Pulse steroid therapy in rheumatoid arthritis: Can equivalent doses of oral prednisolone give similar clinical results to intravenous methylprednisolone?

MALCOLM D SMITH, MICHAEL J AHERN, PETER J ROBERTS-THOMSON

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SUMMARY  Pulse methylprednisolone therapy has dramatic effects on clinical and immunological parameters of disease activity in patients with rheumatoid arthritis. Previous studies of this treatment have all used the intravenous route and methylprednisolone succinate. This study addresses the question of whether oral prednisolone in equivalent doses can substitute for intravenous methylprednisolone in pulse therapy in a double blind parallel study. It is shown that oral prednisolone has clinical and immunological effects equivalent to those of intravenous methylprednisolone, making it possible to administer pulse therapy to patients with rheumatoid arthritis as outpatients without the inconvenience and inherent dangers of intravenous administration.

Pulse methylprednisolone therapy has been used for several years as a treatment for active synovitis for patients with rheumatoid arthritis (RA). Previous studies have examined the response to conventional doses of oral prednisolone or ‘megadoses’ of intravenous methylprednisolone, but no studies have considered whether equivalent doses of oral prednisolone would produce the same clinical effects as megadoses of methylprednisolone administered intravenously. We therefore examined the clinical response and side effects resulting from equivalent oral and intravenous doses of corticosteroids in a double blind manner to see whether oral pulse therapy was an effective substitute for intravenous pulse therapy in rheumatoid arthritis.

Patients and methods

Twenty four patients with definite rheumatoid arthritis (American Rheumatism Association criteria) and active joint disease were prospectively entered into the study and randomly assigned to two patient groups. Clinical details of both patient groups are presented in Table 1; four patients in group 1 and five patients in group 2 started with a new suppressive agent at the time of receiving pulse

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>58.9 (42-69)</td>
<td>62.4 (48-74)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:7</td>
<td>4:8</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>6.4 (3-10)</td>
<td>7.2 (2-12)</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs*</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Gold</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>D-Penicillamine</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>VAS pain (cm)*</td>
<td>7.0 (0-6)</td>
<td>6.9 (2)</td>
</tr>
<tr>
<td>VAS mobility (cm)</td>
<td>6.1 (0-6)</td>
<td>6.4 (0-4)</td>
</tr>
<tr>
<td>Duration of morning stiffness (min)</td>
<td>228 (32)</td>
<td>238 (30)</td>
</tr>
<tr>
<td>Articular index</td>
<td>26 (2-2)</td>
<td>27.6 (2-6)</td>
</tr>
<tr>
<td>ESR (mm/h)*</td>
<td>56.7 (10)</td>
<td>74.9 (9)</td>
</tr>
<tr>
<td>CRP (mg/l)*</td>
<td>64.6 (17.8)</td>
<td>94.9 (17.5)</td>
</tr>
<tr>
<td>Rheumatoid factor (IU/ml)</td>
<td>1297 (611)</td>
<td>2014 (810)</td>
</tr>
<tr>
<td>Immune complexes (units/ml)</td>
<td>27.6 (8-6)</td>
<td>36.2 (9-6)</td>
</tr>
<tr>
<td>Pulse treatment given</td>
<td>Active oral</td>
<td>Active intravenous</td>
</tr>
</tbody>
</table>

*NSAIDs=non-steroidal anti-inflammatory drugs; VAS=visual analogue score; ESR=erythrocyte sedimentation rate; CRP=C reactive protein.
+Values are mean (SEM).

