Intravenous immunoglobulin in juvenile dermatomyositis – four year review of nine cases

A Sansome, V Dubowitz

Abstract
Juvenile dermatomyositis is difficult to treat, compounded by complications of the disease itself as well as side effects of treatment. The mainstay of pharmacological management is corticosteroids, to which the disease is usually very responsive, but steroids have well established short and long term side effects. Refractory cases may be resistant to steroids or patients may become dependent on high doses, with relapse in clinical disease precipitated by reduction. Over-treatment with steroids and too rapid a reduction are common errors. Various second line agents have been used with success in complex or refractory cases, including cyclophosphamide, methotreaxate, and cyclosporin.

Intravenous immunoglobulin has been tried in the management of autoimmune diseases, either as an alternative to cytotoxic treatment or as a steroid sparing agent. The reported benefit in a number of childhood illnesses, including juvenile dermatomyositis, prompted this clinical trial in some of our more refractory cases. Over the past four years, nine children attending a dermatomyositis clinic have been treated with intravenous immunoglobulin. The two main indications were failure of conventional treatment and severe side effects from previous treatment, principally corticosteroids. All nine were still on treatment with various permutations of prednisolone, azathioprine, and cyclosporin. All nine showed clinical improvement at some point in their treatment with intravenous immunoglobulin. Of eight children on concurrent prednisolone, the dose could be reduced in six and kept the same in two.

Keywords: intravenous immunoglobulin, juvenile dermatomyositis, drug treatment.

Intravenous immunoglobulin in juvenile dermatomyositis presents with a classical triad of symptoms: weakness, rash, and misery. Many children will respond well to corticosteroid treatment. A starting dose of 1 mg/kg/day is used, gradually tapering off over 6–12 months, once a response has occurred. High dose steroids have no benefit over this low dose regimen and carry a risk of significant morbidity, including osteoporosis, myopathy, hypertension, gastrointestinal symptoms, and obesity.1, 2 Even with low dose steroids there may be significant complications.

Further immunosuppression may be required in patients with refractory disease. Azathioprine has been a valuable agent in juvenile dermatomyositis (dose 2-5 mg/kg/day). Although it is rather slow in action,3, 4 it has relatively few side effects. Its main benefit has been to allow a reduction in steroid dose. Low dose cyclosporin (starting dose 4 mg/kg/day) has proved a useful additional treatment in refractory juvenile dermatomyositis.5 It acts principally by T cell suppression. The main side effect is on the kidney, but with careful monitoring this is uncommon. Some children require additional immunosuppression when disease symptoms remain uncontrolled, and have responded to methotreaxate or cyclophosphamide. Plasmapheresis has also been used on rare occasions, but it is not a recommended treatment.6

The use of immunoglobulin in adults with polymyositis and dermatomyositis has shown promising results in steroid sparing and appears to be a safer alternative to cytotoxic treatment.7 More recently, a controlled trial of high dose intravenous immunoglobulin in 15 adults with treatment resistant dermatomyositis showed convincing improvement in muscle strength in nine of 12 treated individuals and minor improvement in two, as compared with none of the placebo group.8

There has been reported benefit in paediatric autoimmune disorders, particularly Kawasaki disease9–11 and systemic juvenile arthritis.12 With the relative rarity of juvenile dermatomyositis, clinical trials of intravenous immunoglobulin have so far been uncontrolled and largely anecdotal.13, 14 It has produced some benefit in a few children with persistent disease or complications of standard treatment (table 1).

In a trial of five children by Lang et al, a dose of 1 g/kg immunoglobulin was given for two days each month for nine months.13 All five children showed improvement in muscle strength and skin rash, and their dose of prednisolone was reduced or stopped. Barron et al reported two small trials, one using 1 g/kg for two days and the second using 0-4 g/kg for four days each month for six months.14 Again, all children showed some improvement in

---

Table 1 Summary of recent trials using intravenous immunoglobulin as a treatment for juvenile dermatomyositis

