RHEUMATOLOGY

Editorial

Rituximab in myositis

Hopeful signs in refractory disease

This editorial refers to Rituximab treatment in patients with refractory inflammatory myopathies, by Eilen A. M. Mahler et al., doi:10.1093/rheumatology/ker088, on pages 2206–2213.

The idiopathic inflammatory myopathies (IIMs) are a group of acquired, heterogeneous, systemic CTDs that primarily target skeletal muscles. The diseases include PM and DM. Treating myositis is difficult, and the rarity and heterogeneity of these syndromes and lack of controlled trials add further complexity. A well-documented refractory PM or DM subset has always been a particular therapeutic challenge. The paper by Mahler et al. [1] in this issue of Rheumatology sheds light on the efficacy of rituximab in refractory myositis patients in a cohort of 13 patients.

Mahler et al. [1] prospectively followed 13 IIM patients—refractory to conventional immunosuppression—treated with rituximab. This uncontrolled study reported significant improvement with rituximab in refractory myositis patients in the primary outcome of muscle enzyme [creatine kinase (CK)] and muscle strength tested by hand-held dynamometer, but only a non-significant improvement in manual muscle testing (MMT). All 13 Caucasian PM (n = 5) and DM (n = 8) patients (54% female, mean age 44 years), fulfilled Bohan and Peter criteria for IIM and showed typical histological characteristics. Patients had failed a median of three immunosuppressive agents (including MTX in 76.9% and AZA in 61.5%) and were refractory to corticosteroids. Median CK level for all patients was significantly reduced compared with baseline at every time point from 6 weeks of follow-up, with most patients reaching normal CK levels. Median muscle strength measured with MMT increased 6.1% as compared with baseline (P = 0.06) after 18 months and 7.0% after 24 months, although it did not reach statistical significance. Muscle strength measured with hand-held dynamometry showed significant improvement of 21.5% compared with baseline. Median corticosteroid dose was significantly reduced (15 to 7 mg after 25 months).

Furthermore, several secondary outcomes improved, such as ESR and CRP, patient’s global assessment of health, physician’s global assessment of disease activity, health assessment questionnaire-disability index (HAQ-DI) and the physical and mental component scales of short form-36 (SF-36). Patient’s global assessment of pain did not improve, however.

The Mahler et al. [1] study is definitely valuable and interesting and it adds to our knowledge about the efficacy and safety of rituximab in refractory myositis patients. The strengths of this study are the prospective cohort design, refractory severe active myositis patients and long-term follow-up. All 13 patients were truly refractory, having failed multiple immunosuppressive agents. The median disease duration was 4 years, with baseline CK levels of 949 U/l and MMT (0–70) of 57.5, which suggest chronic active severe disease. All patients had long-term follow-up [median 27 months (18.5–33.0 months)] and none was lost to follow-up. This study by Mahler et al. [1] is one of the largest uncontrolled studies evaluating the efficacy of rituximab in refractory myositis patients to date.

A further strength of the study is that there appears to be no bias from additional or increased doses of concomitant immunosuppressive therapy during the study period, except in two patients. It also measured four out of six International Myositis Assessment and Clinical Studies (IMACS) core set measures (muscle enzyme, MMT, physician global assessment of disease activity and HAQ-DI) and defined response as at least two out of four core set measures improving by >20% without worsening of more than one core set measure by >25% (and worsening core measure not MMT) [2]. The study results showed significant clinical response from rituximab as 69.2% after 3 months, 46.2% after 6 months and 41.7% after 12 months. The authors also report efficacy in several secondary outcomes and show safety of rituximab over 2 years.

In spite of the above-mentioned strengths, the study has a few critical limitations, of which the uncontrolled nature of the study and the small number of patients are the biggest. The efficacy of rituximab as suggested by this study needs to be demonstrated by a large randomized controlled trial before it can gain clinical acceptance. However, due to the rarity of the disease, it is very difficult to do large controlled studies, and most studies to date on myositis involve single centres reporting longitudinal data on small cohorts of refractory patients observed for short periods of time. One large National Institutes of Health (NIH)-sponsored multicentre, randomized controlled placebo phased clinical trial evaluating the efficacy of rituximab in idiopathic inflammatory myositis (RIM trial) was completed recently. The results of the RIM trial have been reported in abstract form, and although the trial failed to reach primary or secondary end-points, >80% patients improved on rituximab. Full publication of the results is awaited.

Apart from the major weakness described above, the present study failed to show significant improvement...
in MMT, which is a core end-point of IMACS for studies on myositis. However, the authors showed significant improvement in another objective measure of muscle strength, i.e. hand-held dynamometer. Three patients received increased doses of corticosteroids 3 months prior to rituximab that led to normalization of CK, which might have influenced results in these three patients. However, the authors showed similar primary and secondary outcomes even after excluding these three patients. Extra-muscular disease activity (including cutaneous in DM) and efficacy were not measured, although these could have been important secondary observations. Patients in the present study were refractory to multiple therapies, but these therapies included anti-TNF agents, which have now been proved not to be efficacious in IIM patients. Thus, excluding anti-TNF agents most patients had failed one to two previous therapies.

The present study supports previously published case series of the efficacy of rituximab in myositis. A single open-label prospective study of rituximab in four patients with PM who were refractory to multiple therapies including IVIG, showed complete or partial remission in all patients [4]. Even the most refractory of myositis subsets, i.e. anti-SRP antibody-positive necrotizing myopathy patients who had severe muscle weakness and high CK levels, unresponsive to many agents, showed a robust clinical response to B-cell depletion therapy in ~70% of the patients [5–8]. The results of rituximab in DM are mixed: an uncontrolled trial of eight patients failed to show a response to rituximab for recalcitrant skin disease and only partial improvement in muscle [9], whereas another uncontrolled trial of seven patients suggested improvement of both muscle and skin disease in DM [10]. Further larger controlled studies like the recently completed RIM trial are needed to provide further evidence on the efficacy of rituximab in refractory myositis.

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References


3 Oddis CV, Reed AM, Aggarwal R. Rituximab in the treatment of refractory adult and juvenile dermatomyositis (DM) and adult polymyositis (PM) – the RIM study. Arthritis Res 2010;62(Suppl. 12):S384.


