A clinical study of CPH 82 vs methotrexate in early rheumatoid arthritis

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Abstract

Objectives. The objectives of this study were to evaluate the therapeutic efficacy of CPH 82 in comparison with methotrexate (MTX) in adult patients with early, active rheumatoid arthritis (RA) and to compare the tolerance and safety profiles of the two drugs.

Methods. The study was a 24-week, double-blind, randomized study in 10 centres of 100 patients with active RA, with a disease duration of less than 2 yr at the start of treatment, which consisted of either CPH 82 300 mg/day or MTX 10 mg/week. The six primary effect variables were: number of swollen joints, Ritchie’s articular index, patient’s pain score, patient’s global score, Health Assessment Questionnaire (HAQ) and C-reactive protein (CRP). Erythrocyte sedimentation rate (ESR), physician’s global score and the efficacy according to the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) response criteria were also analysed.

Results. There was a significant improvement for both drugs in all variables. Significant differences between the drugs in favour of MTX were found only in patient’s pain score, CRP and ESR. By the EULAR criteria, 76% and 86% were judged to be responders in the CPH 82 and MTX groups, respectively. By the ACR criteria, the corresponding figures were 58% and 64%. The most common side-effects were gastrointestinal, which were similar in both groups. The numbers of treatment failures due to adverse events were two with CPH 82 and 14 with MTX.

Conclusions. The clinical effect of CPH 82 in this study was comparable to that of MTX at a dose of 10 mg/week. Both drugs reduced acute-phase reactants, MTX more effectively than CPH 82. The safety profile of CPH 82 was more favourable than that of MTX without folic acid supplementation.

Key words: CPH 82, Semi-synthetic lignan glycosides, Methotrexate, Therapy, Rheumatoid arthritis.
drugs was also prescribed during the study. The patients were allowed to take salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs), if necessary. Patients who had been receiving a low and constant maintenance dose of systemic corticosteroids (not exceeding prednisolone 7.5 mg daily or the equivalent) could be admitted. During the study an increase in the dose of systemic corticosteroid was not allowed. However, if a patient improved, a decrease was allowed. Intra-articular injections of corticosteroids were permitted in cases of pronounced synovitis in a single joint combined with functional impairment. However, if these injections were administered within 2 weeks prior to a clinical effect assessment, the patient had to be withdrawn from the study.

Evaluations
For the evaluation of efficacy, the following outcome variables were regarded as primary variables: number of swollen joints, number of tender joints (Ritchie’s articular index; RAI) [8], patient’s pain rating on a visual analogue scale, patient’s global score on a visual analogue scale, Health Assessment Questionnaire (HAQ) index [9, 10] and serum CRP. The number of intra-articular corticosteroid injections served as a secondary effect variable. The physician’s global rating of disease activity and the erythrocyte sedimentation rate (ESR) were also analysed. In addition to what was prescribed by the original study protocol, efficacy was also assessed according to the European League Against Rheumatism (EULAR) response criteria [11] and the American College of Rheumatology (ACR) response criteria [12].

For the evaluation of safety, continuous adverse event monitoring was performed as well as biochemical monitoring, including variables reflecting bone marrow function, liver function and renal function. If a serum value of levels of aminotransferases (ASAT, ALAT) or creatinine exceeded twice the upper limit of the respective normal range, this was considered to be a treatment failure and the patient was withdrawn from the study.

Statistical analysis
Treatment groups were compared using the chi-squared test for binary variables, Wilcoxon’s rank-sum test for ordered categorical variables and the t-test for continuous variables. All the statistical tests were carried out at the 5% level. Efficacy was assessed in terms of change from baseline values for the outcome variables. In cases of premature termination (i.e. before 6 months of treatment), the patient’s last available data were used in the statistical analyses (endpoint analysis). Differences between treatment groups were given as 95% confidence intervals. For primary effect variables and for the physician’s global rating of disease activity and ESR, where the objective was to test for ‘at least as good’, the 95% confidence intervals were one-sided (90% two-sided), otherwise the intervals were two-sided. ‘At least as good’ was defined so that the upper confidence limit was within the equivalence limit, which means that the one-tailed 95% confidence interval for the difference between the groups did not exceed 15% of the range of changes from baseline values.

Results
Baseline data
The treatment groups should have been comparable as a result of randomization. However, a significant difference in mean age between the treatment groups was found. Demographic and clinical data at baseline are given in Table 1.

Therapeutic efficacy
All six primary variables (number of swollen joints, RAI, patient’s pain score, patient’s global score, HAQ and CRP) showed a significant improvement in both the CPH 82 and MTX groups during the 24 weeks ($P < 0.001$).

For the number of swollen joints and RAI, the improvement was about 50%, while for HAQ and patient’s global score, the improvement was about 40%, the differences between the treatment groups being non-significant. The improvement in patient’s pain ratings was 37% in the CPH 82 group and 51% in the MTX group, which represented a significant difference between the groups ($P = 0.036$). The improvement in CRP was 33% in the CPH 82 group and 66% in the MTX group, which was also a significant difference ($P = 0.001$; Table 2).