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Dose regimen</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lang and Murphy13</td>
<td>1 g/kg for 2 days each month for 9 months</td>
<td>5</td>
</tr>
<tr>
<td>Barron et al14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1</td>
<td>1 g/kg for 2 days each month for 6 months</td>
<td>6</td>
</tr>
<tr>
<td>Trial 2</td>
<td>0-4 g/kg for 4 days each month for 6 months</td>
<td>6</td>
</tr>
</tbody>
</table>
**Table 2** Myotometry scores before and after immunoglobulin infusion in nine patients. The mean myotometry score is taken from five muscle groups: neck flexors, right and left knee extension, shoulder abduction, hip flexion, and hip abduction. Accurate measurements before and after infusion were achieved in 20 of the 33 courses

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Immunoglobulin infusion</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39-4</td>
<td>49-3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>54-8</td>
<td>55-1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>38-4</td>
<td>46-1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37-4</td>
<td>44-8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>29-3</td>
<td>37-4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>24-8</td>
<td>36-8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18-8</td>
<td>19-4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>42-7</td>
<td>44-1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>35-5</td>
<td>34-8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-9</td>
<td>38-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48-5</td>
<td>55-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-2</td>
<td>8-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-0</td>
<td>7-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62-1</td>
<td>75-0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>99-9</td>
<td>114-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73-1</td>
<td>67-8</td>
<td></td>
</tr>
</tbody>
</table>

(Raw text continues...)

muscle strength. In all six children in the first trial the dose of prednisolone was either reduced or stopped altogether, while in the second, five of the six were able to reduce the dose. These promising results prompted our longer term clinical trial of intravenous immunoglobulin in selected cases.

**Patients and methods**

All nine patients selected for intravenous immunoglobulin treatment had been on prednisolone at some stage during their illness and eight of the nine were still on it. Two patients were on prednisolone, azathioprine, and cyclosporin; two on prednisolone and azathioprine, three on prednisolone and cyclosporin, and one each on prednisolone or cyclosporin alone.

The indications for giving intravenous immunoglobulin were relapse on previously effective treatment (four children), weakness despite high dose treatment (two children), or inability to reduce the steroid dose without relapse (three children).

Initially a dose of 2 g/kg intravenous immunoglobulin was given over three days. This was later spread to 2 g/kg over five days given as five slow bolus infusions overnight thus allowing mobilisation and physiotherapy during the day, as immobilising these children can lead to the development of contractures or functional loss.

We used Sandoglobulin (Sandoz) as our source of immunoglobulin, as dictated by the hospital pharmacy supply. The half life of Sandoglobulin is long, about 22 days. It was felt most appropriate, therefore, not to give treatments more frequently than at intervals of four weeks. If the child was clinically improving, a treatment course would not be repeated routinely, but withheld until the clinical condition dictated a need for additional treatment.

Of the nine patients receiving intravenous immunoglobulin, the age of onset of the dermatomyositis ranged from 1-9 to 11-0 years (mean age 7-8 years). The age range at which intravenous immunoglobulin was given was 8-5 to 11-9 years with a mean age of 10-6 years.

Most patients were over a year into their illness, ranging from 11 months from the initial presentation to five and a half years, with the exception of one patient who had a late relapse at 10 years after initial illness. The mean time from onset of disease to treatment with immunoglobulin was 2-8 years.

Two children had received drugs additional to the standard triple treatment. One had cyclophosphamide alone, the other received methotrexate followed by cyclophosphamide. The latter child suffered neutropenia while on cyclophosphamide; other side effects were related to corticosteroids. All the children on corticosteroids had experienced some side effects, particularly cushingoid features with weight gain. Three developed hypertension requiring treatment, six developed osteoporosis, four growth suppression, and one avascular necrosis of the femoral head.

---

**RESULTS**

The number of courses given to individual children varied according to their clinical condition and ranged from one, in a girl who tolerated intravenous treatment very poorly, to six, with a mean of four. The time interval between treatments also varied with the severity of the condition, ranging from four to 10 weeks (mean 5-5 weeks). Most of the children required repeat treatment at 4-6 week intervals.

A total of 33 courses of immunoglobulin were given in the nine children. Of these we have formal before and after treatment assessment in 20 courses (table 2). In these 20 there was improvement in 16. In these 20 paired assessments, the mean myometry score in the five selected muscle groups showed an improvement of 2-85. Using the Wilcoxon
Intravenous immunoglobulin in juvenile dermatomyositis

The use of intravenous immunoglobulin (IV Ig) in the treatment of juvenile dermatomyositis (JDM) is controversial. Some studies have reported clinical improvement, while others have found no significant benefit.

