Commentary on DESIRES trial in SSc: Safety and efficacy of rituximab in systemic sclerosis (DESIRES): open-label extension of a double-blind, investigators-initiated, randomized, placebo-controlled trial

When the game changes: efficacy of rituximab in systemic sclerosis

Voon H, Ong PhD FRCP

Christopher P. Denton PhD FRCP

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by endothelial dysfunction, inflammation and fibrosis of which interstitial lung disease (ILD) is a major cause of morbidity and mortality. Recent years have seen significant advances in our understanding of SSc and connective tissue disease associated ILD with emergence of novel therapies. Rituximab on the other hand has been the therapeutic stalwart for autoimmune rheumatic diseases for the last quarter of century and this reappraisal in SSc coincides with emerging concern of risks from COVID-19 outcomes and reduced protective effect of COVID-19 vaccination.

Previous randomised controlled trials (RCT) on rituximab in SSc have reported benefit for skin and lung involvement and a recent meta-analysis of the three RCTs concluded significant impact on forced vital capacity (FVC) (Std. Mean Difference 0.66 [95% CI 0.23, 1.09], p=0.003) but not skin (mRSS: Std Mean Difference 0.42 [95% CI 0.92,0.11],p=0.12) (1). 2 of the RCTs reported impact on CT scores with no significant change (2,3). More recently, the parent 24-week double-blind, parallel-group DESIRES trial evaluated rituximab in SSc and reported a significant improvement in the primary endpoint, modified Rodnan skin score (mRSS) with stabilisation of FVC as secondary endpoint compared to placebo (4).

In this issue, Ebata and colleagues report the results of 48-week open-label extension period of the DESIRES trial (5). From the initial randomised cohort, 20/26 from the placebo arm and 26/28 from treatment arm transitioned to the extension study. Notably, a majority 42/46 of the subjects in the open-label extension had ILD. The results support durability of the effect of rituximab on both mRSS and FVC decline. Notably, a rapid skin improvement was demonstrated in first four weeks in placebo-rituximab switch supporting benefit of rituximab. This effect on skin trajectory in the open-label phase has not been conclusively demonstrated in prior RCTs noting differences in patient numbers, proportion of antiScl70 antibody specificity and presence of background immunosuppressives (2,3). The authors recently identified baseline peripheral blood CD19 positive cell counts, mRSS and serum SP-D levels as predictors of rituximab efficacy for skin outcomes, and it will be interesting if interval assessments of these indices may guide subsequent infusions (6).

For the effect on lung disease, a dramatic response in the placebo-rituximab cohort with high risk of ILD progression (FVC <80%) indicates potential for disease reversibility; however, interpretation is limited by small numbers. In contrast, there was stability with repeat treatment in the rituximab-rituximab cohort. It would be interesting in the future to explore whether response was more pronounced in patients with anti-Scl70 (n=25) vs nonScl70 (n=21) based on the strong association of this hallmark ANA with development of lung fibrosis and in those with disease duration shorter than 2 years.

Importantly, the open-label extension period reported similar adverse effects as those observed in the initial RCT and are consistent with the known safety profile of rituximab. Risk of infections in particular reduce over time with anti-TNF; reasons for this in unclear but possibly related to better disease control and reduced use of concomitant immunosuppressives. It is not clear if this holds true

for rituximab. Adverse events were no higher with repeat rituximab infusions and lymphocyte count, CD19 and immunoglobulin G levels were stable over the open-label phase. This suggests B cell count recover well over 6-month period. Mature plasma cells are not depleted by RTX and therefore any decline on immunoglobulins will be transient. However, with repeat RTX courses, late-onset immunoglobulin decline may occur with prolonged depletion of plasma cell precursors with reduced recovery of mature plasma cells.

The limitations of this RCT must not be overlooked. No background therapy was permitted in this study. Whilst this does not necessarily affect the results in the open-label phase, an important open question is whether how benefit of rituximab compares with other standard approaches such as mycophenolate mofetil, whether combination immunosuppression is more effective and how use of rituximab might fit with other agents in use for SSc-ILD such as tocilizumab and nintedanib. In the current Covid-19 era, the correlates of protection from vaccination with antibody titre and the impact on immune robustness from B cell depletion from rituximab are not well understood (7,8). These issues will pose challenges to clinicians managing SSc and it is likely that real-life data would be valuable to inform potential biomarkers that may guide appropriate utility of rituximab in management of SSc.

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