CASE REPORT

Rituximab seems to be a safer alternative in patients with active rheumatoid arthritis with tuberculosis

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SUMMARY

Demonstrating the efficiency and safety of rituximab (Rtx) in the treatment of active rheumatoid arthritis (RA) and tuberculosis (TB). Two cases of RA with active TB were followed up to 3 years following the initiation of Rtx. The former case presented with a history of concomitant diagnosis of both RA and TB and the latest one, also diagnosed with RA and reactivation of TB developed during the anti-tumour necrosis factor treatment. After a sufficient time of follow-up, we have observed that Rtx seems to be safer and efficient in the treatment of active RA and TB.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic systemic, inflammatory, disabling and immune-mediated disease. In RA, the rate of infections and infection-related mortality is up to 4–6 times higher as compared with the general population¹ and an increased risk has been associated in particular with the use of some medicine. Anti-tumour necrosis factor (TNF) therapy and reactivation of latent tuberculosis (TB) is well recognised.²

The efficiency of rituximab (Rtx), which is a chimaeric anti-CD20 monoclonal antibody, in the treatment of RA had been already demonstrated through different clinical trials but there is no sufficient data on its reactivation of latent TB as well as it is known in anti-TNF therapy. Moreover, there are two recent case reports concerning the safe use of Rtx in patients with latent TB.^{3 4}

We herein present two cases of RA with active TB were followed up to 3 years after the initiation of Rtx. The first case presented with a history of concomitant diagnosis of both RA and TB and the second one on the other hand, also diagnosed with RA and reactivation of TB developed during the anti-TNF treatment.

CASE PRESENTATION

Case 1

A 56-year-old man admitted to hospital with disturbing complaints such as fever, night sweating, weight loss and cough in the beginning of July 2010. He had a history of increased pain and swelling in his wrists, ankles and small joints of his hands for 6 months. He was diagnosed both active lung TB by acid-resistant bacilli screening test was positive in phlegm and RA by rheumatoid factor: 25 IU/ml, and anti-cyclic citrullinated peptide: 330. Physical examination revealed that the patient had 14 swollen joints and 10 tender joints and due to that his 28-joint disease activity score (DAS28) was 7.2. We have started isoniazid (INH) 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1500 mg/day and ethambutol 1500 mg/day for 2 months as basil clearance period, then INH and rifampicin alone used for a further 4 months as sterilisation period.

We first tried to delay his RA therapy, other than sulphasalazine (SSZ) 2 g/day, hydroxychloroquine (HCQ) 400 mg/day, due to avoiding polypharmacy and misdiagnosing of RA. However, his articular complaints did not improve at all and in the 30th

Figure 1 Illustration of patient's chest x-rays before and after the treatment. Before treatment: homogeneous opacity increment in right top center zone, remarkable volume loss of a left hemithorax, cystic lesions in left top zone, and diffuse non-homogeneous opacity increment in all zones. After treatment: fibrotic sequelae changes in left top zone.

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Table 1 Clinical features of two cases before rituximab treatment markers

C markers	Case 1	Case 2
Laboratory markers		
Sedimentation	110	83
CRP	73	68
Rheumatoid factor	25	120
Anti-cyclic citrullinated peptide	330	121
Acid-resistant bacilli test	Positive	NA
TB culture	Positive	Positive
Clinical findings		
DAS28	6.8	6.4
# of tender joints	14	10
# of swollen joints	10	8
fever	Positive	Positive
Weight loss	Positive	Positive
Cough	Positive	Positive
TB in family members	Negative	Negative
Drug history/months		
Methotrexate	–	120
Sulphasalazine	1	300
Prednisolone	2	110
Isoniazid	–	9*
Leflunomid	2	–
Hydroxychloroquine	1	60
Infliximab	–	15

*According to the Turkish anti-TB guideline, TB prophylaxis starts 3 weeks before the medication and it is terminated on the ninth month of treatment.
CRP, C reactive protein; DAS, disease activity score; TB, tuberculosis.

