Encouraging data on rituximab in polymyalgia rheumatica

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Polymyalgia rheumatica was officially recognised as a distinct clinical entity six decades ago, as acknowledged in an editorial published in *The Lancet* in March, 1961.[1] At that time, the effectiveness of glucocorticoids in treatment of the disease was already noted, initially at doses of 30–40 mg prednisone per day and later at the currently recommended starting dose of 15 mg per day. Glucocorticoids are still the mainstay of treatment in patients with polymyalgia rheumatica; however, there is an unmet need for treatment alternatives, as approximately 50% of patients will relapse, and many patients have clinically significant glucocorticoid-related complications, such as increased body weight, hypertension, bone fractures, development of diabetes, and cataract.[2]

Over the past three decades, treatment options and outcomes have greatly improved for patients with rheumatoid arthritis and spondyloarthritis. This improvement is in sharp contrast to the situation for patients with polymyalgia rheumatica, despite it being the most frequent inflammatory musculoskeletal disease in adults aged 50 years or older. The conventional synthetic disease-modifying antirheumatic drug (DMARD) methotrexate can be used in patients with relapsing polymyalgia rheumatica or in patients at risk of developing side-effects of glucocorticoids,[3] but this is based on studies showing low to moderate efficacy of methotrexate as a glucocorticoid-sparing agent in these patients. The effectiveness of leflunomide has so far only been documented in case series.

Regarding the use of biological DMARDs in patients with polymyalgia rheumatica, studies on tumour necrosis factor blockers yielded negative results,[3] whereas data from two open-label, phase 2 clinical trials[4,5] suggested that the interleukin (IL)-6 receptor inhibitor tocilizumab is potentially effective in newly diagnosed patients. In addition, a randomised, double-blind, placebo-controlled, phase 3 study evaluating safety and efficacy of tocilizumab in patients with polymyalgia rheumatica on chronic glucocorticoid treatment (SEMAPHORE study; NCT02908217) was recently completed, and the results are eagerly awaited.

In *The Lancet Rheumatology*, Diane Marsman and colleagues[6] report the first data on the effect of rituximab, a biological B-cell depleting agent, in patients with polymyalgia rheumatica. The BRIDGE-PMR study was a 21-week double-blind, placebo-controlled exploratory study of 47 patients with newly diagnosed polymyalgia rheumatica (n=38) or with relapsing disease on 7·5 mg per day or more of prednisolone (n=9). Patients were randomly assigned (1:1) to intravenous rituximab (1×1000 mg infusion) or placebo in addition to 50 mg methylprednisolone, followed by a 17-week prednisolone taper to 0 mg. The primary outcome (glucocorticoid-free remission at week 21) was reached in 11 (48%) of 23 patients in the rituximab group compared with five (21%) of 24 patients in the placebo group; the difference of 27% (one-sided 95% CI 4; relative risk 2·3 [1·1]) was at the border of significance (p=0·049).

Several secondary outcomes also favoured the use of rituximab, such as the proportion of patients on a dose of glucocorticoid of 5 mg per day or less (23 [100%] of 23 in the rituximab group *vs* 13 [54%] of 24 in the placebo group; absolute difference 46% [one-sided 95% CI 20]; relative risk 1·8 [1·3]; p=0·0012), and clinical activity defined by the change from baseline in polymyalgia rheumatica activity score (mean change in score of –13·8 [SD 2·9] for rituximab *vs* –3·8 [3·6] for placebo; absolute difference –10·0 [one-sided 95% CI –2·2], p=0·018). Other secondary endpoints, such as cumulative glucocorticoid dose and the percentage of patients who relapsed during follow-up did not show significant differences between the groups. Thus this short-term, exploratory study showed some modest signals of clinical efficacy for rituximab.

The main strength of the study is the novelty of B cells as the chosen target of intervention, which was based on evidence for B-cell involvement in polymyalgia rheumatica.[7,8] Nevertheless, the results of the study should be interpreted cautiously due to the small sample size (which is common in phase 2 trials) and because of the short duration of the study, including the evaluation of the primary endpoint at only 4 weeks after completion of the prednisolone taper.

Why would B-cell depletion therapy work in patients with polymyalgia rheumatica? The rationale for using rituximab is based on studies showing that the distribution of B cells is altered in patients with

active disease, and that B cells constitute a dynamic cell population in these patients. B cells migrate from the peripheral blood to peripheral tissues using chemotactic pathways, particularly the C-X-C motif chemokine ligand 9 (CXCL9)-CXCR3 and CXCL13-CXCR5 pathways.[7] Whereas B cells are found to various degrees in the inflamed vascular wall in the related disease giant cell arteritis, immunohistochemical analysis of arthroscopic biopsies of shoulder synovium obtained from 12 patients with untreated polymyalgia rheumatica and seven patients with treated disease revealed no B-cell infiltration,[8] suggesting an alternative site of B-cell migration, such as the lymph nodes. So far no disease-specific autoantibodies have been found in patients with polymyalgia rheumatica, suggesting an antibody-independent role of B cells, possibly related to production of cytokines. Indeed, the number of IL-6-producing B cells is increased in patients with polymyalgia rheumatica, and these cells appear to leave the circulation during active disease.[8] Moreover, B-cell lymphopenia and abnormal B-cell subset distribution have been associated with disease activity and plasma IL-6 concentrations in patients with polymyalgia rheumatica, and both are normalised by treatment with tocilizumab.[9,10] The study by Marsman and colleagues[6] further suggests that B cells might have an important role in the immune pathology of polymyalgia rheumatica. Comprehensive analysis of B cells in polymyalgia rheumatica, including histopathological investigation of a larger number of synovium biopsies from patients with newly diagnosed and rituximab-treated disease, is warranted.

The results of the BRIDGE-PMR study are encouraging. The study reached its primary endpoint—ie, more patients were in glucocorticoid-free remission in the rituximab group than in the placebo group at week 21. However, a longer-term, phase 3, randomised controlled trial is needed to further substantiate the results of the present study and to inform on the long-term efficacy and safety of rituximab in patients with polymyalgia rheumatica. If these findings are confirmed, rituximab treatment would clearly add to the small therapeutic arsenal available for these patients.

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Tapering and withdrawal in patients with rheumatoid arthritis in stable remission

Some patients with rheumatoid arthritis can now achieve a stable state of low disease activity, or remission, because of advances in treatment. Therefore, an important question for patients and rheumatologists, with implications for both patient safety and health-care costs, is whether treatment can be reduced or even discontinued.

Koray Tascilar and colleagues[1] report the findings from the Rheumatoid Arthritis in Ongoing Remission (RETRO) study. This was a prospective, multicentre,

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