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Correspondence to Dr Malcolm D Smith, Department of Immunology, Flinders Medical Centre, Bedford Park, South Australia 5042.
therapy. There were no significant differences between the two treatment groups at the time of entry into the study. Clinical assessments were made before the start of the study and at 2, 4, 8, 12, 16, 20, and 24 weeks after receiving pulse therapy. Clinical parameters assessed were visual analogue scale for pain (VAS pain) and mobility (VAS mobility), duration of morning stiffness, grip strength (mmHg), and articular index (Ritchie method). Laboratory parameters were assessed at the same time as clinical parameters and included C reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor, circulating immune complex levels (by Clq liquid phase assay),7 and immunoglobulin levels (IgG, IgM, and IgA). Neutrophil and lymphocyte counts were measured as well as T cell markers (helper subset, supressor subset, class II major histocompatibility complex (MHC) positive cells) and B cells using monoclonal antibodies and standard immunofluorescence techniques on mononuclear cells prepared on Ficoll-Hypaque gradients.8 Patients were included in the study if the following criteria were met: definite rheumatoid arthritis of at least six months' duration, articular index greater than 10, CRP estimation greater than twice the normal range (normal <6 mg/l), ESR greater than twice the upper limit of normal (normal <10 mm/h), and duration of morning stiffness exceeding 60 minutes.

Patients were given both an intravenous infusion (over 40 minutes by an infusion pump) and oral medication, with only one of these containing the active treatment. The active medication was given as 1 g intravenous methylprednisolone succinate or 1 g oral prednisolone (40×25 mg tablets). All medications were prepared and administered in a double blind fashion with matching placebos consisting of either compound lactose tablets or 100 ml intravenous saline. Patients were given the same treatment at the same time in the morning on three successive days.

Response was defined as a greater than 50% reduction in three or more of the clinical parameters of disease activity and relapse was defined as an increase of greater than 30% in three or more of the clinical parameters of disease activity compared with the lowest value for each parameter before or after treatment. The time of relapse was defined as that time when the first clinical parameter increased to greater than 30% above the lowest value obtained.

**Statistics**

Analysis of between group differences was performed by the Scheffe method of one way analysis of variance.
Analysis of within group effects with time was performed using a multiple analysis of variance and Bonferroni's method for multiple comparisons. Statistical significance was accepted at the 5% level.

An estimate of the β error in the study was made.9 With a 90% response rate in the intravenous methylprednisolone group and a significance of 5%, we would not be able to detect any less than a 35% difference between the two treatment groups in this study.

Results

There were 12 patients in each treatment group, one group receiving intravenous methylprednisolone and placebo tablets, while the other group received oral prednisolone and intravenous saline. Mean duration of response was 13 weeks in the group receiving the active oral preparation and 13.6 weeks in the group treated with the active intravenous preparation. Two patients in each group had not relapsed at completion of the study and one patient in the active oral preparation group had a duration of response of less than four weeks.

The effects of pulse therapy on the clinical and laboratory parameters of disease activity and on neutrophil and lymphocyte counts and cell surface markers are presented in Figs 1–7 and Tables 2 to 4.

Analysis of effect of time, within groups, showed significant changes (p<0.05) in VAS pain and mobility, duration of morning stiffness, grip strength, and articular index up to 16 weeks follow up compared with pretreatment levels in both groups. CRP, immune complexes, IgA, and rheumatoid factor levels were also significantly decreased in both groups up to eight weeks follow up in both groups, but no significant change was seen in either group for IgG and IgM levels or for neutrophil and lymphocyte counts when compared with pretreatment levels. There were no significant

![Fig. 3](image-url) **Fig. 3** Effect of oral and intravenous pulse therapy on duration of morning stiffness. Error bars indicate standard error of the mean.

![Fig. 4](image-url) **Fig. 4** Effect of oral and intravenous pulse therapy on articular index. Error bars indicate standard error of the mean.
changes in any of the lymphocyte subsets measured in either group at any period of follow up when compared with pretreatment values.

Between group assessments did not show any significant difference between the two treatments at any of the follow up times for any of the clinical or laboratory parameters measured, though there was a trend towards greater response in the group treated with intravenous methylprednisolone.

Side effects were minimal with either treatment, though one patient had a gastrointestinal haemorrhage four weeks after receiving intravenous methylprednisolone succinate which may have been related to the pulse therapy or the non-steroidal anti-inflammatory drug (NSAID), sulindac, concurrently being taken. One patient developed an infection as a direct result of the intravenous method of treatment.

