**Tocilizumab as a potential therapeutic option for children with severe, refractory Juvenile Localised Scleroderma**

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Sir,

Scleroderma causes chronic inflammation in the skin and soft tissues leading to fibrosis and eventually atrophy. Complications such as joint contractures, limb length discrepancy and facial atrophy can occur and the disease can have marked psychological and functional impact[1]. Optimal treatment for juvenile localised scleroderma (JLS) is unknown and there have been few therapeutic trials. First line medical treatment for active JLS is often methotrexate with corticosteroids supported by data arising from a randomised placebo-controlled trial (RCT) and observational cohort studies[2,3]. Mycophenolate mofetil (MMF) is increasingly used, although evidence is restricted to a single case series[4]. A wide range of disease-modifying anti-rheumatic drugs (DMARDs) and biologics are used off–label in refractory cases[5]. The pathophysiology of localised scleroderma is poorly described. Cytokines including interleukin-6 have been suggested to play an important role[6]. An RCT of subcutaneous tocilizumab in adult systemic sclerosis demonstrated a trend towards skin thickness reduction compared to placebo[7]. We therefore hypothesised that tocilizumab may have a role in patients with refractory JLS.

Patients were treated with tocilizumab following persistent active disease despite escalation to maximum tolerated doses of methotrexate and one other DMARD/biologic and clinician decision to treat with tocilizumab in conjunction with informed consent/assent from the patient and family. Outcome measures were collected prospectively as part of routine clinical care at baseline and approximately 3 monthly intervals to assess disease activity, damage, quality of life and functional status and reviewed as part of a service evaluation. Ethical approval was therefore not required, in accordance with the UK National Health Service Health Research Authority guidelines. The dosing regime was 8mg/kg (children weighing ≥30kg) and 12mg/kg (those <30kg) given at 0, 2 and 4 weeks and then at 4 weekly intervals. Regular blood monitoring was performed as per local guidelines. Adverse events were enquired about at three monthly review. Data was analysed descriptively and where appropriate, statistical analysis done using Wilcoxon signed-rank test.

Five patients with long-standing disease that remained active despite multiple doses of IV corticosteroids alongside other treatments received tocilizumab. Details of patients and outcomes are summarised in Table 1.

Table : Details and outcomes of patients treated with tocilizumab

To date, all patients remain on IV tocilizumab and have been treated for between 12-25 months. All patients tolerated tocilizumab with no serious adverse reactions. Patients showed some improvement in disease activity scores with statistically significant improvement in physician’s global assessment of activity (PGA-A) at 6 months. Improvements in disease damage, function and quality of life were not seen. Patient 3 was re-started on methotrexate and MMF but all other patients were treated with tocilizumab as monotherapy. Patients and families were extremely positive about treatment with tocilizumab. Patient 1 described it as the ‘*best treatment they had had’*; patient 4 described ‘*softer skin*’ which is ‘*not aching anymore*’; patient 5 described their scleroderma as ‘*the best it has ever been*’.

This case series is encouraging, indicating a potential new therapeutic option for children with the most severe and refractory JLS where standard treatments have failed and recurrent corticosteroid courses are necessary. Importantly, three patients did not require any concomitant corticosteroid treatment with commencement of tocilizumab because of rapid disease control. Two patients did not require any corticosteroids for disease flare over 25 months and 17 months treatment respectively. Three patients required methylprednisolone for disease flare after 12 months of treatment with tocilizumab. Some patients may benefit from dual therapy with a DMARD/biologic. All patients have remained on tocilizumab and four patients had intolerance of previous treatments.

Whilst improvement in PGA-A was statistically significant at 6 months, changes in modified localised scleroderma skin activity index (mLoSSI) were not statistically significant. Many of our patients had low mLoSSI scores at baseline. The mLoSSI measures activity in skin by 3 domains[8]. Several of our patients had deep longstanding lesions, including facial hemiatrophy where skin changes are often minimal. The mLoSSI does not capture deeper tissue disease activity and PGA-A may be more appropriate in these patients.

Damage scores were unaffected by treatment with tocilizumab; this might be expected as changes from previous disease activity may have less potential to be reversible. It may be prudent to focus future studies of tocilizumab in children at an earlier stage in their disease course.

Limitations include the small number of patients treated and the non-controlled nature of this case-series. Data was collected in a real-world setting and not in context of a clinical trial therefore the outcome measures were collected within two months of the specified time point. However, these preliminary data indicate that future clinical studies of the efficacy and safety of tocilizumab should be considered, particularly given the paucity of therapeutic trials in this potentially disfiguring disease.

In summary, these results suggest that IV tocilizumab is safe, well tolerated and may have therapeutic benefit in patients with severe, refractory JLS.

Key messages

* Tocilizumab may have a role in the management of refractory juvenile localised scleroderma (JLS).

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Conflict of Interest Statement

There are no conflicts of interest.

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