SCIENTIFIC CORRESPONDENCE

Campath-1H therapy in refractory ocular inflammatory disease

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Abstract

Background—Standard therapy for severe, immune mediated, ocular inflammation has significant side effects, and may fail to control the disease. T cell directed monoclonal antibody (mAb) therapy can provide long term remission of inflammatory disease in experimental models. The Campath-1H mAb was administered to patients with severe, refractory, ocular inflammation.

Methods—10 patients with severe, refractory, non-infectious ocular inflammatory disease were treated with Campath-1H mAb. This is a fully humanised mAb which recognises the pan-lymphocyte antigen CD52.

Results and discussion—Following Campath-1H therapy, all 10 patients showed an initial resolution of their ocular symptoms and signs. Long lasting remissions were achieved in eight patients, in whom baseline immunosuppression could subsequently be reduced to minimal levels. The possible mechanisms of action of Campath-1H therapy are discussed.

Non-infectious ocular inflammatory disease represents a wide spectrum of immune mediated pathology, which may result in severe visual handicap. In addition to numerous idio-pathic inflammatory conditions specific for the eye, a number of systemic conditions, such as Wegener’s granulomatosis, Behçet’s disease, and sarcoidosis, also have serious ocular complications. Immunosuppression is generally effective in controlling these conditions, using systemic corticosteroids plus adjunctive therapy with cyclosporin A, cyclophosphamide, azathioprine, or newer agents such as FK-506 and mycophenolate mofetil. There is usually a requirement for chronic therapy, however, with associated toxicity, and there is also a subset of patients who are refractory to even the most aggressive regimens. The ideal therapy would, therefore, provide long term remission of inflammatory disease following a short course of treatment, and also be effective across the severity spectrum. In animal models of immunopathology, anti-T cell monoclonal antibody (mAb) therapy achieves such effects by inducing antigen specific unresponsiveness and immunoregulation. Similar immunomodulatory mAb therapy has been used in patients with aggressive autoimmune and inflammatory diseases and, occasionally, long term responses have followed short term treatment. Campath-1H is a humanised mAb which recognises the pan-lymphocyte antigen CD52, and which has been used in such circumstances. Beneficial effects were transient in some conditions, such as rheumatoid arthritis, but were longstanding in others such as multiple sclerosis. In cases of severe refractory vasculitis, remissions of several years’ duration were achieved. In addition, single case studies have reported the success of Campath-1H therapy in controlling severe posterior uveitis and in preventing recurrent corneal graft rejection, both cases refractory to conventional immunosuppression. We now present data on a cohort of 10 patients treated with Campath-1H for severe, refractory, non-infectious, immune mediated, intraocular and orbital inflammatory disease, and recurrent corneal allograft rejection.

Methods and patients

Patients with refractory, non-infectious, ocular inflammatory disease were offered therapy with Campath-1H mAb on a compassionate, “named patient” basis. The indications for therapy are shown in Table 1. Patients 1, 3, 4, and 9 had ocular disease as a complication of a systemic inflammatory disease, although the latter was clinically inactive at the time of Campath-1H treatment. In all patients vision was already severely impaired, and was continuing to deteriorate despite conventional therapy with, most commonly, prednisolone, cyclosporin A, and azathioprine. These drugs were titrated to maximum recommended doses, unless limited by toxicity. Campath-1H was administered by intravenous infusion at 10–12 mg daily for 5 days; patients 2 and 4 received two courses of therapy. Patients were monitored closely after therapy, both ophthalmologically, and also systemically for adverse reactions.
Table 1  Clinical course of patients with immuno-inflammatory ocular disease treated with Campath-1H (C1H) monoclonal antibody