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Oral pulse therapy in rheumatoid arthritis

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Fig. 5  Effect of oral and intravenous pulse therapy on C-reactive protein. Error bars indicate standard error of the mean.

Fig. 6  Effect of oral and intravenous pulse therapy on erythrocyte sedimentation rate. Error bars indicate standard error of the mean.

Fig. 7  Effect of oral and intravenous pulse therapy on circulating immune complex levels. Error bars indicate standard error of the mean.
### Table 2  Effect of pulse therapy on rheumatoid factor and immunoglobulin levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Day 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>Active oral</td>
<td>1297</td>
<td>926</td>
<td>1360</td>
<td>1432</td>
<td>1422</td>
<td>1406</td>
<td>1403</td>
</tr>
<tr>
<td>Factor (units/ml)</td>
<td>Active intravenous</td>
<td>(611)*</td>
<td>(427)</td>
<td>(694)</td>
<td>(627)</td>
<td>(629)</td>
<td>(632)</td>
<td>(632)</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>Active oral</td>
<td>2014</td>
<td>1143</td>
<td>1034</td>
<td>1955</td>
<td>1628</td>
<td>1323</td>
<td>1312</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(810)</td>
<td>(491)</td>
<td>(351)</td>
<td>(760)</td>
<td>(685)</td>
<td>(679)</td>
<td>(681)</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>Active oral</td>
<td>13-37</td>
<td>11-03</td>
<td>16-67</td>
<td>11-67</td>
<td>11-67</td>
<td>11-22</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(1-13)</td>
<td>(1-08)</td>
<td>(1-09)</td>
<td>(1-44)</td>
<td>(2-23)</td>
<td>(0-69)</td>
<td>(0-7)</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>Active oral</td>
<td>1-75</td>
<td>1-52</td>
<td>1-67</td>
<td>1-88</td>
<td>1-47</td>
<td>0-94</td>
<td>0-68</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-28)</td>
<td>(0-24)</td>
<td>(0-35)</td>
<td>(0-37)</td>
<td>(0-54)</td>
<td>(0-28)</td>
<td>(0-23)</td>
</tr>
</tbody>
</table>

*Values are mean (SEM).

### Table 3  Effect of pulse therapy on neutrophil, lymphocyte, and lymphocyte subset numbers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Day 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count × 10^9/l</td>
<td>Active oral</td>
<td>6-9</td>
<td>6-5</td>
<td>6-2</td>
<td>6-2</td>
<td>5-34</td>
<td>4-7</td>
<td>5-2</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-74)*</td>
<td>(0-79)</td>
<td>(0-74)</td>
<td>(1-03)</td>
<td>(1-01)</td>
<td>(1-7)</td>
<td>(0-44)</td>
</tr>
<tr>
<td>Lymphocyte count × 10^9/l</td>
<td>Active oral</td>
<td>7-3</td>
<td>6-7</td>
<td>7-2</td>
<td>6-88</td>
<td>6-47</td>
<td>6-73</td>
<td>6-8</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-67)</td>
<td>(0-79)</td>
<td>(0-91)</td>
<td>(0-94)</td>
<td>(1-03)</td>
<td>(0-51)</td>
<td>(1-1)</td>
</tr>
<tr>
<td>OKT4 positive cells × 10^9/l</td>
<td>Active oral</td>
<td>1-84</td>
<td>1-63</td>
<td>1-68</td>
<td>1-74</td>
<td>1-52</td>
<td>1-62</td>
<td>1-77</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-27)</td>
<td>(0-2)</td>
<td>(0-23)</td>
<td>(0-17)</td>
<td>(0-16)</td>
<td>(0-16)</td>
<td>(0-11)</td>
</tr>
<tr>
<td>OKT8 positive cells × 10^9/l</td>
<td>Active oral</td>
<td>1-59</td>
<td>1-49</td>
<td>1-57</td>
<td>1-62</td>
<td>1-89</td>
<td>2-36</td>
<td>1-52</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-19)</td>
<td>(0-15)</td>
<td>(0-13)</td>
<td>(0-19)</td>
<td>(0-24)</td>
<td>(0-28)</td>
<td>(0-2)</td>
</tr>
</tbody>
</table>

*Values are mean (SEM).

