fostamatinib is an oral Syk inhibitor being evaluated for the management of autoimmune rheumatic diseases [Morales-Torres J *Expert Rev Clin Immunol* 2012, **8**(7):609-615].

4. Quite a few trials were terminated due to increased risk of serious infections.
Conventional immunosuppressive therapies have radically transformed patient survival in SLE, but their use is associated with considerable toxicity and a substantial proportion of patients remain refractory to treatment. A more comprehensive understanding of the complexity of SLE immunopathogenesis has evolved over the past decade and has led to the testing of several biologic agents in clinical trials. An array of promising new therapies are yet to emerge or an under development. There is a clear need for new therapeutic strategies that overcome these issues, and biologic agents offer exciting prospects as future SLE therapies. The role of new therapeutic agents to date has chiefly centred on SLE patients who have been refractory to conventional therapies. There are few clinical trials examining their role as first line induction or maintenance therapy. The questions remains, how can these therapies be potentially combined with existing proven treatments and indeed with one another to achieve maximum clinical benefit while minimising toxicity.

Although so far many biologics have been generally well tolerated, we must not be complacent regarding potential toxicity of these new agents, as we do not yet know the long-term effects of these medications on the immune system. Some novel biologic therapies have been associated with significant toxicity leading to premature discontinuation of clinical trials such as the association of anti-CD40L and thromboembolic events and the high frequency of reported severe and opportunistic infections associated with ocrelizumab. In the case of belimumab, there is a known increased susceptibility to infection, the commonest being pharyngitis, bronchitis, cystitis and viral gastroenteritis [Navarra SV, Guzman RM, Gallacher AE, et al 2011]. In the clinical trials serious infections have been reported in 6% of belimumab treated patients as compared to 5.2% in placebo controls but there have been no reports to date of PML in belimumab treated patients [Dennis, G. J.
2012]. The prematurely terminated randomized, double-blind, placebo-controlled Phase II/III, 52-week study APRIL-LN study reported adverse events in the patients randomised to atacicept (n=4). Patients developed significant IgG hypogammaglobulinemia below the protocol-defined criteria for discontinuation (n=3) and serious infections which included Haemophilus influenza pneumonia, Legionella pneumophilia pneumonia and Bacillus bacteremia. Interestingly, atacicept trials in rheumatoid arthritis have not yielded this extent of adverse events which implies that the immune-pathogenesis of lupus nephritis amongst other factors may have influenced the results of this trial. At present the clinical trial data is insufficient to determine clinical efficacy of atacicept in lupus nephritis therefore a review of future studies is required.

When considering interferon blocking therapies such as sifalimumab and rontalizumab, given the role of IFN-α in the host defence against viral infection, close clinical monitoring is mandatory in the development of any potential agents targeting this pathway.

As clinicians the onus is on us to minimise the risk of serious infection in our patients when using biologic agents. It is not advisable to administer intravenous biologic therapy in the context of active infection, in order to minimise the risk of severe or fatal events. It is also recommended that patients are screened for chronic infections such as tuberculosis and hepatitis prior to the initiation of biologic therapy due to the potential risk of disease reactivation. There are no established guidelines, as yet, concerning immunisation prior to biologic therapy, however because it is important to minimise the chance of severe infection, clinicians should consider vaccinating patients against pneumococcal pneumonia, haemophilus influenza type B and influenza prior to commencing therapy.

A number of key questions remain. How can these therapies be potentially combined with existing proven treatments and indeed with one another to achieve maximum clinical benefit with minimal side effects such as increased risk of serious infection. As is clear to all physicians involved in the day
to day management of SLE patients, this is a heterogeneous disease and there is not one therapeutic regimen suitable for all. With a deeper understanding of the pathophysiology of SLE particularly from a genetic perspective, the era of personalized therapy may represent the greatest advance that yet to come in optimising treatment of SLE.

5. How do the authors envision the use of these new biologic agents in the management of lupus? This is especially important in view of the results of the belimumab trials showing only modest clinical benefit that takes time to achieve. With the exception of B-cell depleting agents, will other agents be suitable as induction or as maintenance regimens? Or, is it that they will be used to minimize residual disease activity and/or exposure to steroids?

