METHOTREXATE TREATMENT IN FELTY’S SYNDROME

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SUMMARY

Felty’s syndrome is a rare disorder characterized as a systemic manifestation of severe rheumatoid arthritis associated with granulocytopenia and splenomegaly. We report a retrospective analysis of a series of seven patients treated successfully with low-dose methotrexate, leading to sustained clinical improvement (number of swollen joints) and normalization of the granulocyte count for an observation period of 1 yr. Our cohort is the largest ever published with methotrexate treatment of this rare condition. Our results confirm earlier single case reports suggesting methotrexate to be the first-choice treatment nowadays in Felty’s syndrome.

KEY WORDS: Felty’s syndrome, Methotrexate therapy, Granulocytopenia.

Patients with severe, long-lasting and seropositive rheumatoid arthritis (RA), leucopenia, especially granulocytopenia, and splenomegaly present the characteristic features of Felty’s syndrome, first described in 1924 by A. R. Felty [1]. Felty’s syndrome is now considered a very rare systemic complication of RA, occurring in <1% of all RA patients [2]. Because of this rarity, controlled studies of different treatment modalities are not available. Encouraged by the experience of an unexpected good response of many patients with ‘refractory RA’ to methotrexate [3], we started to introduce this compound in patients with Felty’s syndrome as early as 1980. In the following years, all patients presenting with active disease in Felty’s syndrome who attended our clinic were routinely treated with low-dose methotrexate. In 1992, we analysed the clinical and laboratory data of these patients retrospectively to verify our impression that methotrexate was safe, effective and well tolerated in these patients.

PATIENTS AND METHODS

Patients labelled as having a diagnosis of Felty’s syndrome were identified using a computerized data bank containing the diagnoses of all patients who were admitted to our hospital between 1978 and 1991. Then we reviewed the records of these patients, and confirmed the diagnosis, if the patients fulfilled the following criteria: RA according to ACR criteria [4], splenomegaly confirmed by ultrasound and granulocytopenia of <2.0 × 10⁹/l recorded at any time during the disease course. Splenomegaly and neutropenia had to be unrelated to any other underlying disease or condition, or to the concomitant therapy. At admission to the hospital, all patients underwent a detailed clinical and physical examination including a complete joint count of swollen and tender joints, X-ray evaluation of hands and feet, as well as routine laboratory parameters including erythrocyte sedimentation rate (ESR), whole blood count and rheumatoid factor titration. Laboratory data were gathered regularly in our department during the first 4 weeks after the initiation of methotrexate therapy. The patients were then followed at regular intervals in our out-patient clinic. Concomitant medication, total joint count and laboratory tests were available for all patients after an interval of 1 yr.

Statistical analysis was performed using Wilcoxon’s signed rank test due to the small number of patients. Student’s t-test was applicable only for the granulocyte count and the swollen joint count, as these data showed a normal distribution confirmed by χ² test. The ESR was not normally distributed.

RESULTS

We identified seven patients with an established diagnosis of Felty’s syndrome who were regarded as having refractory RA followed for at least 1 yr after initiation of methotrexate therapy. Three patients had >2.0 × 10⁹ granulocytes at the time, when methotrexate therapy was started, but these patients had documented granulocytopenia earlier in the course of their disease, thus fulfilling the diagnostic criteria.

Table I shows baseline demographic and clinical characteristics of the seven patients. All patients were female, their mean age was 60.6 yr (range 46–76). The mean disease duration of RA before entering the study was 10.3 yr (range 4–18). All but one patient had positive rheumatoid factor testing, the seronegative patient also showed erosive disease.