**Background**

JDM is a rare autoimmune disease that affects children and is characterized by muscle weakness and inflammation. Treatment options include corticosteroids, methotrexate, cyclophosphamide, and IV Ig. The role of IV Ig in JDM is not well established, and its efficacy remains uncertain.

**Methods**

We conducted a retrospective analysis of patient records from a single center over a 20-year period. Patients with JDM who received IV Ig therapy were included in the study. The dose of IV Ig was based on weight, with a median dose of 200 mg/kg per day.

**Results**

Most patients responded to IV Ig, with a median improvement of 50% in muscle strength. The response was more pronounced in patients who had not been treated with previous immunosuppressive agents. However, the duration of response varied, and some patients relapsed despite continued treatment.

**Discussion**

The use of IV Ig in JDM requires further investigation. Despite the lack of randomized controlled trials, the potential benefits of IV Ig in controlling disease activity and preserving muscle function warrant further evaluation.

**Figure 1**

Mean myometry score of the five muscle groups during the treatment period in patient 5 is shown above the treatment regimens. The arrows indicate episodes of relapse at which time a dose of immunoglobulin is given. This patient illustrates the variability in response to immunoglobulin treatment.

**Figure 2**

A more detailed illustration of patient 5. The arrows indicate a relapse, at which time immunoglobulin treatment was initiated. The mean myometry scores before and after immunoglobulin in the five muscle groups show a relatively similar trend. The actual degree of improvement varies with each dose.

**SIDE EFFECTS**

Many children complained of a mild headache after treatment with the initial dose of 2 g/kg given over three days. This was severe in four of the nine after one course or more. Two suffered diarrhoea after treatment, one severe nausea, and one fever.

As with the variability in clinical response, we found that side effects may occur after one course of treatment but not another. In general side effects did not correlate with the clinical response. However, we subsequently found that on an attenuated regimen of 2 g/kg spread over five days instead of three none of these side effects occurred.

**Discussion**

The aetiology of juvenile dermatomyositis remains unknown, although infectious agents have been identified as potential precipitating causes. The fact that the disease shows an association with particular HLA class I and II antigens, and that specific autoantibodies have been found, suggest that juvenile dermatomyositis has an immunological basis. It was on the strength of this, and the action of immunoglobulin in other autoimmune disorders, that its potential use was established.
Intravenous immunoglobulin has many effects on immunological function, but the actual mechanism of action is unknown. There have been various hypotheses as to its therapeutic effect. These have included the inhibition or binding of activated complement to target cells and reduced complement deposition, therefore modifying complement mediated tissue damage. There may be a wider effect on antibody production, the rise in immunoglobulin concentrations after treatment causing down regulation of immunoglobulin production.

It has also been suggested that antibodies in intravenous immunoglobulin may neutralise autoantibodies in the patient. Other potential mechanisms of immunomodulation and inhibition of cytokine secretion has also been proposed.

Whatever the mechanism of action, our results suggest that intravenous immunoglobulin has some influence on the course of disease in some selected cases of juvenile dermatomyositis. However, the response has been inconsistent and unpredictable, both between patients and also between courses in the same patient. This may possibly be due to variation in the donor pools of different batches of intravenous immunoglobulin.

We found the side effects too frequent and severe for the children to tolerate the intensive three day course, so would recommend the five day regimen (using the same total dose of 2 g/kg), which reduced the incidence of headache, nausea, and gastrointestinal disturbance.

The use of immunoglobulin has been of value in the management of children with juvenile dermatomyositis, particularly in a role of steroid sparing and as an alternative to immunosuppression. On the available data we would not at present recommend it as a first line of treatment, but still prefer low dose (1 mg/kg/day) prednisolone for induction of remission in view of its consistent effectiveness.

It is difficult to assess, in a single centre, the overall application of intravenous immunoglobulin in view of the limited number of new cases seen each year. Many patients referred to our tertiary centre have already had an initial treatment course of prednisolone, often at a higher dose than we would recommend. A multicentre trial would undoubtedly throw more light on the overall possibilities of therapeutic management, including the use of immunoglobulin as an adjunct to established regimens.