For three of the six primary variables (number of swollen joints, the patient’s global assessment and HAQ), the upper 90% confidence limit values were within 15% of the equivalence limit. In the remaining two clinical variables (RAI and patient’s pain score), this confidence interval was within the 20% equivalence limit. For CRP, however, the upper 90% confidence interval was outside the 20% equivalence limit, indicating that the acute-phase response in MTX-treated patients was better than that in CPH 82-treated patients.

In addition to the primary variables, the physician’s global ratings and the ESR were also assessed. The physician’s global ratings improved by 48% in the CPH 82 group and by 57% in the MTX group, a difference which was not significant ($P = 0.1$). Consistent with the CRP response, ESR decreased significantly in both groups, by 22% in the CPH 82 group ($P = 0.0097$) and
by 51% in the MTX group ($P = 0.0001$), amounting to a significant difference ($P = 0.0005$).

The analysis of the individual ACR and EULAR responses was made using the values after 24 weeks or the last available values (endpoint analysis). Twenty-nine patients in the CPH 82 group and 32 patients in the MTX group reached ACR20 response criteria. ACR50 response criteria were reached by 13 CPH 82 patients and 20 MTX patients, the differences between groups in both categories (ACR20 and ACR50) being non-significant, $P = 0.539$ and $P = 0.137$, respectively.

According to the EULAR criteria, 23 patients in the CPH 82 group (46%) and 24 patients in the MTX group (48%) reached the criteria for moderate response. The corresponding figures for good response were 15 (30%) and 19 (38%), respectively. There was no significant difference between the groups in EULAR response ($P = 0.22$). Twelve (24%) of the CPH 82 patients and seven (14%) of the MTX patients failed, being non-responders according to the EULAR definition.

Responses to both drugs were parallel in time and near the maximum after 12 weeks of treatment. This improvement persisted throughout the 24 weeks of the study. Five patients in the CPH 82 group and one in the MTX group terminated the study prematurely due to lack of efficacy. There were no significant group differences in the number of patients who terminated prematurely due to lack of response, the number of intra-articular corticosteroid injections given or the number of patients on systemic corticosteroids, NSAIDs or analgesics.

**Safety**

In total, 52 adverse events in the CPH 82 group and 73 in the MTX group were assessed by the investigators as having a possible association with the study drug. In the CPH 82 group, one case each of nausea and diarrhoea and in the MTX group, two cases of leucopenia, three elevated liver enzymes and one each of nausea, diarrhoea, hearing impairment and hyperhidrosis were classified as severe adverse events (Table 3). Gastrointestinal manifestations were the most common adverse events, being characterized by similar frequency, symptomatication and severity in both treatment groups. No patient terminated the study prematurely due to gastrointestinal side-effects.

In the CPH 82 group, two adverse events led to a treatment failure: one case of pruritus and one case of periorbital oedema. In addition, one patient had a transient facial oedema and one patient had transient mild anaemia and leucopenia. No case of liver toxicity was observed in the CPH 82 group. In the MTX group, 14 adverse events led to treatment failure: one progressive leucopenia (minimum 2.8 $\times 10^{9}$/l), one progressive leucopenia with thrombocytopenia (minimum 2.6 $\times 10^{9}$/l and 122 $\times 10^{9}$/l, respectively), 11 increased liver enzymes, one pruritus and rash. There was a significant increase in mean serum levels of ASAT and ALAT in the patients treated with MTX.

**Discussion**

MTX has a well-documented therapeutic effect in the treatment of RA, and rheumatologists in many countries have long experience of its use. However, a considerable number of patients do not tolerate long-term treatment with MTX, due to toxicity to the liver, the lungs, the haemopoietic system and other organs. Moreover, some patients derive insufficient benefit from the drug. Thus, there is obviously a need for alternative drugs, and the purpose of the present study was to investigate whether CPH 82 might be such an alternative, in terms of efficacy and of safety.

The dose of MTX in this study has been under debate. Some rheumatologists would commence with 7.5 mg/week and increase the dose if needed, while others have claimed that the mean dose of MTX currently used is well over 17.5 mg/week. However, unpublished data from the Swedish RA register show that the mean dose of MTX given to RA patients in Sweden within the first 12 months of disease is just below 10 mg/week (S. Lindblad, personal communication).