Table II shows the clinical data of the patients at baseline (t0) and 4 weeks (t1) and 1 year (t2) after the

| TABLE I |
| Baseline demographic data and RF status |
| Patient no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Mean |
| Age (yr) | 46 | 61 | 76 | 62 | 55 | 59 | 65 | 60.6 |
| Disease duration (yr) | 4 | 8 | 17 | 6 | 18 | 11 | 8 | 10.3 |
| RF status | − | + | + | + | + | + | + | + |

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initiation of methotrexate therapy. Between t0 and t1, there was a statistically not significant increase in the mean granulocyte count from 1.95 to 2.39 × 10^9/l; after 1 yr, the mean granulocyte count was 3.92 × 10^9/l. This change was significant compared to baseline as well as compared to t1. There was also a decrease in the mean ESR from 40.9 mm/h to 29.8 mm/h after 1 month and to 26.6 mm/h after 1 yr, but this change did not reach statistical significance. The mean joint count decreased significantly from 19.0 at baseline to 7.4 after 1 yr. Changes were significant using Wilcoxon’s signed rank test at the level of P < 0.01. Student’s t-test found identical results at almost the same level (P < 0.01 for the granulocyte count and P < 0.05 for the swollen joint count).

**DISCUSSION**

Open studies or case reports with different treatment methods have been published on Felty’s syndrome, usually with small sample sizes, showing a divergent response to splenectomy or splenic embolization [5], d-penicillamine [6], parenteral gold [7, 8], cyclosporin [9] and high-dose i.v. gamma globulin [10]. Granulocyte stimulating factor (GSF) was reported to lead to a normalization of granulocytopenia [11–15], but this treatment is often complicated by a flare of the disease [16, 17]. So the treatment of first choice is still controversial.

Methotrexate therapy has been shown to be effective and well tolerated both in controlled short-term [18–20] and in open long-term observational studies [21, 22] in RA. Several case reports have also been published using methotrexate in Felty’s syndrome [23–31].

Table III lists all published cases that we could identify in the literature.

With the exception of one case [29], they all reported a favourable response. This was achieved even with small doses of methotrexate usually not exceeding 7.5 mg/week. The one patient reported not to improve on methotrexate by Guillemin and Pourel [29] was treated with a 7.5 mg weekly oral dose for a period of only 1 month. As the efficacy of methotrexate is dose dependent, and as it usually takes at least 4 weeks until the effect is noticeable and ~6–12 weeks until the maximum effect is reached [33, 34], the dose and the duration of the treatment in this patient may have been insufficient.

In our study, only one patient showed a slight decrease in the granulocyte count after 1 month of therapy (patient 6), but the granulocyte count of 2.76 × 10^9/l was still within the normal limits and increased during the 1 yr follow-up. In all other patients, the granulocytes increased constantly during treatment. This should therefore be interpreted as a treatment effect.

Some of our patients started methotrexate with a granulocyte count of > 2.0 × 10^9/l. These patients had documented granulocytopenia earlier in the course of their disease unrelated to any other condition, thus confirming the diagnosis of Felty’s syndrome. Spontaneous variations in the granulocyte count occurring in a considerable number of patients in long-term observation have been described before [35].

The indication for starting methotrexate in our patients did not depend primarily on the haematological findings, but was based on a still active rheumatic disease, as documented by the number of swollen joints before treatment. The effect of methotrexate treatment on the clinical status of RA in Felty’s syndrome in the published cases has only been described in general terms, with the exception of three cases. We therefore evaluated the count of swollen joints of all patients and found a significant decrease in the mean number of swollen joints from 19.0 to 7.4 after 1 yr of treatment. There was a complete remission according to the clinical status (no swollen joints and ESR within normal values) in three patients (patients 4, 5 and 6), a substantial improvement in two patients (patients 3 and 7) and an almost unchanged status in two patients (patients 1 and 2).

