Clinical trials in lupus: what have we learned so far?

Understanding the gap between reality and expectation

Despite the advances in understanding the aetiology and pathogenesis of SLE, a sobering fact is that no new drug has yet been licensed for its treatment. This is interesting when set against the backdrop of promising open-label experience with rituximab in particular [1]. The apparent gap between expectation and reality raises questions about the true efficacy of these drugs, and whether trial design, outcomes measured or the choice of co-therapies have clouded the issue, running the risk that effective drugs may be inappropriately discarded. For the patient and physician, this gap translates into a longer wait for approved drugs to become available. So far, clinical trials have highlighted many observations and lessons that might help inform their future planning and execution.

It goes without saying that patients should have active SLE as a prerequisite for entry into a trial. Certain clinical features such as tender joints and long-standing rashes can, however, reflect damage or comorbidities. The recently published Phase II belimumab trial included only 72% of patients with a positive ANA or double-stranded DNA antibody at entry, raising the possibility that some chronic features may have been misinterpreted as active inflammation [2]. In both the Aspreva Lupus Management Study (ALMS) and the Rituximab in patients with Severe Systemic Lupus Erythematosus (EXPLORER) trials, secondary analyses of Hispanic and African ancestry patients showed a statistically significant response to mycophenolate mofetil (MMF) and rituximab, respectively [3, 4]. This observation may be explained by genetic differences in these populations, but may also reflect the more active unstable disease that these patients often experience. In the EXPLORER trial, larger numbers of patients who were not white and received placebo did less well, suggesting the latter possibility.

Another possibility is that only specific organ systems or biological subgroups will respond to a particular agent. Secondary analysis of the abatacept trial found that patients with arthritis showed a statistically significant response to the drug [5]. Similarly, in an exploratory analysis of the Phase II trial, belimumab showed a significant signal in patients who were seropositive, which may reflect a more appropriate population for this treatment, i.e. patients who are more likely to have ongoing B-cell activity [2]. Other agents may only be useful for other particular subgroups of disease, e.g. patients with an IFN signature might be good candidates for IFN-α antagonists or patients with high B lymphocyte stimulator (BLYS) levels might be the best candidates for BLYS antagonism. Smaller targeted early-phase trials, with comprehensive biological assessment of responders and non-responders could be valuable for more rational later-phase trial designs.

The use of concomitant medications is also important. Clinical and ethical dilemmas exist about the standard of care therapy used in the placebo group and the degree of and variability in background medications that can be tolerated in a trial setting. In the Rituximab in Class III/IV Lupus Nephritis (LUNAR) trial, patients with lupus nephritis were treated with MMF 3 g daily plus rituximab or a placebo [6]. The comparator arm is, therefore, actively managed and may have a higher than anticipated response rate that reduces the power of the study to detect a difference between groups.

In addition, concomitant steroids are frequently given in a boost and taper manner. In the ALMS trial (MMF vs cyclophosphamide in lupus nephritis), over the 6 months of the trial, the mean dose of steroid used was 25 mg/day [3]. In the EXPLORER trial, patients were started on high-dose steroids and were also given intravenous steroids with every rituximab or placebo infusion at baseline and 6 months [4]; therefore, both the treatment and placebo groups had large mean decreases in global BILAG disease activity scores during the period of steroid therapy, which did not increase again during the trial in the placebo group indicating a sustained response. The recent positive Phase III trial with belimumab, with 865 enrolled patients, showed the potential trial size needed to observe a statistically significant treatment effect [7]. Clearly from the high rate of placebo group responses, some signal-to-noise ratio remains in this trial design. A specific comparison of final background treatments used in these various studies might be enlightening for understanding trial design.

Another difficulty is determining the most clinically relevant outcome. The original National Institutes of Health trials on lupus nephritis showed that short-term outcomes measured over 6–12 months may not be the most clinically important [8]. Long-term outcomes such as chronic renal impairment or damage accrual may ultimately be of most importance. We, therefore, need to consider how to design, power and fund long-term trials or whether validated surrogate markers for long-term outcomes can be identified and used.

A final area to consider is the sensitivity and precision of instruments used to assess disease outcome. Since common primary outcomes used include flare rate or time to flare, both sensitivity and clinical relevance of the outcome measurement are important. Many patients have low-grade grumbling disease, which fluctuates from month to month. When an outcome measurement is defined as highly sensitive, minor fluctuations can score...
as a flare and increase the signal-to-noise ratio. Training is needed for disease activity instruments such as the SLEDAI 2000 and BILAG 2004 [9, 10]. These scoring systems reflect interpretation of primary data and in many clinical trials, the actual primary data such as tender and swollen joint counts and precise skin area involved have not been collected.

SLEDAI 2000 requires complete resolution of a clinical or laboratory item before it no longer scores. Therefore, for example, a patient who has a major but incomplete reduction in joint counts after exposure to a drug will not change their arthritis score (4 points) [9]. On the other hand, BILAG 2004 is a relative instrument that compares disease activity in the past 28 days with the previous 28 days [10]. This lack of a measured anchor point means that certain scores (in particular, BILAG B scores) may encompass a wide variation in underlying disease activity. Recently, studies have used a combination of an accepted disease activity instrument along with specific joint scores to allow a more homogeneous entry population [11]. In addition, secondary analysis of the Phase II belimumab trial developed a composite end-point, which has been subsequently used with success in a Phase III trial [7, 12]. A similar composite end-point developed for a Phase II epratuzumab trial based on the BILAG score has also been used in an exploratory, dose-finding trial, and according to a company press release, it has detected a treatment signal in preliminary data analysis [13]. These composite scores have not, however, been independently validated or shown to be reliable or sensitive to change.

In conclusion, several recent SLE clinical trials have not achieved their primary outcome. Exploratory analysis has, however, suggested novel end-points, which might be beginning to succeed in further trials. Subgroup analyses have underscored the heterogeneity of the disease relating to genetic background, organ subgroups and biological subsets. Continuation or simultaneous initiation of a new immunosuppressive along with the investigational product may also limit the power to detect a difference between groups, as will permitting doses of steroids that are too high and given for too long a period within the trial. We need to improve the ability to collect primary data and the precision of the instruments used for assessment so that outcomes used become more robust.

Finally, some of the most important clinical outcomes such as damage prevention and steroid-sparing will only be appreciated in the long term and for which a 3- to 5-year window may be more relevant [14]. Despite these difficulties, we are optimistic and feel that by applying the lessons learned from the trials to date, we will be able to develop a broad and evidence-based armamentarium to treat this challenging condition.

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Ian N. Bruce1,2, Caroline Gordon3, Joan T. Merrill4 and David Isenberg5

1ARC Epidemiology Unit, School of Translational Medicine, Manchester Academic Health Sciences Centre, University of Manchester, 2Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, Manchester, 3Rheumatology Research Group, University of Birmingham, Birmingham, UK, 4Clinical Pharmacology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA and 5Centre for Rheumatology, Department of Medicine, University College, London, UK

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Correspondence to: Ian N. Bruce, arc Epidemiology Unit, School of Translational Medicine, University of Manchester, Manchester M13 9PT, UK. E-mail: ian.bruce@manchester.ac.uk

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