The promise of rituximab in connective tissue disease-associated interstitial lung disease

In a single-centre 11-year retrospective analysis, Seedat *et al.*[1] report their experience using rituximab (RTX) as salvage treatment in 19 patients with progressive connective tissue disease-associated interstitial lung disease (CTD-ILD), followed up for 24 months. The study population comprised 9 patients with rheumatoid arthritis (RA), 4 with systemic sclerosis (SSc), 3 with systemic lupus erythematosus (SLE), 1 with anti-synthetase syndrome, 1 with dermatomyositis and 1 with mixed connective tissue disease (MCTD). The majority (79%) had nonspecific interstitial pneumonia (NSIP), while the remainder had usual interstitial pneumonia (UIP). None of the patients received antifibrotic therapy. The impact of RTX was assessed on follow-up with pulmonary function tests, high-resolution computed tomography of the chest (HRCT) and World Health Organization (WHO) functional class. Notwithstanding the limitations of a small retrospective study, it is noteworthy that over the 2-year period, forced vital capacity (FVC) stabilised (mean decrease from baseline 100 mL), the majority of the patients (82%; *n*=14/17) showed no radiological progression, and overall there was no decline in WHO functional class. No significant adverse drug effects were observed.

RTX is a humanised mouse chimeric monoclonal antibody directed against CD20, a transmembrane protein expressed on B cells[2] first approved for the treatment of B-cell non-Hodgkin's lymphoma in 1997. CD20 is expressed by normal pre-B and mature B lymphocytes, but not stem cells or plasma cells.[3] The resulting depletion of B cells following administration of RTX lasts ~2 - 6 months before gradual recovery to normal levels at 9 - 12 months.[2,4] Not only does this drug affect B cells and humoral immunity, but it also affects cellular immunity by depleting CD4+ T cells.[5] B cells are central to the pathogenesis of autoimmune diseases. Interestingly, it has recently been shown *in vitro* that B-cell-fibroblast crosstalk probably plays a role in the pathogenesis of idiopathic pulmonary fibrosis by upregulating fibrotic proteins.[6,7]

In a review of 29 studies (22 retrospective, 4 prospective, 3 randomised controlled) involving 827 patients with CTD-ILD, Wang and Li[8] found that in the observational studies, there was a decline in FVC percent predicted and diffusing capacity for carbon monoxide (DLCO) percent predicted following administration of RTX. However, in the randomised controlled trials, while FVC percent predicted declined, there was no impact on DLCO percent predicted. The radiographic ILD pattern was documented in only 242 patients, of whom 58.7% had an NSIP pattern. RTX was associated with an increase in adverse events (29.7%), all-cause mortality (11.6%) and infections (20.9%).

In a comprehensive overview of RTX in CTD-ILD, Vacchi *et al.*[9] conclude that RTX has been shown to stabilise or improve ILD in RA, idiopathic inflammatory myositis (IIM) and SSc. However, for ILD in Sjögren's syndrome, SLE and antineutrophil cytoplasmic antibody-associated vasculitis, the evidence is tenuous.

There have been two recent randomised controlled trials involving RTX in CTD-ILD. In RECITAL,[10] a multicentre UK prospective randomised double-blind phase 2b study, 97 patients with ILD associated with SSc, IIM or MCTD were randomised to receive either RTX or cyclophosphamide. A real-world pragmatic selection of study participants was employed. Extrapolating from guidelines for SSc-ILD, the investigators selected patients with severe or progressive ILD for whom cyclophosphamide would have been the next conventional therapeutic option. Both drugs improved lung function (gain of 99 mL and 97 mL for FVC in the cyclophosphamide and RTX arms, respectively) and quality of life scores at 24 weeks. RTX was not superior to cyclophosphamide, but was associated with fewer adverse events and less corticosteroid exposure.

The second trial, EVER-ILD,[11] a phase III trial, compared RTX plus mycophenolate mofetil (MMF) with MMF plus placebo in 122 patients with CTD-ILD (SSc, IIM, Sjögren's syndrome, RA, MCTD), ILD with autoimmune features, and idiopathic interstitial pneumonia. Only patients with an NSIP pattern who had demonstrated no response, or relapsed following corticosteroids and/or immunosuppressive drugs, were included. This study showed superiority of RTX plus MMF over MMF alone, indicated by improvement in FVC at 6 months (~3.6 percent predicted and 100 mL) and longer progression-free survival (crude hazard ratio 0.47). There was no difference in 6-minute walk distance, DLCO, dyspnoea, cough or fibrosis on HRCT. However, the combination therapy group experienced more infections.