The management of SLE will change tremendously with the introduction of a multitude of new biological therapies and the discovery of other therapeutic targets in SLE. The exact role of all these drugs will be determined after completion of the trials and with clinical experience. It is envisioned that the majority of the biological therapies will initially be reserved for patients who have failed to respond satisfactorily to optimal conventional immunosuppressive drugs. The new biological drugs will need to be used appropriately to target disease remission; reduction of the severity and frequency of lupus flares and the subsequent high morbidity associated with lupus.

Rituximab is currently used off-license for the management of severe refractory SLE and is likely to continue to be used for this indication due to overall positive clinical experience.

Based on the clinical trial and extension study data, belimumab has a modest level of clinical effectiveness when used in combination with standard immunosuppressive drugs in autoantibody-positive SLE patients. The BILAG data at week 52 of the BLISS trials suggested more favourable outcomes in the mucocutaneous, musculoskeletal domains. The SELENA-SLEDAI cutaneous,
musculoskeletal, immunologic, vascular and central nervous system components significantly improved at week 52 in the BLISS trials. Physicians will therefore be inclined to closely monitor patients on belimumab and switch to alternate therapeutic regimens if the clinical response is inadequate after 6 months.

SLE patients of black ethnicity are to be studied in greater numbers than in the original BLISS trials in order to ascertain whether or not belimumab is beneficial in this group of patients.

As belimumab use becomes more prevalent and the results of the on-going belimumab clinical trials are published, the group of SLE patients likely to benefit the most from this drug may be identified and this will guide future use of this medication.

The place for other therapeutic agents in development for the management of SLE such as epratuzumab, ocrelizumab, blisibimod, tabalumab and atacicept as induction or maintenance therapy will be determined after robust reviews of the clinical trial data which is expected upon completion of the studies. It is anticipated that only drugs which show long-term clinical effectiveness, benefit as steroid-sparing agents and satisfactory safety profiles in SLE will gain approval for clinical use.

Although some drugs have not progressed to phase II or III clinical trials after phase I studies, research into cytokine therapies; drugs targeting FcγRIIB and small molecule targets is on-going and may yield important results for the future of SLE management.

Health economic studies will be essential in determining the future use of the new therapeutic agents in SLE and may influence the international use of these drugs.
6. Table 1. I would add a separate column to define the type of lupus (ie, nephritis, general SLE) that is targeted in each trial.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Target</th>
<th>Study Participants</th>
<th>Mechanism of action</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>257 SLE patients with moderately-to-severely active disease (≥1 BILAG A score or ≥2 BILAG B scores) 144 patients with class III or class IV lupus nephritis</td>
<td>B cell apoptosis or lysis</td>
<td>EXPLORER, LUNAR</td>
</tr>
<tr>
<td>Belimumab</td>
<td>Humanised anti-BLyS monoclonal antibody</td>
<td>865 seropositive SLE patients with SELENA-SLEDAI score ≥6. Severe active lupus nephritis &amp; severe CNS disease excluded. 819 seropositive SLE patients with SELENA-SLEDAI score ≥6. Severe active lupus nephritis &amp; severe CNS disease excluded.</td>
<td>BLyS inhibition blocks soluble BLyS and prevents binding to B cell receptor</td>
<td>BLISS-52, BLISS-76</td>
</tr>
<tr>
<td>Blisibimod</td>
<td>Anti-BLyS antagonist fusion protein</td>
<td>Active SLE</td>
<td>BLyS inhibition blocks soluble BLyS and prevents binding to B cell receptor</td>
<td>PEARL-SC</td>
</tr>
<tr>
<td>Atacicept</td>
<td>Recombinant fusion protein to TACI-Ig</td>
<td>SLE excluding lupus nephritis. Lupus nephritis study discontinued due to reports of increased</td>
<td>Inhibition of B cell activation by BLyS and APRIL</td>
<td>Phase II/III</td>
</tr>
<tr>
<td><strong>Epratuzumab</strong></td>
<td>Humanized anti-CD22 monoclonal antibody</td>
<td>227 moderate to severe SLE patients. Moderate to severe SLE patients excluding severe renal &amp; neuropsychiatric disease.</td>
<td>B cell apoptosis</td>
<td>EMBLEM EMBODY</td>
</tr>
<tr>
<td><strong>Abatacept</strong></td>
<td>CTL4-Ig fusion protein</td>
<td>SLE with polyarthritis, discoid lesions, or pleuritis and/or pericarditis. Data reanalysed for lupus nephritis</td>
<td>Blockade of co-stimulatory interaction of T and B lymphocytes</td>
<td>Phase III</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>Humanized anti-IL6 receptor monoclonal antibody</td>
<td>SLE patients with mild-to-moderate disease activity.</td>
<td>Inhibition of membrane bound and soluble IL-6 receptor</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>Sifalimumab</strong></td>
<td>Humanized anti-IFNα monoclonal antibody</td>
<td>Moderately active SLE. Moderate to severe non-renal SLE</td>
<td>Inhibition of type I IFN signature</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Rontalizumab</strong></td>
<td>A recombinant humanized monoclonal antibody to IFN-α</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reviewer 2 comments:

