Concise Report

Adverse events and efficacy of TNF-α blockade with infliximab in patients with systemic lupus erythematosus: long-term follow-up of 13 patients

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Objective. To follow-up on all available infliximab-treated SLE patients for safety and long-term efficacy in order to extract information that is useful for planning appropriate controlled trials with infliximab in SLE.

Methods. We analysed charts of six patients treated in an open-label safety trial and seven additional patients treated with infliximab on a compassionate care basis for uncontrolled SLE organ inflammation.

Results. Out of nine patients with lupus nephritis, six had a long-term response after four infusions of infliximab in combination with AZA, lasting for up to 5 years. All five patients with lupus arthritis responded, but this response did not last for >2 months after the last infusion. One additional patient had a long-lasting improvement in SLE interstitial lung disease. No symptoms suggestive of infliximab-induced SLE flares occurred in any patients. Short-term treatment appeared relatively safe, but one patient developed deep-vein thrombosis and several infections. Under long-term therapy, two patients had life-threatening or fatal events, namely CNS lymphoma and Legionella pneumonia. Retreatment and treatment without concomitant immunosuppression led to drug reactions.

Conclusions. Short-term therapy with four infusions of infliximab in combination with AZA was relatively safe, and had remarkable long-term efficacy for lupus nephritis and, potentially, also interstitial lung disease. Long-term therapy with infliximab, however, was associated with severe adverse events in two out of three SLE patients, which may have been provoked by infliximab and/or by their long-standing refractory SLE and previous therapies.

KEY WORDS: Systemic lupus erythematosus, Lupus nephritis, Tumor necrosis factor-α, Infliximab, Safety.

Introduction

Some murine lupus data and the occurrence of antibodies to dsDNA under TNF blockers, occasionally associated with self-limiting lupus-like syndromes, suggest that TNF-α is relevant for controlling autoimmunity [1–6]. However, other murine and human data highlight its role as a pro-inflammatory mediator in SLE patients, and thus support TNF-α blockade in SLE [7–13]. Indeed, when we first used short-term TNF-α blockade in SLE, no SLE flares were observed, although autoantibodies characteristic of SLE transiently increased, and inflammatory organ disease improved rapidly [14, 15].

We have previously reported these successful results of the first month follow-up for the first six patients [14], as well as detailed analyses of changes in their autoantibody profiles [15]. To understand the potential safety issues better and to help focus on potential safety hazards in future trials of TNF-α blockade in SLE, it was deemed important to learn if longer term therapy and the use of infliximab in additional patients had similar safety and efficacy.

Patients and methods

We gathered all relevant safety data for 13 patients (11 females, mean ± s.d. of age 36 ± 11 years) who fulfilled the ACR criteria for SLE [16] and received the chimeric monoclonal anti-TNF-α antibody, infliximab. These patients were the only ones who had received infliximab out of ~1200 patients who were followed up in six centres in Europe. Three patients suffered from secondary anti-phospholipid syndrome, two of whom were under anticoagulation with phenprocoumon.

Patients 1–6 were treated in an open-label trial performed in accordance with the Declaration of Helsinki, and approved by the local ethics committee [14]. The seven additional patients were treated in four different centres on an individual compassionate care basis after standard therapy had failed. All patients gave their written informed consent and underwent routine tuberculosis screening before receiving TNF-α blockade.

Patients 1–10 were treated with an induction therapy of four infusions of infliximab [14], usually corresponding to ~5 mg/kg, at Weeks 0, 2, 6 and 10. Patient 6 received an additional 300 mg infusion at Week 21 (11 weeks after the fourth infusion), and every 8 weeks thereafter for additional 15 months. Patient 7 received the induction regimen at 300 mg per infusion amounting to ~3 mg/kg and, subsequently, two additional infusions of 5 mg/kg at Weeks 24 and 28. Patient 11 received infusions of 5 mg/kg at Week 0, 2 and 6, and then every 8 weeks for a total of 10 months. Patient 12 received five infusions of 3 mg/kg at Weeks 0, 2, 4, 6 and 10. Patient 13 was treated with five infusions of 5 mg/kg at Weeks 0, 2, 6, 8 and 12. Patient 2 was retreated 18 months after the last of first four infusions.
Twelve patients received AZA, mycophenolate mofetil (MMF) or MTX (Patient 3 only) in addition to infliximab, which most patients received for at least 3 months before the first infliximab infusion (Table 1). Patients 2 and 12 were started or re-started on AZA together with infliximab, Patient 13 received infliximab monotherapy.