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>C1H indication</th>
<th>Previous therapy</th>
<th>C1H dose (mg)</th>
<th>Current clinical status*</th>
<th>Current daily therapy</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†‡ 70</td>
<td>Rheumatoid slerokeratits: left recurrent corneal graft rejection</td>
<td>Refractory to treatment</td>
<td>Pred, Aza, CsA</td>
<td>60</td>
<td>Clear graft for 24 months, then proteus keratitis resulting in enucleation of left eye. Melt right eye, controlled with CsA</td>
<td>Pred (7.5 mg) CsA (2.5 mg/kg)</td>
<td>72</td>
</tr>
<tr>
<td>2 39</td>
<td>Diabetic proliferative retinopathy: recurrent corneal graft rejection and secondary glaucoma</td>
<td>Refractory to treatment Toxicity</td>
<td>Pred, Aza, CsA</td>
<td>120</td>
<td>Clear graft</td>
<td>Pred (8 mg) No antiglaucoma medication</td>
<td>25</td>
</tr>
<tr>
<td>3 68</td>
<td>Wegener's granulomatosis: sclerosis/PUK/ perforated globe</td>
<td>Refractory to treatment</td>
<td>Pulsed IV methylpred, cyclo</td>
<td>60</td>
<td>Resolution of PUK, and ENT symptoms</td>
<td>Pred (10 mg)</td>
<td>8</td>
</tr>
<tr>
<td>4 61</td>
<td>Wegener's granulomatosis: orbital pseudotumour</td>
<td>Refractory to treatment</td>
<td>Pred, Cyclo, Aza, cycloph, Dxt</td>
<td>60 (5/97)</td>
<td>Initially improved Relapse requiring 2nd course, followed by improved orbital disease and resolution of pseudotumour on CT scan</td>
<td>Pred (5 mg alternate days)</td>
<td>12 (from 2nd course)</td>
</tr>
<tr>
<td>5‡ 46</td>
<td>Non-infectious retinal vasculitis</td>
<td>Toxicity Refractory to treatment</td>
<td>Pred, Aza, CsA, Ivlg</td>
<td>60</td>
<td>Improved</td>
<td>Pred (15 mg) at time of death</td>
<td>15 (died, myocardial infarction)</td>
</tr>
<tr>
<td>6 58</td>
<td>Non-infectious retinal vasculitis</td>
<td>Toxicity</td>
<td>Pred, Aza, CsA</td>
<td>60</td>
<td>Improved (relapse of anterior uveitis only)</td>
<td>Pred (5 mg) FK 506 (0.05 mg/kg)</td>
<td>22</td>
</tr>
<tr>
<td>7 38</td>
<td>Non-infectious retinal vasculitis</td>
<td>Refractory to treatment Toxicity</td>
<td>Pred, MM, CsA</td>
<td>60</td>
<td>Improvement Relapse anterior uveitis only</td>
<td>Pred (15 mg)</td>
<td>5</td>
</tr>
<tr>
<td>8 57</td>
<td>Sympathetic ophthalmia</td>
<td>Refractory to treatment Toxicity (CyA)</td>
<td>Pred, CsA</td>
<td>60</td>
<td>No further deterioration Blood pressure and renal function stabilised off CsA</td>
<td>Pred (10 mg)</td>
<td>5</td>
</tr>
<tr>
<td>9 51</td>
<td>Behçet's disease</td>
<td>Refractory to treatment Toxicity</td>
<td>Pred, Aza, CsA</td>
<td>50</td>
<td>Improved retinal inflammation Relapse anterior uveitis only Stable CNS signs</td>
<td>CsA Pred Thalidomide</td>
<td>18</td>
</tr>
<tr>
<td>10 42</td>
<td>Non-infectious retinal vasculitis</td>
<td>Refractory to treatment, other eye enucleated from secondary rubecotic glaucoma 6 years previously</td>
<td>Pred, CsA, Aza</td>
<td>60</td>
<td>Improvement and resolution of rubecosis</td>
<td>Pred (7 mg) CsA (200 mg)</td>
<td>14</td>
</tr>
</tbody>
</table>

*Improvement was noted by one or more of resolution of orbital clinical signs; maintained clarity of corneal graft and no further rejection episodes; resolution of vasculitic peripheral corneal melting episodes; improved visual acuity; resolution of intraocular inflammation.
†‡Previously published case reports. Now longer follow up.1, 4
PUK = peripheral ulcerative keratitis; Pred = prednisolone; Aza = azathioprine; CsA = cyclosporin A; Cyclo = cyclophosphamide; Dxt = radiotherapy; Ivlg = intravenous gammaglobulins; MM = mycophenolate mofetil.

**Results and discussion**

Following Campath-1H all patients showed initial improvement with an increase in visual acuity, resolved clinical inflammation, or maintenance of corneal graft function. In one patient (case 4) an initial improvement was followed by a relapse of disease, which was controlled with a higher dose (150 mg) of Campath-1H. Case 2 required two courses of Campath-1H (total dose of 120 mg) to suppress ongoing corneal allograft rejection. Some patients experienced a mild first dose reaction but toxicity was otherwise minimal, and no patient sustained refractory and/or opportunistic infections. Furthermore, it was usually possible to substantially reduce baseline immnosuppression after Campath-1H.

These data suggest that ocular immuno-inflammatory disease is a particularly sensitive target for T cell mAb therapy. Despite progressive, sight threatening pathologies refractory to treatment, remission was achieved with Campath-1H therapy in eight of 10 patients. It was then possible to reduce baseline immnosuppression to very low levels. Disease was stabilised, and became easier to control in the remaining two patients (cases 8 and 9). The mechanism by which Campath-1H achieved these effects is currently unknown. Infectious tolerance in animal models is achieved with non-depleting mAbs, and invokes regulatory mechanisms that seem to operate within the antigen presenting cell microenvironment but which have not yet been fully defined.2 In contrast, Campath-1H is a lymphocytotoxic mAb and, while total peripheral blood lymphocyte (PBL) numbers return to normal after therapy, there is a protracted reduction in CD4+ PBL counts, with inversion of the CD4:CD8 ratio. It is conceivable that Campath-1H facilitates the re-establishment of ocular immunoregulation by altering lymphocyte subset ratios, but both autoaggressive and regulatory T cells reside within the CD4+ subset2 and, without more specific markers for these cells, it will remain difficult to explain...
the beneficial effects of Campath-1H. Additionally, until its actions are more fully understood, this treatment should not be viewed as a panacea for non-infectious ocular immune-inflammatory disease. Although the long term lymphopenia that follows Campath-1H therapy has not been linked to an increased risk of infection or malignancy in any of the conditions treated, follow up remains relatively short. Notwithstanding such reservations, Campath-IH appears to be a very useful agent in ocular inflammation and we would encourage its further application, on an experimental basis, in difficult and refractory cases.

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