while continuing belimumab and tapering prednisolone to zero.

These cases illustrate the potential added value of belimumab after rituximab treatment in active LN. It should be noted that both patients continue to have low disease activity while on belimumab monotherapy. To our knowledge, this is the first report of LN patients treated with two consecutive B cell targeted treatments. In both patients, belimumab halted the full repopulation of circulating B cells after rituximab. From a pathophysiological point of view, it is well appreciated that autoantibody-positive disease is found specifically in LN and that B cell hyperactivity is a landmark in SLE [5]. It is tempting to speculate that the clinical improvement of these patients is due to a synergic effect of rituximab and belimumab.

Previously, two randomized trials (BLISS-52 AND BLISS-76) showed beneficial effects of belimumab in reducing concomitant immunosuppression in autoantibody-positive SLE without major organ involvement and without previous rituximab treatment. Recently one patient with active LN was reported to have a beneficial response to belimumab, albeit in conjunction with pulse steroids [6]. Currently we await the results of a randomized trial assessing belimumab’s efficacy in LN (NCT01639339). This report describes belimumab as rescue treatment in refractory LN due to commonly seen gastrointestinal intolerance to MMF [7]. The present report encourages further research into the clinical yield of combining B cell targeted treatment in the difficult population of SLE patients with major organ involvement or refractory disease.

Rheumatology key message

• This report illustrates the potential added value of combining B cell targeted treatment in SLE patients with major organ involvement or refractory disease.

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Anti-belimumab antibodies in paediatric rheumatology patients: a pilot experience

Sir, It has been reported that immunogenicity of anti-TNF agents is involved in treatment failure [1]. Despite its humanized structure, adalimumab may induce the formation of antidrug antibodies (ADAbs), although the percentage of positive cases, ~40%, depends on the assay used in its determination [2]. Experience in the paediatric population is poor [3].

Measurements of serum adalimumab levels and ADAbs from 25 children were available in our unit in March 2013. They received 0.8 mg/kg (s.d. 0.3, range 0.3–1.5) every 12 days (s.d. 3, range 7–14). The objective was to explore the relationship between the presence of ADAbs, the activity of the disease and therapeutic decisions through a cross-sectional retrospective study.

Adalimumab levels in serum were determined by capture ELISA, with >5 ng/ml being considered positive. ADAbs by two-site bridging ELISA, being considered positive at >10 arbitrary units (AU)/ml. Assays were similar to those described by our group to determine infliximab and anti-infliximab antibody values [4]. Samples were obtained within 24 h before drug administration. Since conventional analytical tests are not useful for determining the activity of uveitis, it was assessed by the physician visual analogue scale (VAS), with values ranging from

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TABLE 1 Characteristics of 25 children treated with adalimumab

<table>
<thead>
<tr>
<th>ADAbs</th>
<th>Girls</th>
<th>JIA</th>
<th>ANA positive</th>
<th>Uveitis</th>
<th>Active uveitis*</th>
<th>Active arthritis</th>
<th>MTX</th>
<th>Drug switching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (n = 8)</td>
<td>6 (75)</td>
<td>4 (50)</td>
<td>4 (50)</td>
<td>8 (100)</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>2 (25)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Absent (n = 17)</td>
<td>13 (77)</td>
<td>15 (88)</td>
<td>6 (35)</td>
<td>13 (77)</td>
<td>3 (18)</td>
<td>5 (29)</td>
<td>6 (35)</td>
<td>4 (24)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%). *P = 0.01. ADAbs: antidrug antibodies.

0 (total lack of activity) to 10 (maximum level of activity). It was obtained the same day as the blood sample was taken.

Statistical analysis was carried out using SPSS version 11.0 (SPSS, Chicago, IL, USA). Frequency data were compared by Fisher’s exact test. Differences in quantitative variables between groups were calculated with the Mann–Wilcoxon U test. Duration of treatment was analysed by the Kaplan–Meier method and all P-values <0.05 were considered significant.

Table 1 shows the characteristics of the patients (19 girls and 6 boys). They had been diagnosed with JIA with or without uveitis in 19 cases, idiopathic uveitis in 5 cases and Blau syndrome in 1 case. Their ages were 11.9 years (s.d. 4, range 6.9–18.6). Disease duration was 7.3 years (s.d. 4, range 2–16) and treatment duration was 1.7 years (s.d. 0.7, range 0.5–2.5). Seventeen cases (60%) presented some activity of the disease (arthritis, uveitis or both), with a physician VAS of 1.7 (s.d. 0.9, range 1–4). Eight children (32%) had detectable ADAbs, with levels from 12 to 30,000 AU/ml, and an absence of serum adalimumab. All cases with positive ADAbs showed active disease, except one who had received a periocular corticosteroid injection the previous month. However, 8 of 17 patients without ADAbs also had active disease. The only adverse effect was an urticarial rash that appeared at 6 months of therapy, coinciding with the highest value of ADAbs in this series, 30,000 AU/ml.

The results showed that the presence of ADAbs is related to a higher frequency of active uveitis (P = 0.01), as can be seen in Table 1. Furthermore, in patients with inactive disease, free serum adalimumab levels tended to be higher but not significant (P = 0.06).

