While MTX and steroids were continued, the patient received two infusions of 1000 mg RTX at a 2-week interval without any side-effects. During the following weeks, the vasculitic lesions started to heal and resolved completely within 5 months (Fig. 1b). In addition, articular symptoms improved with the 28-joint disease activity score (DAS28) decreasing from 5.05 to 2.97 at week 16, when the patient showed complete depletion of her peripheral B cells as determined by minimal residual disease flow cytometry (MRD-FLOW) as defined elsewhere [8]. ESR returned to normal and corticosteroids were slowly tapered.

The second patient is a 61-yr-old white female who was referred to us with severe erosive seropositive RA of 12-yr duration and a history of malignant melanoma. Her present medication consisted of oral prednisolone (10 mg/day), MTX (10 mg/week) and NSAIDs. Etanercept had previously been stopped after 12 months for inefficacy. At initial presentation, the patient had a DAS28 of 7.2 and several vasculitic ulcers of her legs (Fig. 1c). RV was confirmed by histopathology. Her ESR was elevated to 75 mm/h and titres of RF were 3070 kU/l. MTX and steroids were continued and two doses of 1000 mg RTX were given 2 weeks apart and well tolerated without any side-effects. During the subsequent 7 months, the vasculitic lesions of the lower limb resolved completely (Fig. 1d) in addition to the decreased DAS28 of 5.8. By week 16, the patient showed a complete depletion of peripheral B cells as determined by MRD-FACS. Retreatment with RTX was performed at week 24, resulting in a DAS28 of 4.1 after another 16 weeks. Finally, the ESR returned to almost normal (23 mm/h), titres of RF decreased to 256 kU/l and prednisolone was slowly tapered to 5 mg daily.

In patients with long-standing RA, RV may develop as a complication potentially involving skin, eyes or visceral organs. Despite the availability of a wide range of new and potent drugs for the treatment of RA, no evidence-based therapeutic guidelines for the management of RV have been developed and treatment therefore remains largely empirical. Although the successful use of TNF inhibitors in patients with RV has been reported [3], alternative treatment options for patients who are unresponsive or not eligible for TNF blockers are needed. Reports on the use of RTX in RV are rare. Recently, a patient with RV-associated foot drop was successfully treated with RTX [9]. Preliminary data from the French registry also suggests that RTX may represent a therapeutic option in patients suffering from RV [10].

In summary, we reported on two patients with long-standing RA suffering from severe RV-associated cutaneous ulcers who did not respond to conventional DMARD and steroid treatment. The course of these patients indicates the potential efficacy of RTX in improving both RV and articular symptoms as demonstrated by complete healing of ulcers within a few months and a concomitant decrease in DAS28. Although more research and clinical data is required to more fully delineate the role of RTX in patients with extra-articular RA manifestations. RTX may at present represent a suitable therapeutic option in patients who do not respond to TNF inhibitors or in whom TNF blockade is contraindicated.

Rheumatology key message

- Rituximab may represent a therapeutic option in patients with rheumatoid vasculitis.

Disclosure statement: The authors have declared no conflicts of interest.
e.g. walking to school, were impossible. Mouth opening decreased, chewing was severely impaired. Patient’s history did not support previous infections. The boy was on no medication or food supplementation and there were no hints for exposure to toxic agents. Clinical examination showed a significant limitation of motion-range in all joints, including spine and temporo-mandibular joints without definite signs for arthritis. Skin thickening was obvious, affecting mainly distal parts of the extremities and peau d’orange was noted on the thighs.

Laboratory findings were compatible with systemic inflammation, revealing highly elevated ESR (with a maximum of 80 mm/h), CRP (maximum 5.3 mg/dl) and leucocytosis (without steroids up to 10,000/µl) with predominant eosinophilia (with a maximum of 57.5%) (Fig. 1A). Repeatedly ANAs were only slightly positive with a titre of 1:160 both in the immunofluorescence test (IFT) on cryostat sections and cell cultures. Also antibodies against nucleoli (antifibrillarin I) showed only low-grade positivity. Antibodies to Scl-70 and centromeres were not present.

The following tests were within normal range: liver and kidney laboratory parameters, C3/C4/CH50, virological tests (HIV, hepatitis A, B, C), Borrelia burgdorferi serology, PPD test for tuberculosis, chest X-ray, pulmonary function tests with CO diffusion capacity, oesophageal motility (X-ray), MRI of the cervical spine (no signs of arthritis) and bone marrow analysis (no evidence for malignancy). Urine analysis did not show any abnormalities. Capillaroscopy was performed revealing a normal pattern. HLA tests were not done.

Skin–muscle–fascia biopsy showed increased skin thickening and fibrosis of the dermis as well as oedematous fascia with low-grade fibrosis. Supporting the diagnosis of EoF discrete inflammatory infiltrates as well as isolated eosinophilic granulocytes were also found (Fig. 1B).

The response to steroids (orally given prednisolone, 2 mg/kg body weight and repeated i.v. methylprednisolone 1 g/day for 3 days) and subcutaneously administered MTX (20 mg/week) was insufficient and further disease progression was noted, leading to total loss of foot mobility, continuing skin thickening and further ESR elevation. Meanwhile, a severe artificial Cushing syndrome had occurred as a side-effect of the prolonged steroid treatment. In terms of gaining control over disease activity and reducing steroids, infliximab was initiated at a dose of 300 mg at week 0, 2 and then every 4 weeks and oral steroids were continued initially (Fig. 1A).

