Recent therapeutic advances in the treatment of systemic lupus erythematosus

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William Stohl received a BS from the Massachusetts Institute of Technology in 1973, a MD from the University of Pennsylvania in 1977 and a PhD from the University of Pennsylvania in 1979. After completing his internship and residency in internal medicine, he joined the laboratory of the late Henry Kunkel at the Rockefeller University in 1982. It was there that Dr Stohl began his investigative career focused on B cells, with an emphasis on their dysfunction in systemic lupus erythematosus (SLE). In 1986, Dr Stohl joined the faculty in the Division of Rheumatology (Department of Medicine, University of Southern California, Los Angeles, CA, USA) where he has remained throughout his professional career, rising to the Chief of the Division in 2007. For the past 11 years, the major focus of Dr Stohl's investigations has been B lymphocyte stimulator (BLyS, also known as BAFF), its role in SLE pathogenesis and its therapeutic neutralization. Dr Stohl maintains an active laboratory that studies BLyS in SLE mice and runs an active clinical trials program which tests B cell-directed agents (including belimumab) in patients with SLE and related conditions.

■ **How did your education/training lead to your interest in rheumatology & more specifically systemic lupus erythematosus?**

I was first fascinated by life sciences in general during my time at college, and it was in medical school where I specifically took an interest in immunology. Here, I learned about disorders in which the immune system became dysregulated, not only protecting cells from the outside unsterile world but also attacking 'self' cells.

■ **In your opinion, what has been the greatest advance in basic/clinical research in systemic lupus erythematosus over the last year?**

I do not think it is necessarily fair to narrow the timeframe for a disorder as complex and heterogeneous as systemic lupus erythematosus (SLE) to the last year. Looking back further – over the last decade or so – the advent of the biologics has been a major breakthrough. They were first applied to rheumatoid arthritis, and with their efficacy in this setting, other autoimmune diseases, such as SLE became reasonable targets. There is great interest in attempting to understand the actual biological pathways involved in SLE, in order to identify candidate targets. I am especially interested in B cells and especially their immunology, function and role in the pathological state of SLE. Therefore, therapies that address B cells and B-cell functions are very exciting to me, although I think the jury is still out in terms of how effective B-cell agents will be.

If I could answer your original question more globally, I think what is important in SLE is that many investigators from many backgrounds are beginning to actually study SLE pathways on a molecular and cellular basis, and we are beginning to identify candidate therapeutic targets. I am reasonably confident that as time goes on we will be getting better and better in terms of identifying and targeting specific pathways or molecules which are important in disease, thereby maximizing the efficacy and minimizing toxicity of future treatments.

■ **Over the last decade, numerous clinical trials examining the efficacy of B-cell modulation in SLE have ended with unfavorable results? What do you feel were the main reasons for this?**

One of the major problems is the labeling of SLE as a homogeneous disorder. SLE is undoubtedly a collection of various disorders, and it is almost certain that the prominent pathogenetic pathways involved in the onset of SLE in patient A will be less important in patient B, and vice versa. So part of the problem currently facing us is to better identify patients with a high *a priori* likelihood of responding to a specific B-cell agent.

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I think the predominant reasons for some of the unsuccessful trials exploring B cell-targeted therapy are twofold. Firstly, the appropriate patients had not been identified. In hindsight, we can now see that patients who should not have been enrolled led to background noise, making it difficult to demonstrate a meaningful result. Secondly, sometimes the trial design has been such where the odds were stacked against meeting the primary end point. For example, in the rituximab trial for lupus nephritis, patients were treated with high-dose corticosteroids and mycophenolate mofetil. This combination is quite effective, so asking rituximab to improve on the already high degree of efficacy is a near-impossible task and led to the failure of the trial. Trials can be better designed, such as the BLISS trials for belimumab, and newer trials are, in fact, following the lines of the BLISS trials. The likelihood of obtaining positive results in such trials is much greater as a result.

■ **The approval of belimumab by the US FDA was the first time in more than 50 years that a drug specifically for the treatment of SLE has been approved. In terms of a model for the development of the future generation of drugs to treat SLE, what do you feel this approval has taught us?**

The main impact of belimumab's approval is that it has taught us that it is possible to have a SLE drug approved. Many researchers were becoming frustrated and disconsolate having gone over 50 years without any SLE therapies successfully completing clinical trials. The fact that belimumab was successful is an encouraging sign that it can be done. In addition, the SLE responder index [1] that was used in the Phase III belimumab trials is now being used in many ongoing or proposed SLE therapeutic trials. It is a bit of a concoctive index, but the bottom line is that it worked. We had tried many other metrics in the past and they did not yield positive results, so we tried this.

There is an additional positive feature to the belimumab approval. The approval of belimumab has documented that an agent targeting B cells does have a significant therapeutic effect in SLE. How it does so and which subsets are important remain to be determined, but the basic principles of the B-cell therapeutic approach have been shown to yield success.

■ **What were the main findings from the BLISS-52 & BLISS-76 trials?**

Both sets of trials were identical in terms of entry criteria, but BLISS-52 ended in 52 weeks and BLISS-76 continued for an additional 24 weeks. The demographics of the population enrolled in each of the trials, however, differed. BLISS-76 primarily enrolled patients from North America and western Europe, whereas patients enrolled in BLISS-52 were predominantly from Asia, South America and eastern Europe. This provided a broader appreciation of the therapeutic effect of belimumab by testing it in people from different societies and cultures.

The main finding in both BLISS trials is that the study subjects, who were all seropositive and had at least a mild-to-moderate disease activity defined by a SLEDAI score of 6 or greater, had a greater response (defined by the SLE responder index) at 52 weeks if they were treated with belimumab plus standard-of-care medication than if they were treated with placebo plus standard-of-care medication. The difference was not earth shattering but it was significant, and to my detractors who argue that the delta between belimumab and placebo was only 10–15%, I would argue that if you are one of those 10–15% of patients, it makes a lot of difference. The challenge is now to better identify who will or will not respond to belimumab in order to better focus our therapy to individuals who have a greater chance of response.

■ **What progress in the treatment of SLE do you envisage in the next 5 years?**

The challenges we will face in the next 5 years are the same as the challenges that we face today. We have therapies that can be very effective but are incredibly toxic. Physicians walk a fine line between on the one hand increasing control and, hence, increasing toxicity, and on the other hand decreasing toxicity and, hence, decreasing disease control. Finding agents that might be more specific to an individual's pathway and targeting specific cells that play a pathogenic role to avoid any significant 'collateral' damage remains the challenge. Belimumab has given us a step in right direction, but we have many more steps to take. There are plenty of individuals that do not respond in a meaningful way to belimumab. Moreover, many sets of patients were excluded from clinical trials, so we have no real idea if belimumab has an effect in these populations. Therefore, we must continue to find therapies for such individuals, for example those with active renal disease.

■ **What are the future directions of your research?**

My scientific training is in immunology, especially as it is related to SLE. B cells have been my focus for the last 30 years, which continues to be the

case. I have no doubt that targeting a single pathway is not going to be the therapeutic answer to all of SLE. There may be a few patients in whom one pathway is so predominant that targeting it will have a significant therapeutic effect, but what we will have to do for the majority of SLE patients is find a combination of therapies that will target multiples arms of the immune systems, including B cells, T cells and the innate immune system.

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Reference

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