### Table 4  Effect of pulse therapy on lymphocyte subsets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Day 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells × 10^9/l</td>
<td>Active oral</td>
<td>1-1</td>
<td>1-16</td>
<td>1-32</td>
<td>1-19</td>
<td>1-089</td>
<td>1-34</td>
<td>1-38</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-2)*</td>
<td>(0-14)</td>
<td>(0-2)</td>
<td>(0-15)</td>
<td>(0-2)</td>
<td>(0-248)</td>
<td>(0-07)</td>
</tr>
<tr>
<td>B cells × 10^9/l</td>
<td>Active oral</td>
<td>1-04</td>
<td>1-18</td>
<td>1-14</td>
<td>1-205</td>
<td>1-195</td>
<td>1-46</td>
<td>1-11</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(0-16)</td>
<td>(0-13)</td>
<td>(0-12)</td>
<td>(0-21)</td>
<td>(0-23)</td>
<td>(0-262)</td>
<td>(0-09)</td>
</tr>
<tr>
<td>MHC class II positive cells</td>
<td>Active oral</td>
<td>250</td>
<td>261</td>
<td>232</td>
<td>301</td>
<td>124</td>
<td>142</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Active intravenous</td>
<td>(98)</td>
<td>(149)</td>
<td>(70)</td>
<td>(95)</td>
<td>(57)</td>
<td>(45)</td>
<td>(30)</td>
</tr>
</tbody>
</table>

*Values are mean (SEM).
Methylprednisolone

beneficial
temporary
Several authors
with active RA.1–6 We have also shown this
significant improvement in patients treated not only
with pulse therapy with intravenous methylprednisolone but also with oral prednisolone. This study
suggests that equivalent doses of oral prednisolone and intravenous methylprednisolone have equivalent clinical and immunological effects, but has not established the minimum dose of either treatment
required to achieve this response. Although it is
possible that larger patient numbers in each treatment group would have demonstrated a statistically
significant difference in favour of the intravenous
pulse, it appears unlikely from this study that this
would outweigh the obvious clinical advantages of
oral pulse therapy. Side effects were minimal with
either treatment despite the theoretical concerns of
high doses of oral corticosteroids on the upper
gastrointestinal tract mucosa.10 Some doubt has
recently been cast on the association of corticosteroid
treatment with gastrointestinal tract ulceration,11–13 and there was no evidence of this side effect in patients who received oral prednisolone pulse therapy. Most studies examining the
relation between steroid therapy and peptic ulcer
have involved much lower doses of oral corticosteroids than those used in this study and there is little
information in the literature on peptic ulcer complications when large doses of oral prednisolone or
intravenous methylprednisolone are administered.
As no significant difference was detected between
the two treatment groups with respect to duration of
remission or effects on the clinical and laboratory
parameters of disease activity measured in this study
it appears that oral prednisolone can safely and
effectively replace intravenous methylprednisolone
in pulse therapy for RA. This would remove the
additional hazards of intravenous cannulation and
administration and allow pulse therapy to be conducted as an outpatient procedure with less interference
to patients and fewer demands on medical and nursing resources.

We thank Dr R Geddes and Dr W Hill for contributing patients
to this study, Mrs J Smith for statistical advice, and Miss B Roylance
for typing the manuscript. M D Smith is a grateful recipient of an
NH and MRC postgraduate scholarship. This study was supported
in part by a grant from the Department of Veterans Affairs.

Discussion

Several authors have shown that intravenous pulse
methylprednisolone therapy has a significant but
temporary beneficial effect on the synovitis of
patients with active RA.1–6 We have also shown this
significant improvement in patients treated not only
with pulse therapy with intravenous methylprednisolone but also with oral prednisolone. This study
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