day of therapy leflunomide (Lef) 20 mg/day with prednisolone (Pred) 20 mg/day was started and previous drugs stopped due to lack of response. Lef combined with Pred therapy lasted 8 weeks (DAS28: 6.8). Rtx 1000 mg (1st and 15th days/6 month) was started afterwards and his complaints were reduced significantly and TB reactivation was not observed during the 12 weeks of follow-up (DAS28: 4.1). The patient is still using Lef 20 mg/day, Pred 5 mg/day and Rtx (1st and 15th days/6 month). TB therapy was stopped after 6 months.

Case 2

A 73-year-old woman with a 25-year history of RA had regularly used SSZ 2 g/day; methotrexate 15 mg/week, non-steroids, Pred 5 mg/day and HCQ 200 mg/day irregularly for 15 years. She was on remission for the last 10 years until her last activation and anti-TNF treatment (infliximab) was added. She was carefully controlled before initiation of the biological, but any comorbidity was detected. INH was prescribed for TB prophylaxis despite to a 3 mm induration of tuberculin skin test and a normal lung x-ray. She was admitted to hospital on the 15th month of her infliximab therapy. Fever, weight loss and abdominal distension were the distinctive symptoms. TB was diagnosed with multiple lymphadenopathies and parenchymal nodular involvement of her lungs, an elevated adenosine deaminase level and a positive culture from her ascites (August 2008). The same anti-TB protocol was started as in the previous case and then INH and rifampicin alone used for 10 months.

While her RA is progressively active, she had DAS28 score: 6.4. Rtx 1000 mg (1st and 15th days/6 month) was added at the end of the first week of her anti-TB treatment. DAS28 score was 3.8 after 3 months. She is still on SSZ 2g/day, HCQ 200 mg/day

Figure 2 Treatment process time-line for two cases of rheumatoid arthritis with active tuberculosis.

and Rtx treatment for 2 years without any activation of TB (figure 1).

DISCUSSION

In this case report we present two interesting cases in which one patient had TB reactivation during the anti-TNF treatment, and the second one diagnosed with TB and RA at the same time, and both cases reached remission and inactive TB following the RTX treatment during the 18 months and 36 months of follow-up, respectively. Clinical features of two cases before Rtx treatment were showed in table 1. Two cases of RA with active TB were followed up to 3 years were showed in figure 2.

The association between TNF- α antagonists and reactivation of latent TB is well recognised.^{2 5 6} More obviously, patients with such complain generally presented with diffuse infection which brings a complex series of diseases leading to mortality. Treating reactivated latent TB is very usual but management of active TB and active flare RA at the same time is very much rare and an unusual case.

Obviously, there are limited data concerning the simultaneous treatment of RA with Rtx and TB. Burr *et al*³ published a case report with RA who was successfully treated with Rtx on the 10th month of the anti-TB therapy after developing disseminated INH-resistant TB following treatment with infliximab. Jung *et al*⁴ reported a case where a patient with active RA, who developed TB during treatment with steroids and MTX, followed by chronic disseminated pulmonary aspergillosis as a secondary complication and successful treatment by Rtx after a year from anti-TB.

The treatment of active RA with an active TB is a real problem in a small group of unlucky patients. In these two cases of TB and RA, Rtx was safely tolerated, and both patients have a regular follow-up up to 3 years without any problem.

Consequently, these results demonstrate that, Rtx could be used safely in TB patients during their anti-TB treatment.

Further randomised clinical studies needed to be held to verify the findings stated in this case report.

Learning points

- ▶ First two cases of RA with active TB in the literature that were followed up to 3 years after the initiation of Rtx under clinical remission.
- ▶ Rituximab is safe and well tolerated in patients with active RA and TB.
- ▶ New therapeutic alternative beside TNF inhibitors for the treatment of TNF naïve RA patients with active TB.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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