Minor essential revisions

This is a nice review of biologicals in SLE however some details about the BAFF/Blys and APRIL molecules and the role of dimerization of these molecules in that system might give the reader insight into just how complex the system is.

Also data now exists suggesting the absence of TACI may be linked to poor immune responses in newborns to polysaccharides, some comment on potential mechanisms of adverse effects on host immunity should be considered.

In addition, the atacicept experience in lupus nephritis has been published and should be cited Ginzler et al. Arthritis Res Ther. 2012 Feb 7;14(1):R33. doi: 10.1186/ar3738.

BAFF/BLys is expressed by several cells including dendritic cells, monocytes, activated neutrophils and T cells. It is vital in facilitating the maturation and survival of B cells via signalling through the BAFF-R, BCMA and TACI receptors with high, intermediate and low affinity respectively. APRIL, a BAFF homologue proliferation-inducing ligand binds with higher affinity to the TACI receptor than BAFF [19]. Dimerisation of BAFF and APRIL to the BCMA receptor is required to support the maturation of plasma cells [Schneider P J Exp Med 1999, 189(11):1747-1756]. A strong interaction of BAFF to the BAFF-R propagates the maturation and survival of naive B cells and the interaction of BAFF/Blys, APRIL and TACI to
the TACI-R facilitates immunoglobulin gene class switching in the germinal centre [Schneider 

In the presence of an excess amount of BAFF/BLys, low-affinity self-reactive B cells may survive and 
mature into self-reactive auto-antibody secreting plasma cells implicated in autoimmune disease 
pathogenesis. As a result, it has been deduced that the inhibition of BAFF/BLys by belimumab has 
therapeutic implications in SLE.

The increased susceptibility to infection after belimumab treatment may be as a 
consequence of alterations in the signalling pathways involving BAFF/BLys and the TACI 
receptor. The TACI molecule has a complex role in host immunity involving activation of B 
cells and T cell independent immune regulation, however this is yet to be completely 

In light of this, it has been postulated that the post-belimumab low BAFF/BLys levels result 
in a reduction in TACI signalling and hamper the host immune defences against pathogens 
such as polysaccharide encapsulated bacteria. Patients treated with belimumab have an 
increased susceptibility to infection, the commonest being pharyngitis, bronchitis, cystitis 
and viral gastroenteritis [Navarra SV *Lancet* 2011, 377(9767):721-731]. In the clinical trials 
serious infections have been reported in 6% of belimumab treated patients as compared to 
5.2% in placebo controls but there have been no reports to date of PML in belimumab 
treated patients [Dennis GJ *Clin Pharmacol Ther* 2012, 91(1):143-149].

The prematurely terminated randomized, double-blind, placebo-controlled Phase II/III, 52 
week study APRIL-LN reported adverse events in the patients randomized to atacicept (n=4). 
Patients developed significant IgG hypogammaglobulinemia below the protocol-defined 
criteria for discontinuation (n=3) and serious infections including, haemophilus influenza
pneumonia, legionella pneumophilia pneumonia and bacillus bacteremia. Interestingly, atacicept trials in rheumatoid arthritis have not yielded this severity of adverse events [Genovese MC Arthritis Rheum 2011, 63(7):1793-1803]. This implies that the immunopathogenesis of lupus nephritis may have influenced the results of this atacicept trial.