Results

Safety of short-term infliximab therapy (induction therapy)

None of the 12 patients on background immunosuppressive developed infusion-related adverse reactions during the first series of four infusions. Patient 13, who was on infliximab monotherapy, developed an itching, macular skin rash after the third infusion, which resolved 8 weeks after the fifth and last infliximab infusion, and was therefore attributable to therapy. Other than several minor infections (Table 1), none of them associated with leucocytopenia or low complement levels, no noteworthy safety issues occurred for the first 22 weeks. Despite increases in antibodies to dsDNA in many patients [15] (Fig. 1), no patient issues occurred for the first 22 weeks. Despite increases in antibodies to dsDNA in many patients [15] (Fig. 1), no patient

Long-term safety follow-up after short-term infliximab

Nine patients, who never received further infliximab courses, were followed up for a mean ± S.D. of 4.4 ± 1.3 years (range 2.9–6.1). Patient 10, who had transiently increased preformed IgG antinuclear factor (A/NF) levels during the induction therapy (from 7.6 to 18.1 U/ml), developed deep-vein thrombosis at Week 24, shortly after her A/NF antibody levels had returned to baseline values. With anticoagulation, the patient recovered rapidly and at the last visit, 2.5 years after the last infusion, she was well on AZA and phenprocoumon. Neither of the other three events (fatal loss for >2 years, new onset of membranous nephritis for 2.5 years and fatal rupture of a cerebral aneurysm for 4 years after the last infliximab infusion) were rated as related to the past TNF-α blocker therapy.

Adverse events under longer term infliximab

Retreatment of Patient 2, 18 months after the end of the induction regimen, due to a flare of her nephritis subsequent to cessation of all immunosuppressive agents, which led to a moderate reaction with lower back pain and urticarial rash (then attributed to NSAIDs) due to the second infusion followed by a severe reaction reminiscent of a maltransfusion reaction, with abrupt massive back pain, after the infusion of a few millilitres of the third infliximab, which was immediately stopped. With appropriate therapy, the patient fully recovered within few hours. The same patient was diagnosed with renal cell carcinoma of the right kidney without metastases that was treated with cryoablation followed by nephrectomy 4.5 years after the first infliximab series and ~6 years after the last cyclophosphamide infusion.

Patient 6, who had received a total of 16 infliximab infusions for her erosive arthritis, developed cerebral B-cell lymphoma. She recovered with radiochemotherapy and has since done well apart from recurrent arthritis. Patient 11 acquired Legionella pneumonia, when travelling in the Middle East, and died in an intensive care unit. This patient had been pre-treated with pulse cyclophosphamide, pulse methylprednisolone, MMF and rituximab before receiving long-term infliximab therapy. She had received her eighth infusion of infliximab 8 weeks before the fatal infection.

Preliminary efficacy data

All five SLE patients (four non-erosive, one erosive) with persistent lupus arthritis in the past 6 months before infliximab experienced rapid remission of their joint symptoms (Table 1), defined as absence of swollen joints in 32 joint counts. Remission lasted until ~8 weeks after the last infusion. Continued infliximab therapy maintained this effect in two patients. In Patient 6, joint symptoms were absent until therapy was ceased due to the development of cerebral lymphoma. In Patient 11, however, arthritis relapsed before the eighth infliximab infusion and was not controlled by this infliximab course.

Seven of the nine patients with lupus nephritis experienced reduction of proteinuria by >50% (Table 1), whereas none of the nine patients had improved by 50% in the 6 months preceding therapy (Fig. 1). Serum creatinine stayed stable or improved slightly (Fig. 1). Two (22%) patients showed no improvement during infliximab therapy; Patient 7 had no sustained benefit. The incomplete cycle of infliximab retreatment of Patient 2 after 1.5 years led to short-term efficacy only (Fig. 1), presumably due to human anti-chimeric antibodies. Prolonged therapy in Patient 11 could not prevent a relapse of nephritis after seven infusions.