**Therapeutic efficacy**

Both drugs yielded a significant improvement in all six primary effect variables, and for three of the variables, the response to CPH 82 was at least as good as that of MTX, according to the equivalence criteria used. The results suggest that the clinical effects of CPH 82 300 mg/day and MTX 10 mg/week are essentially the same. Despite the similarity of the two drugs in their effect on clinical variables, the significant difference in

<table>
<thead>
<tr>
<th>Change in outcome variables</th>
<th>CPH 82</th>
<th>MTX</th>
<th>Significance of difference between drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen joints (mean number)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAi (mean score)</td>
<td>19.2</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Patient’s pain score (VAS; mean value)</td>
<td>31.5</td>
<td>51.5</td>
<td></td>
</tr>
<tr>
<td>HAQ index (mean value)</td>
<td>1.21</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>Patient’s global score (VAS; mean value)</td>
<td>51.2</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>Physician’s global score (mean value)</td>
<td>51.4</td>
<td>51.4</td>
<td></td>
</tr>
<tr>
<td>S-CRP (mean value)</td>
<td>48.1</td>
<td>48.1</td>
<td></td>
</tr>
<tr>
<td>ESR (mean value)</td>
<td>46.0</td>
<td>46.0</td>
<td></td>
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Table 2. Change in outcome variables
indicating the possibility of further subsequent increases podophyllotoxin derivative (CPH 82) versus azathioprine and ALAT increased continuously over the 24 weeks. 5. Korpela M, Tiitinen S, Nissila
ects. Eleven
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to toxicity of the haemopoietic system, owing to the with Reumacon. A placebo controlled study. Scand
show decreased serum levels of steroids. Thus, the 1. Larsen A, Petersson I, Svensson B. Podophyllum derivat-occurrence ... the treatment ofin steroid production in patients treated with CPH 82. rheumatoid arthritis. Br J Rheumatol 1989;28:124
We would like to thank Lennart Jo
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Safety
The present findings suggest that the gastrointestinal side-effects of CPH 82 reported in earlier studies have been largely overcome by the introduction of the enteric-coated capsules used in this trial. For both drugs, these side-effects can be reduced or even eliminated by reducing the daily dose. In the case of MTX, folic acid supplementation may also be beneficial.

In the present study, one case of transient facial oedema was reported, which disappeared despite continued treatment. Another patient was withdrawn from the study due to periorbital oedema. The reason for oedema in these two patients and in earlier reported cases is not clear. The swelling has invariably disappeared following discontinuation of the treatment. As in some of the earlier cases of oedema, the two patients in this study had been taking systemic corticosteroids and/or injections of corticosteroids, which may have been a contributory factor. One study of 18 patients with RA (none of whom developed oedema) who had not been treated with systemic corticosteroids during the preceding 24 months showed that the blood levels and urinary excretion of steroids diminished slightly within reference limits in parallel with increases of the daily dose of CPH 82 from 150 to 300 to 450 mg and in parallel with a reduction in disease activity [13]. In other studies, patients with oedema have been found to show decreased serum levels of steroids. Thus, the occurrence of oedema cannot be explained by an increase in steroid production in patients treated with CPH 82. Two patients treated with MTX were withdrawn due to toxicity of the haemopoietic system, owing to the potentially dangerous nature of such side-effects. Eleven patients on MTX were withdrawn due to increased liver enzymes. The study protocol stipulated that any serum value of ASAT or ALAT exceeding twice the upper normal limit should result in premature withdrawal, a rule which is possibly stricter than that which most rheumatologists would follow in clinical practice today. On the other hand, the median values of both ASAT and ALAT increased continuously over the 24 weeks, indicating the possibility of further subsequent increases necessitating dose reduction or drug withdrawal during prolonged treatment. However, some of the premature withdrawals would probably not have been necessary if the current guidelines for monitoring liver toxicity in patients on MTX had been applied in the present study [14].

The clinical effect of CPH 82 in this trial was comparable with that of MTX 10 mg/week. Both drugs reduced acute-phase reactants, MTX more effectively than CPH 82. MTX was associated both with a greater overall prevalence of adverse events and with potentially severe side-effects involving the liver and haemopoietic organs. However, some of the side-effects of MTX, including hepatotoxicity, might have been reduced if folic acid supplementation had been used. An important advantage of CPH 82 over MTX is the lack of contraindications in terms of previous disease of haemopoietic organs, liver or lungs. CPH 82 would, therefore, seem to be a useful alternative to MTX, particularly in patients who do not tolerate MTX well or where pre-existing disease of the liver, lungs or haemopoietic organs constitutes a contraindication for the use of MTX.

Acknowledgements
We would like to thank Lennart Jönnson, Conpharm AB, for skilful monitoring of this multicentre study, Roland Pettersson for very valuable work on the statistical analysis and Conpharm AB for sponsorship of the study.

References
5. Korpela M, Tiitinen S, Nissilä M. Clinical open study of podophyllotoxin derivative (CPH 82) versus azathioprine in treatment of rheumatoid arthritis and reactive (AA)

Table 3. Number of symptoms reported. Each indication represents the maximum severity of the respective adverse event

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal system disorders</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Liver and biliary system disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haemopoietic system disorders</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other different system disorders</td>
<td>19</td>
<td>5</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>10</td>
<td>2</td>
<td>47</td>
</tr>
</tbody>
</table>

*Two cases were not rated for the severity of the hepatic function disorder.