Effectiveness and safety of tocilizumab for the treatment of refractory systemic sclerosis associated interstitial lung disease: a case series

We read with great interest the results of the double-blind phase 2 fAscinate clinical trial,1 in which there was encouraging (although not statistically significant) numerical improvement in skin thickening and evidence of less decline in lung function in patients with systemic sclerosis (SSc) treated with tocilizumab (TCZ) compared with those receiving placebo. Initial investigations with TCZ in patients with SSc demonstrated improvements in skin sclerosis and polyarthitis.2,3

Scleroderma-associated interstitial lung disease (SSc-ILD) is a severely debilitating complication with high mortality in extensive disease. There is no approved disease-modifying treatment, and few effective treatment options are available. One of the most urgent needs is to determine which drugs can be useful as a rescue treatment in patients who do not respond to conventional therapies for SSc-ILD (evidence of clinical and functional decline despite previous treatment with low–medium prednisone doses, immunosuppressants and rituximab (RTX)). They were treated with a compassionate use of TCZ for at least 4 months. In all cases, written informed consent was obtained from the patients, and the off-label use of TCZ (and previously of RTX) was approved by our local health authorities.4

The median durations of SSc and ILD were 8 years (range: 2–15 years) and 7 years (range: 2–12 years), respectively. All cases corresponded to fibrosing non-specific interstitial pneumonia. Progressive interstitial lung disease (ILD) was defined when there was a worsening of ≥10% in percent predicted forced vital capacity (%pFVC) or ≥15% in percent predicted diffusing capacity for carbon monoxide corrected for haemoglobin (%pDLCO) during the follow-up (over 1 year).

Previous or ongoing therapies for SSc-ILD included MMF (100%), CYC (67%), azathioprine (11%) and RTX (100%). In all cases, the time elapsed since the last dose of CYC was greater than 2 years and 6 months in the case of RTX. The mean number of RTX cycles previously administered was 3±1.7 (range: 1–6): in four patients (44%) RTX was discontinued due to adverse events (mainly respiratory or urinary infections and/or transient neutropenia) and in the remaining (56%) due to inefficacy.

TCZ was administered intravenously in two patients (at a dose of 8 mg/kg monthly) and subcutaneously in the remaining 7 (162 mg weekly). In all cases, it was administered with MMF (eight patients received 2 g/day and one patient received 1 g/day). Seven (78%) patients received concomitant treatment with prednisone (≤5 mg/day). Ongoing therapy with MMF and oral prednisone remained unchanged in all cases.

The baseline clinical features and outcome of these patients are summarised in table 1. At the end of the follow-up period (median 12 months; IQR 25th–75th: 6–33 months), only four patients (44%) were still in treatment. In the other five patients (56%) TCZ was discontinued, due to serious adverse events in one case and due to inefficacy in the other four cases. One of these,

### Table 1: Baseline clinical features and outcome of our nine patients with refractory systemic sclerosis-associated interstitial lung disease treated with tocilizumab

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>SSc duration (years)</th>
<th>SSc cutaneous subset</th>
<th>Chest HRCT pattern of ILD</th>
<th>ILD duration (months)</th>
<th>Autoantibodies</th>
<th>Previous or ongoing therapies for SSc-ILD</th>
<th>No of RTX cycles</th>
<th>Follow-up after first dose of TCF (months)</th>
<th>Lung responses to TCF therapy a</th>
<th>Adverse events</th>
<th>Discontinuation of the treatment at the endpoint of patient follow-up and reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>F</td>
<td>9</td>
<td>1</td>
<td>Fibrosing NSP</td>
<td>12</td>
<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 61.7056.1 (STB)</td>
<td>No</td>
<td>Yes: herpes zoster; 1; bacterial infections; 3; needing hospitalisation in one of them (nasogastric)</td>
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<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>12</td>
<td>1</td>
<td>Fibrosing NSP</td>
<td>4</td>
<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN</td>
<td>5</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 77.3806.4 (STB)</td>
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<td>No</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>12</td>
<td>4</td>
<td>Fibrosing NSP</td>
<td>12</td>
<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 41.4441.8 (STB)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>F</td>
<td>12</td>
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<td>CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 78.8737.3 (STB)</td>
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<td>No</td>
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<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>12</td>
<td>4</td>
<td>Fibrosing NSP</td>
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<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 103.10101 (STB)</td>
<td>Yes</td>
<td>Yes, due to inefficacy. Autologous stem cell transplantation</td>
</tr>
<tr>
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<td>M</td>
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<td>4</td>
<td>Fibrosing NSP</td>
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<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 9.016.9 (STB)</td>
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<td>No</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>12</td>
<td>4</td>
<td>Fibrosing NSP</td>
<td>12</td>
<td>Scl-70 (+) Rf 2</td>
<td>CYC, MMF, RTX and PDN; MMF and RTX; CYC, MMF, RTX and PDN</td>
<td>4</td>
<td>23</td>
<td>Pred-TCF: Post-TCF %pFVC 41.4441.8 (STB)</td>
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<td>No</td>
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<td>8</td>
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<td>Pred-TCF: Post-TCF %pFVC 103.10101 (STB)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Note:** HRCT was assessed by one chest radiologist blinded to clinical state or change in lung function. Categorisation of radiological responses: (1) improvement (no lung fibrotic changes and improvement ≥20% of the extent of ground glass opacities); (2) stabilisation; (3) worsening (increase of pre-TCZ %pFVC >10% or %pDLCO >15% numerical improvement in skin thickening and evidence of less decline in lung function); (4) no change (%pFVC or %pDLCO unchanged); (5) deterioration (%pFVC or %pDLCO increased). Patients included in group 1 (improvement) and group 2 (stabilisation) were treated for at least 6 months. In all cases, written informed consent was obtained from the patients, and the off-label use of TCZ (and previously of RTX) was approved by our local health authorities.

**Correspondence:**


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**Competing interests:** None declared.

**Ethics approval:** The study was approved by the ethical committee of our local institution. All patients provided written informed consent.

**Patient consent:** Not required.

**Provenance and peer review:** Not commissioned; internally peer reviewed.
Correspondence

four patients died due to progression of ILD. The frequency of adverse events was low, occurring in only one patient (11%) who developed repeat infections including an osteomyelitis complicating a digital ulcer requiring hospitalisation.

Although it is difficult to draw any firm conclusions from these data, according with our experience in this small cohort, TCZ appears to be safe. Its effectiveness as a rescue treatment in patients with refractory SSc-ILD seems modest but not negligible, achieving an improvement or stabilisation of pulmonary function in 44% of patients.

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Patient consent Not required.

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