Adalimumab was switched to another drug in eight children with active disease, four with positive ADAbs and four with negative ADAbs. The rest of the ADAb-positive patients continued treatment after decreasing the dosing interval from 14 to 7 days, thus ADAbs disappeared and the disease became inactive. In contrast, in the cases with active disease and negative ADAbs, treatment with steroid eye drops was intensified and/or IA corticosteroid injections were performed. Our impression was that the drug did not completely control the activity, but was a support. Concomitant administration of MTX has shown its utility in decreasing adalimumab antibody production [5]. However, at the time of data collection, only eight patients were receiving the drug, as Table 1 shows.

Despite the limitations of this study, its results are similar to those already published regarding immunogenicity in adult patients [6]. ADAbs may explain half of the cases of active disease and their presence is associated with treatment discontinuation. Uveitis is a complication that leads to blindness in certain patients. Weekly administration in the most severe cases appears to help in controlling eye inflammation, despite higher cost. This is balanced by spacing injections (every 2 or 3 weeks) in patients with inactive disease.

Finally, ELISA is sensitive to the effect of drug interference, so ADAbs are detected if they exceed the levels of the drug in circulation [7]. For this and for other reasons, some authors consider ELISA inappropriate for therapeutic guidance [8]. RIA also has disadvantages, and attempts to develop new assays for clinical use have not been definitive. In addition, regarding daily practice, there is no agreement on whether it is sufficient to assess only free drug levels (clinically relevant) or if it is more useful to test for ADAbs as well. However, despite these considerations, both determinations by ELISA explained disease activity in particular cases and an adverse effect in one patient and helped us to make therapeutic decisions.

Rheumatology key message

- Anti-adalimumab antibodies correlate with serum adalimumab levels and disease activity in paediatric patients.

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Time to diagnosis of axial spondylarthritis in clinical practice: signs of improving awareness?

Sir, The spectrum of axial spondylarthritis (SpA) ranges from symptoms of mild inflammatory back pain to the diagnosis of AS. This group of diseases affects the vertebrae, sacroiliac joints (SIJs) and their associated entheses with a pathophysiological process ranging from acute inflammation to an exaggerated repair process resulting in excessive new bone formation. This disease has the potential to lead to structural changes, deformity and loss of function. Historically there has been a significant delay in the diagnosis of axial SpA as a result of the lack of awareness of the early stages of the disease, lack of clinical findings on examination, inconsistent imaging findings and overreliance on radiographic changes to make a diagnosis. The most recent and comprehensive study by Feldtkeller et al. [1] reports an average time to diagnosis of 10 years. Such a delay in diagnosis results in prolonged periods of pain and disease activity without a diagnosis, loss of confidence in the ability of the medical system to diagnose and treat the disease and delay in the implementation of therapies that can effectively treat the disease symptomatically and potentially prevent radiographic progression [2, 3].

The lack of diagnostic criteria facilitating the recognition of axial SpA and the poor awareness of the spectrum of disease across primary care has contributed to this well-recognized delay. The Assessment of SpondyloArthritis International Society (ASAS) classification criteria has helped with the recognition of those patients with inflammatory back pain without radiographic changes by highlighting the importance of MRI in detecting early disease and also by recognizing disease without radiographic evidence of sacroiliitis [4].

Within the military, a specific back pain pathway for the aid of primary care doctors and community physiotherapists has been in place since 2009 (Fig. 1). This promotes recognition of inflammatory back pain symptoms and axial SpA and also promotes early referral to Defence Medical Rehabilitation Centre (DMRC) Headley Court, a specialist rheumatology and rehabilitation facility for military personnel. This, in combination with the new diagnostic criteria for axial SpA, has resulted in a faster time to diagnosis of axial SpA compared with the previously published findings of Feldtkeller et al. [1].

A cohort of 138 service personnel with a diagnosis of axial SpA who attended the axial SpA inpatient rehabilitation and education course at DMRC Headley Court from March 2010 to November 2012 were reviewed as part of an assessment of the efficacy of the service in making a prompt and timely diagnosis. Information regarding age, time to diagnosis and radiological findings were retrieved from medical records.

The mean age of patients was 35.2 years, 73.5% were diagnosed with AS, 20.5% with undifferentiated non-radiographic axial SpA and 6% with psoriatic spondylitis. X-ray of the SIJs was used to confirm a diagnosis of AS, MRI scanning of the SIJs or the SIJs and the spine was used in 78% of patients to assist in the diagnosis and assessment of disease.

The mean time to diagnosis for all patients was 5.72 years (range 0.25) from symptom onset, with a mean age of diagnosis of 31.9 years (range 19–49) and a mean age at symptom onset of 25.8 years (range 10–48). The time to diagnosis between the sexes was quite markedly different, with SpA being diagnosed on average 3 years later in women (male 5.56 years, female 8.5 years).

These data highlight a significantly reduced time to diagnosis of axial SpA/AS in this cohort of military axial SpA patients. The mean delay reported was 5.72 years, 4.3 years faster than the previously published landmark study [2].

These data were collected in a military population that is serviced by specialist outpatient clinics and inpatient rehabilitation services for axial SpA. The ASAS criteria have been fully embraced by the clinicians running the clinics and so has the role of MRI in making an early diagnosis and assessing disease activity and predicting prognosis [6, 7]. An important element of this reduced delay in