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**Table 1. Patients, adverse events within 6 months after infliximab therapy, and preliminary efficacy data of infliximab in SLE**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Therapy 12 months before infliximab</th>
<th>Infliximab, g</th>
<th>Adverse events</th>
<th>GN WHO (A/C)</th>
<th>Proteinuria Swollen joint count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Start–best</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/24 h (at week)</td>
</tr>
<tr>
<td>Short term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/24 h (at week)</td>
</tr>
<tr>
<td>1</td>
<td>AZA, steroids</td>
<td>4 ×/1.2</td>
<td>None</td>
<td>III</td>
<td>1.2–0.2 (135)</td>
</tr>
<tr>
<td>2</td>
<td>AZA, steroids, CP, IAS</td>
<td>4 ×/1.2</td>
<td>UTI</td>
<td>IV (4/2)</td>
<td>5.7–1.1 (52)</td>
</tr>
<tr>
<td>3</td>
<td>MTX, steroids</td>
<td>4 ×/1.2</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>AZA, steroids</td>
<td>4 ×/1.2</td>
<td>UTI</td>
<td>IV</td>
<td>3.1–0.5 (147)</td>
</tr>
<tr>
<td>5</td>
<td>AZA, steroids</td>
<td>4 ×/1.2</td>
<td>UTI</td>
<td>V (4/3)</td>
<td>6.4–0.1 (70)</td>
</tr>
<tr>
<td>6</td>
<td>AZA, steroids, CP</td>
<td>4 ×/1.2</td>
<td>None</td>
<td>IV (10/4)</td>
<td>3.2–2 (4)</td>
</tr>
<tr>
<td>7</td>
<td>AZA, steroids, CP</td>
<td>4 ×/1.2</td>
<td>Enteritis (Salmonella)</td>
<td>IV (6/6)</td>
<td>4.6–2.7 (17)</td>
</tr>
<tr>
<td>8</td>
<td>AZA, steroids, CsA</td>
<td>4 ×/1.2</td>
<td>DVT</td>
<td>V</td>
<td>3.4–0.1 (30)</td>
</tr>
<tr>
<td>9</td>
<td>AZA, steroids, CP</td>
<td>5 ×/1.1</td>
<td>Abscess secondary to molluscum contagiosum</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>AZA, steroids, CP</td>
<td>5 ×/1.5</td>
<td>Macular rash</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>AZA, steroids, MTX</td>
<td>16/4.18</td>
<td>Cerebral lymphoma</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>AZA, steroids, MMF, rituximab, CP</td>
<td>8 ×/1.6</td>
<td>Fatal pneumonia (Legionella)</td>
<td>IV (12/1)</td>
<td>3.4–0.5 (27)</td>
</tr>
<tr>
<td>Long term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/24 h (at week)</td>
</tr>
<tr>
<td>13</td>
<td>AZA, steroids</td>
<td>5 ×/1.5</td>
<td>Macular rash</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Where reported, renal activity and chronicity scores (A/C) are listed. Since all patients had failed standard therapy, renal biopsies had been performed 30 ± 37 months before infliximab was started.

Patient 10 received pulse methylprednisolone shortly before infliximab. Short-term data on Patients 1–6 had been reported [14]. GN WHO: glomerulonephritis WHO class; A/C: activity index/chronicity index; NA: not applicable; CP: cyclophosphamide; IAS: immunoglobulin adsorption; UTI: urinary tract infection; DVT: deep vein thrombosis.
Infliximab in interstitial lung disease

Patient 12, who had deteriorating lung function for at least 18 months [decrease in total lung capacity (TLC) from 4.87 to 4.55 l; in diffusion capacity of the lungs for carbon monoxide (DLCO) from 6.4 to 5.5 mmol/min/kPa] despite MMF therapy for 6 months followed by i.v. cyclophosphamide pulses for 12 months, stabilized clinically and on high-resolution CT scans within 2 months of starting with infliximab. He started to reduce prednisolone at Week 10. Within 6 months of starting TNF-α blocker therapy, the patient was less limited by dyspnoea than in the previous 2 years. By 8 months, AZA was stopped, HCQ was continued and prednisolone was reduced slowly over the following 18 months to 7.5 mg/day without deterioration (TLC 4.81 l; DLCO 5.4 mmol/min/kPa). The patient showed no deterioration in lung function until >4 years after infliximab while on 5 mg prednisolone.

Discussion

Despite all the limitations, these long-term follow-up data of infliximab, >4 years in several patients, suggest the substantial and lasting benefit in some patients with lupus nephritis previously not responding to standard therapy. Importantly, when substantial improvement was achieved with four infliximab infusions, such benefit appeared to last for at least 4 years. It is interesting that the same may be true for interstitial lung disease in SLE, as seen in Patient 12.

