GLOMERULAR DISEASE

Lupus nephritis trials end in disappointment

Two potential new treatments for lupus nephritis have failed to meet their efficacy end points in phase III clinical trials. Development of rituximab for induction therapy of lupus nephritis and abetimus sodium for maintenance therapy of the condition looks set to be abandoned after negative results from the LUNAR and ASPEN trials.

Current treatment of lupus nephritis typically comprises corticosteroids in combination with cyclophosphamide, azathioprine or mycophenolate mofetil; however, such regimens have limited efficacy and a range of toxic effects, including serious infections, metabolic disturbances, malignancy and infertility. None of the currently used second-line agents are licensed specifically for lupus nephritis; in fact, no new drug has been launched to treat the condition for more than 30 years. Improved, better-targeted therapies are desperately needed.

Currently approved in the US to treat rheumatoid arthritis and non-Hodgkin lymphoma, rituximab is a chimeric monoclonal antibody that selectively targets CD20-expressing B cells. Abetimus comprises four double-stranded oligodeoxyribonucleotides attached to polyethylene glycol, and is designed to induce tolerance to pathogenic, anti-double-stranded-DNA autoantibodies by crosslinking these antibodies both in the circulation and on the surface of autoreactive B cells.

The LUNAR trial tested rituximab in 144 patients in the US, Canada, Mexico, Argentina and Brazil who had class III or IV lupus nephritis—as determined by a renal biopsy within the previous 12 months—and proteinuria. Patients received two infusions of either rituximab or placebo every 6 months, in addition to corticosteroids and mycophenolate. Analysis revealed that rituximab did not notably improve the likelihood of achieving a renal response (defined as improvement in renal function, urinary sediment and proteinuria) at 52 weeks.

The goal of ASPEN was to determine whether intravenous infusion of abetimus at a dose of either 300 mg or 900 mg per week for 52 weeks would delay renal flare compared with placebo. The investigators enrolled 943 patients with systemic lupus erythematosus and a history of renal disease from 203 centers in North and South America, Europe, Asia and Australia; however, they stopped the trial when an interim efficacy analysis indicated that continuation would be futile.

Several features of LUNAR hinder interpretation of the findings. Investigator Mary Anne Dooley acknowledges that the steroid pulse regimen used in the trial differed from that employed in other studies. Furthermore, variation in the duration of disease activity among participants before randomization "may have diluted potentially favorable results" according to Heather Reich, a nephrologist and clinician–scientist at the University Health Network in Toronto. Of note, some of the uncontrolled case series that paved the way for LUNAR used rituximab in combination with agents other than mycophenolate.

Hopes for anti-B-cell therapy in lupus nephritis had earlier suffered a setback when investigators terminated a phase II/III, placebo-controlled, safety and efficacy trial of atacicept, corticosteroids and mycophenolate in 200 patients in October 2008 on the grounds that the regimen was associated with an increased risk of severe infection. Atacicept is a soluble receptor that binds to BLyS and APRIL, two B-cell-stimulating cytokines from the tumor necrosis factor superfamily.

The failures of rituximab and abetimus come as a bitter blow to researchers and patients, having occurred during a period of unprecedented research activity in lupus nephritis. For many decades, clinical trials in this field were hamstrung by a limited understanding of the disease, a lack of financial incentive for drugmakers, the need for long follow-up periods, and ethical constraints that preclude sole use of placebo as a comparator in active disease.

"It is still possible that there is a future for B-cell-depleting therapy in lupus," says Reich. Recruitment is underway for the phase III BELONG trial, which will evaluate two doses of the humanized anti-CD20 antibody ocrelizumab in combination with steroids, cyclophosphamide and mycophenolate. The investigators plan to enroll 369 patients with class III or IV lupus nephritis and assess rates of complete and partial response after 6 months of therapy. Completion is expected in January 2013.

Other approaches could also prove fruitful. Researchers in Austria, Germany and The Netherlands are currently recruiting patients with class V lupus nephritis for a phase II/III trial of the chimeric antitumor necrosis factor antibody infliximab. They hope to show that the addition of four 5 mg/kg infusions of infliximab to azathioprine treatment hastens the reduction of proteinuria to ≤1.5 g per day.

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Original articles Genentech. *Phase III study of Rituxan in lupus nephritis did not meet primary end point* [online], http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=11947 (2009).
Biomarin. *Results of first interim efficacy analysis for Riquent Phase III ASPEN trial: continuation of the trial is futile* [online], http://phx.corporate-ir.net/phoenix.zhtml?c=106657&p=irol-newsArticle&ID=1255856&highlight (2009).