Anti-TNF-α treatment initiation led to a continuous and marked improvement of skin thickening, limitation of motion range and an ESR drop-down (Fig. 1A). After 1 yr of treatment, infliximab was discontinued. Another year later, MTX was discontinued as well, and the patient maintained a full clinical and laboratory remission. At the last observation no residual signs of the disease could be noticed with reconstitution of the full range of motion for all joints, normal skin appearance, normal blood count and inflammatory parameters.

![Figure 1](image.png)

**Fig. 1.** (A) Medication and laboratory parameters during disease course. ESR in mm/h; CRP in mg/dl; LEUCO, leucocytes × 10⁹/µl; Eo, eosinophils in percent. MTX subcutaneous application in mg/m²/week; INFLIX, infliximab in mg/month; PREDN, prednisolone in mg/day. (B) Detailed view of muscle and fascia (magnification ×40, haematoxilin–eosin): oedematous fascia with low-grade fibrosis. Discrete inflammatory infiltrates as well as isolated eosinophilic granulocytes (asterisk).
EoF is a rare autoimmune condition during childhood particularly with regard to the published literature. Elevated inflammatory parameters, elevated eosinophil counts, skin thickening and peau d’orange as well as eosinophilic infiltration of muscle fasciae support the diagnosis. Initial reports suggest that EoF is a condition responsive to corticosteroids. However, therapeutic effects must be judged against the background of spontaneous resolution, which may occur within 3–5 yrs of onset in a large proportion of cases [10]. Irrespective of the patients with spontaneous remission or those who respond well to steroids, some EoF patients will have a more severe and steroid-resistant disease course, leading to diffuse cutaneous fibrosis and posing the question of further treatment for sufficient disease control.

We report our experience in a child with treatment-resistant disease of a histologically proven EoF. Only after infliximab initiation could steroids be gradually tapered and a marked symptom attenuation was achieved. It is well known that TNF-α antagonists may offer an alternative to control disease activity in chronic inflammatory disorders. Certainly, self-limitation of the disease could not be excluded in our patient, but the close chronological relation between clinical response and initiation of anti-TNF-α treatment rather suggests a therapeutic effect.

**Disclosure statement**

Processing.

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**Rheumatology key message**

- Infliximab may be effective in steroid-resistant juvenile EoF.

**Letters to the Editor**

**Efficacy and safety of rituximab in a patient with active rheumatoid arthritis and chronic disseminated pulmonary aspergillosis and history of tuberculosis**

Sir. In RA, the rate of infections and infection-related mortality is up to 4 to 6 times higher as compared with the general population [1] and an increased risk has been associated in particular with the use of steroids [2] and TNF inhibitors [3]. Therefore, treatment of RA in patients with underlying chronic infections represents a challenge given that therapeutic options are limited.

We here report on a patient with active RA, who developed tuberculosis during treatment with steroids and MTX, followed by chronic disseminated pulmonary aspergillosis as a secondary complication. Rituximab, a chimeric monoclonal antibody directed against CD20, was applied as monotherapy and led to a long-lasting improvement of signs and symptoms of RA. During a follow-up period of 15 months there was no evidence for progression of pulmonary disease.

A 63-yr-old Caucasian woman presented to our clinic with active seropositive RA from which she had been suffering for >10 yrs. Initial therapies including gold, chloroquine, SSZ and AZA proved ineffective. In 1995, treatment with oral MTX (15 mg once weekly) was initiated but was stopped when active pulmonary tuberculosis was diagnosed. Quadruple tuberculostatic therapy was administered, upon which the patient improved. Upon aggravation of RA symptoms, low-dose steroids were restarted. Ten months later, the patient presented with cough, spiking fever and increasing dyspnoea. An X-ray and computer scan (CT) were carried out and revealed a single, contrast-enhancing peripheral lesion within the right upper lobe, consistent with the diagnosis of an aspergilloma inhabiting a pulmonary cavity (Fig. 1). Moreover, a fine, interstitial bilateral shadowing was noted suggesting accompanying disseminated aspergillosis. The patient was started on amphotericin, and then switched to liposomal amphotericin, but this medication had to be discontinued when kidney function deteriorated. The patient then received a 4-week course of intravenous voriconazole, which was well tolerated and followed by surgical lobectomy of the right upper lung. Diagnosis of aspergillosis was confirmed histologically. The patient recovered well and oral voriconazole was continued. During the follow-up period, RA symptoms were mainly controlled using NSAIDs and analgesics.

In August 2006, the patient experienced a severe exacerbation of arthritis with a 28-joint disease activity score (DAS28) of 7.4. A CT scan at that time did not reveal any active pulmonary lesions. Given that the patient’s RA symptoms continued to worsen, therapy with rituximab was initiated. The patient received two infusions of rituximab 1000 mg 2 weeks apart without concomitant methylprednisolone, which were well tolerated. Upon that regimen, the patient’s condition improved dramatically during the following weeks. Three months later, a DAS28 of 4.1 was recorded and at 6 and 12 months after rituximab, a DAS28 of 3.2 indicated low disease activity. The patient is still receiving prophylactic oral voriconazole and has had no relapse of pulmonary symptoms to date.

In summary, we report on a patient with active RA and a past medical history of pulmonary tuberculosis and aspergillosis, in whom rituximab monotherapy resulted in significant reduction of disease activity without adversely affecting the pulmonary condition.

Although rituximab has been approved for the treatment of RA in patients with an inadequate response to TNF inhibitors in combination with MTX, rituximab may also be applied to