As compared with short-term therapy, prolonged infliximab therapy did not show any further benefit with regards to nephritis. For lupus arthritis, where, as in RA, inflammation relapsed after the fourth infusion, continued therapy might prolong the therapeutic response. However, while short-term therapy induced only transient autoantibody increase, patients given repeated therapy tended to further increase their antibody levels to dsDNA [15]. Moreover, life-threatening complications, namely Legionella pneumonia and cerebral lymphoma, occurred under longer term therapy. However, increased mortality due to infections and increased incidence of lymphomas are well-known in SLE [17–19], and both patients had previously received many other immunosuppressive therapies. Thus, while both fatal pneumonia and brain lymphoma may represent unfortunate coincidence in severely sick patients rather than association with TNF-α blockade, the possibility that this was due to longer term TNF-α inhibition has to be recognized.

TNF-α blockade is known to induce autoantibodies [4, 15], and it is reassuring to see that no adverse event was due to autoantibodies induced de novo by TNF-α blockade. In particular, even long-term infliximab therapy has not been associated with infliximab-induced lupus flares to the best of our knowledge. Therefore, the data reported here do not support the concept that TNF-α blockade causes a deterioration in clinical manifestations of SLE.

As a caveat, deep-vein thrombosis diagnosed in one patient (Patient 10) was in close temporal relationship with the increase in ACL autoantibodies probably induced by TNF-α blockade. Although such increases have occurred in other patients without clinical consequences [14, 15], we think it likely that TNF-α blockade was associated with the thrombotic event in this particular patient. Since this patient had preformed ACL IgG antibodies, and since two other APS patients under phenprocoumon did not develop thrombotic events, anticoagulation may have to be considered in such patients.

It is also important to point out that all but one of the patients treated with infliximab were on AZA, MMF or MTX. With such combined therapy, the only infusion reactions observed occurred in a patient retreated 18 months after the first series of infusions. In contrast, the single patient not given concomitant immunosuppressive therapy developed a rash that led to infliximab

Short-term infliximab therapy had long-term effects on lupus nephritis in the majority of the nephritic patients (Fig. 1, Table 1), as judged by persistently low-level proteinuria and inactive urinary sediments. Patients 1, 4 and 10 still showed inactive renal disease at their last visits at 69, 42 and 33 months, respectively, after the end of infliximab therapy and under continued immunosuppression. Patients 2 and 6 started to increase their proteinuria 17 and 29 months after infliximab, respectively.

Fig. 1. Long-term follow-up of seven patients with lupus nephritis treated with infliximab. The levels of proteinuria (black triangles, left y-axis), serum creatinine (white triangles, left y-axis) and anti-dsDNA antibodies (RIA, right y-axis) are shown. Time is given in weeks (x-axis), with yearly marks. Arrows depict infliximab infusions. Other therapies are depicted as bars below the x-axis.
discontinuation and resolved after infliximab was stopped. This is in line with the observation of Katz et al. [20], who reported severe infusion reactions in six out of nine patients with lupus arthritis treated with infliximab [20], without AZA, MMF or MTX.

Taken together, our long-term follow-up data on 13 infliximab-treated patients with SLE suggest that an induction regimen of four infusions of the TNF-α blocker infliximab, combined with background immunosuppression, can achieve significant improvement in patients with refractory lupus nephritis. Importantly, patients who do not respond to this induction regimen appear to not benefit from further therapy, whereas prolonged TNF-α blockade may be associated with an increased risk of life-threatening adverse events. These observations may help to design the appropriate, randomized, controlled clinical trials required for proving or disproving the concept of TNF blockade as a treatment for SLE.

### Rheumatology key messages

- No SLE flares were observed, but thrombotic events associated with aPL antibodies are of concern.
- Infections and potential lymphoma may be a consequence of prolonged TNF-α blockade in SLE patients.
- Short-term TNF-α blockade may induce long-lasting remissions in lupus nephritis, but not in lupus arthritis.

### Acknowledgements

The authors want to thank all the patients for allowing us to present their data. We would also like to particularly acknowledge the role of Dr Thomas Karonitsch, Dr Peter Petera, Dr Georg Schett and Dr David Thickett in sharing the care for patients involved or preparation of this manuscript, or both.

**Disclosure statement:** M.A. has received grant support and support for a controlled trial of infliximab in SLE from Centocor, the manufacturer of infliximab, and has received occasional consulting fees from Wyeth. J.S.S. has received honoraria and grants/research support from Centocor and Schering-Plough. All other authors have declared no conflicts of interest.

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