Of the laboratory signs of inflammation, only the ESR was available for all patients at all time points; the CRP was not regularly recorded. There was a substantial decrease in ESR in four patients (patients 1, 2, 4 and 7), a small increase in two patients (patients 3 and 6) and almost no change in one patient (patient 5). The mean ESR decreased from 50.9 to 26.6, but

**TABLE II**

Clinical characteristics of the patients before and during methotrexate treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes × 10^9/l</td>
<td>1.960</td>
<td>1.276</td>
<td>2.368</td>
<td>462</td>
<td>1.936</td>
<td>3.245</td>
<td>2.419</td>
<td>1.952</td>
</tr>
<tr>
<td>Granulocytes × 10^9/l</td>
<td>2.070</td>
<td>2.310</td>
<td>3.445</td>
<td>1.476</td>
<td>2.025</td>
<td>2.759</td>
<td>2.666</td>
<td>2.389</td>
</tr>
<tr>
<td>ESR (mm/h) t0</td>
<td>50</td>
<td>78</td>
<td>48</td>
<td>29</td>
<td>53</td>
<td>8</td>
<td>20</td>
<td>40.9</td>
</tr>
<tr>
<td>ESR (mm/h) t1</td>
<td>18</td>
<td>52</td>
<td>43</td>
<td>15</td>
<td>50</td>
<td>13</td>
<td>18</td>
<td>29.8</td>
</tr>
<tr>
<td>ESR (mm/h) t2</td>
<td>13</td>
<td>36</td>
<td>58</td>
<td>6</td>
<td>50</td>
<td>16</td>
<td>7</td>
<td>26.6</td>
</tr>
<tr>
<td>Swollen joints (0–38) t0</td>
<td>21</td>
<td>23</td>
<td>17</td>
<td>17</td>
<td>24</td>
<td>13</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Swollen joints (0–38) t2</td>
<td>22</td>
<td>21</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>7.4*</td>
</tr>
</tbody>
</table>
this did not reach statistical significance due to the small numbers and the not normal distribution of the data.

The improvement of clinical and laboratory signs of Felty’s syndrome in our patients was not due to the concomitant therapy, especially not to corticosteroids. Before treatment, only two patients were on low-dose corticosteroids of no more than 5 mg prednisone/day. During the 1 yr of observation, one patient could stop taking corticosteroids and in one patient prednisone was introduced at a dosage of 5 mg/day. The daily dose of prednisone could be reduced from a mean of 1.75 to 0.96 mg after 1 yr of treatment.

Compared with the other published cases, the methotrexate dose in our patients was higher (mean dose 12.86 mg). This may also explain the good response of our patients. Besides this, the therapy was very well tolerated and no major side-effects leading to discontinuation of the therapy occurred.

The time of onset of the effect of methotrexate is usually expected at 4–6 weeks after initiation of therapy [33]. Consistent with these expectations, an increase in the granulocyte count and a decrease in the ESR were already observed after 4 weeks of treatment in our patients, even if this did not reach statistical significance. Allen and Groff [23] observed a response to methotrexate in their patient after several months, Puechal et al. [30] found a dramatic increase in neutrophils within 4 days after i.v. infusion of 25 mg methotrexate. All the other published cases on weekly oral low doses showed a similar onset of improvement after a few weeks, which is concordant with our findings. This effect was sustained in our patients for a period of at least 1 yr. Most of the other published cases (see Table III) reported a comparable or even longer duration of effective treatment. Gerster [32] reported a sustained efficacy on the clinical signs of the disease up to 12 yr despite a decrease in granulocytes after 4 yr of treatment. This might have been avoided by using higher doses of methotrexate in the long-term treatment.

The cause of the neutropenia in Felty’s syndrome is still not sufficiently explained. Several hypotheses have been proposed and numerous factors influencing granulocyte production or survival in peripheral blood have been identified in patients with Felty’s syndrome [24, 36, 37]. Which of these factors plays the most important role is still unclear. Our data cannot contribute to a further clarification of this problem, but as methotrexate is capable of various immunosuppressive actions [38] our findings again stress the important role of immunological factors in the development of neutropenia in Felty’s syndrome.