Since not all patients with CTD-ILD respond to RTX, it would be useful to predict which patients are likely to benefit. An innovative prospective phase II study[12] utilised immuno-positron emission tomography (PET)/CT with RTX radiolabelled with ^{89}Zr to determine levels of CD20 cells in the lung. In 21 patients with progressive ILD non-responsive to corticosteroids and either azathioprine or cyclophosphamide, those who had a clinical response to RTX also had higher lung uptake of ^{89}Zr-rituximab at baseline, suggesting that this technique may be a predictive biomarker for selection of patients likely to respond to RTX.

Biological drugs are not innocuous. Adverse effects to RTX include fever, chills and flushing, which usually occur within the first 2 hours of infusion of the drug. Other side-effects include nausea, vomiting, hypotension, angio-oedema, bronchospasm and chest pain. Infectious complications are reportedly not very frequent or severe. However, the administration of RTX in patients with autoimmune disease was associated with an increased risk of severe COVID-19 pneumonia during the pandemic.[13] Both RECITAL and EVER-ILD were conducted prior to COVID-19 . Haematological derangements include late-onset neutropenia (3 - 4 weeks after infusion),[14,15] transient thrombocytopenia[4] and hypogammaglobulinaemia. The latter may last up to 2 years following exposure and rarely necessitates administration of intravenous immunoglobulin.[15] Athni and Barmettler[15] emphasise the importance of monitoring immunoglobulin levels, a practice frequently neglected by prescribing practitioners.

RTX-induced lung injury is a rare complication that had not been reported prior to approval of the drug.[3,16-18] The pathogenesis is possibly related to complement activation and the release of inflammatory cytokines such as tumour necrosis factor alpha, interleukin 8 and interferon gamma. In a systematic review of 45 patients receiving RTX,[3]

the most common histological finding was organising pneumonia with or without associated NSIP or UIP. Intra-alveolar haemorrhage[19] and a host of other pathological findings have also been described.[20] The onset of pulmonary toxicity may be hyperacute (within hours), delayed (days 8 - 21) or late (1 - 3 months).[3] In general, withholding RTX and administration of corticosteroids results in recovery, although deaths have been reported.[3,21] It is noteworthy that almost all cases of RTX-induced lung injury have been documented in association with lymphoma and other haematological malignancies. There are no convincing reports of RTX-induced lung injury superimposed upon pre-existing ILD for which RTX had been administered, although some authors speculate that some cases may be subclinical or erroneously attributed to progression of severe ILD.[22,23] This discrepancy may perhaps be related to the different dosage and therapeutic regimens used in autoimmune diseases as opposed to haematological malignancies.

Other rare adverse effects[24] include reactivation of hepatitis B, progressive multifocal leucoencephalopathy and toxic epidermal necrolysis. Administration of live vaccines is contraindicated within 4 weeks of, or during, RTX treatment. Other vaccines should be given at least 4 weeks before a dose of RTX is administered. Safety in pregnancy and lactation is unknown.

Analysis of the effect of RTX in CTD-ILD is confounded by several factors. RTX is often used as a 'last resort' when more conventional therapies have failed; ILD patterns, severity and evolution differ within the same CTD disease; reports generally involve small retrospective case series; patients often receive other concomitant immunomodulating drugs; and the multisystem nature of many CTDs may complicate the interpretation of data.

Biological drugs such as RTX hold promise for the management of CTD-ILD and represent progress in personalised medicine. A significant limiting factor, however, is their prohibitive cost. Accessibility to biological agents remains limited in South Africa, not only in the state sector but even in the private sector.[25] Fortunately, a biosimilar of RTX has been registered, a welcome cost-reducing advantage for patients and clinicians.

Further prospective studies of RTX are warranted in the field of CTD-ILD. The findings of RECITAL and EVER-ILD are likely to prompt trials utilising this drug earlier in the therapeutic algorithm, and in combination with other already established therapies.

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