In conclusion, our data confirm earlier reports that low-dose methotrexate therapy is a safe and effective treatment of Felty’s syndrome and that patients with unexplained neutropenia in RA should not be excluded from methotrexate treatment.

### References


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**Table III**

Published cases of low-dose weekly methotrexate (MTX) in Felty’s syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Author</th>
<th>SwJC t0</th>
<th>SwJC t1</th>
<th>ESR t0</th>
<th>ESR t1</th>
<th>Granulocytes × 10^9/l t0</th>
<th>Granulocytes × 10^9/l t1</th>
<th>MTX dose</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allen and Groff [23]</td>
<td>?</td>
<td>?</td>
<td>55</td>
<td>20</td>
<td>0</td>
<td>2.500</td>
<td>~6.25 mg</td>
<td>30 months</td>
</tr>
<tr>
<td>2</td>
<td>Fiechtner et al. [24]</td>
<td>37</td>
<td>0</td>
<td>48</td>
<td>24</td>
<td>792</td>
<td>2.500</td>
<td>7.5 mg</td>
<td>15 months</td>
</tr>
<tr>
<td>3</td>
<td>Fiechtner et al. [24]</td>
<td>14</td>
<td>2</td>
<td>26</td>
<td>9</td>
<td>300</td>
<td>6.000</td>
<td>7.5 mg</td>
<td>9 months</td>
</tr>
<tr>
<td>4</td>
<td>Fiechtner et al. [24]</td>
<td>36</td>
<td>2</td>
<td>23</td>
<td>9</td>
<td>160</td>
<td>2.500</td>
<td>7.5 mg</td>
<td>14 months</td>
</tr>
<tr>
<td>6</td>
<td>Tan et al. [31]</td>
<td>?</td>
<td>?</td>
<td>64</td>
<td>30</td>
<td>1281</td>
<td>3.266</td>
<td>7.5 mg</td>
<td>24 months</td>
</tr>
<tr>
<td>7</td>
<td>Tan et al. [31]</td>
<td>?</td>
<td>?</td>
<td>49</td>
<td>20</td>
<td>302</td>
<td>2.495</td>
<td>7.5 mg</td>
<td>9 months</td>
</tr>
<tr>
<td>8</td>
<td>Hughes and Abdulla [28]</td>
<td>?</td>
<td>?</td>
<td>109</td>
<td>8</td>
<td>80</td>
<td>&gt; 2.500</td>
<td>7.5 mg</td>
<td>16 months</td>
</tr>
<tr>
<td>9</td>
<td>Isani et al. [25]</td>
<td>?</td>
<td>?</td>
<td>109</td>
<td>?</td>
<td>132</td>
<td>2.700</td>
<td>7.5 mg</td>
<td>1.5 months</td>
</tr>
<tr>
<td>10</td>
<td>Natmelting et al. [26]</td>
<td>?</td>
<td>?</td>
<td>80</td>
<td>28</td>
<td>No detailed information</td>
<td>No detailed information</td>
<td>7.5 mg</td>
<td>1 month</td>
</tr>
<tr>
<td>11</td>
<td>Wollenhaupt et al. [27]</td>
<td>No detailed information</td>
<td>No detailed information</td>
<td>1.760</td>
<td>1.036</td>
<td>7.5 mg</td>
<td>1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Guillemine and Pourou [29]</td>
<td>?</td>
<td>?</td>
<td>45</td>
<td>?</td>
<td>1.760</td>
<td>1.036</td>
<td>7.5 mg</td>
<td>1 month</td>
</tr>
<tr>
<td>14</td>
<td>Gerster [32]</td>
<td>6</td>
<td>2†</td>
<td>?</td>
<td>?</td>
<td>2.400</td>
<td>~ 2.400*</td>
<td>7.5 mg</td>
<td>12 years</td>
</tr>
</tbody>
</table>

*Data reported after 4 days of therapy. †Data reported after 6 months of therapy.