A topic dermatitis (AD) is a frequent chronic inflammatory skin disorder secondary to the activation in the skin of allergen-specific T cells [1-5]. The available therapies for moderate to severe AD include topical agents and systemic drug treatment. Topical agents (corticosteroids, immunomodulators) are very effective but their use is limited by the body surface affected by the eczema [6]. Systemic therapies (UV light therapy and cyclosporine) are associated with immunosuppression and therefore to an increased risk of carcinoma, and lymphoma and nephropathy, respectively. Methotrexate (MTX) is a well-known drug used for more than 40 years at low doses in the treatment of psoriasis [7-9]. Its side-effects mostly affect the bone-marrow, the liver and the lung and are easily prevented by regular clinical and biological follow-up. At the doses used in psoriasis, MTX has no immunosuppressive activity. Recent studies by Genestier et al. have shown that MTX selectively depletes activated T cells by an apoptosis-dependant mechanism without effect on naive and memory T cells [10]. Its side-effects mostly affect the bone-marrow, the liver and the lung and are easily prevented by regular clinical and biological follow-up. At the doses used in psoriasis, MTX has no immunosuppressive activity. Recent studies by Genestier et al. have shown that MTX selectively depletes activated T cells by an apoptosis-dependant mechanism without effect on naive and memory T cells [10]. Since AD lesions are mediated by activated T cells and since MTX has been shown to improve the clinical symptoms of eczema in a model of antigen-specific dermatitis in mice, we hypothesized that MTX could be used to treat AD patients eligible for systemic therapy. We report here on an open retrospective study of 20 patients with moderate to severe AD who received low dose MTX for 3 to 30 months.

Patients and methods

Patients
Twenty patients (ten females and ten males), 17 to 68 years old, received MTX for the treatment of moderate to severe AD from 2002 to 2004. Table 1 summarizes the main characteristics of the patients. These patients were eligible for systemic treatment, i.e. presented with AD with low response to routine treatment or with an affected body surface area too important for local treatment. 14 patients had AD since childhood and 6 as adults. The AD affected the face for 17 patients, the body for 18 patients with flexural folds, the neck, the V neck and the limbs. Only 2 patients had a localisation only on the face but the subjective perceptions of symptoms were severe. The intensity of the disease was classified as mild, moderate and severe according to the following criteria: the degree of itching, the intensity of inflammatory signs (erythema, papulation/infiltration with oozing/crusting) and the body surface area. AD was moderate in 7 patients and severe in 13 patients.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
<th>Beginning of AD</th>
<th>Intensity</th>
<th>Lesion site</th>
<th>Dosage per week during the first 3 months</th>
<th>Treatment Duration</th>
<th>Improvement Time to clinical improvement After 3 months of MTX*</th>
<th>Side Effects during the first 3 months of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>Adult</td>
<td>Moderate</td>
<td>Face</td>
<td>25 mg IM</td>
<td>8 months</td>
<td>6 weeks 80%</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>M</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>25 mg IM</td>
<td>6 weeks</td>
<td>6 weeks 80%</td>
<td>80% not evaluable</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>F</td>
<td>Childhood</td>
<td>Severe</td>
<td>Body</td>
<td>25 mg IM</td>
<td>5 weeks</td>
<td>No improvement</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>F</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>25 mg IM</td>
<td>7 months</td>
<td>1 month 90%</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>F</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>25 mg IM</td>
<td>2 months</td>
<td>2 months 90%</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>F</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>7.5 mg 2 months then 10 mg</td>
<td>4 months</td>
<td>6 weeks 50%</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>Childhood</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>12 months</td>
<td>2 months 90%</td>
<td>90%</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>M</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>25 mg IM</td>
<td>18 months</td>
<td>2 months 70%</td>
<td>70%</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>M</td>
<td>Childhood</td>
<td>Severe</td>
<td>Face</td>
<td>7.5 mg</td>
<td>12 months</td>
<td>2 months 90%</td>
<td>80%</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>M</td>
<td>Childhood</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>2 months</td>
<td>No improvement</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
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<td>Severe</td>
<td>Face</td>
<td>15 mg</td>
<td>1 month</td>
<td>Worsening</td>
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<tr>
<td>12</td>
<td>58</td>
<td>F</td>
<td>Adult</td>
<td>Severe</td>
<td>Face</td>
<td>7.5 mg 10 weeks then 25 mg IM</td>
<td>13 weeks</td>
<td>No improvement</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>F</td>
<td>Childhood Adult</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>24 months</td>
<td>2 months 90%</td>
<td>90%</td>
</tr>
<tr>
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<td>41</td>
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<td>Adult</td>
<td>Severe</td>
<td>Members</td>
<td>25 mg</td>
<td>4 months</td>
<td>2 months 50%</td>
<td>70%</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>M</td>
<td>Childhood</td>
<td>Moderate</td>
<td>Face</td>
<td>7.5 mg</td>
<td>3 months</td>
<td>2 weeks 100%</td>
<td>100%</td>
</tr>
<tr>
<td>16</td>
<td>52</td>
<td>F</td>
<td>Adult</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>27 months</td>
<td>6 weeks 60%</td>
<td>80%</td>
</tr>
<tr>
<td>17</td>
<td>30</td>
<td>M</td>
<td>Adult</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>30 months</td>
<td>5 weeks 40%</td>
<td>75%</td>
</tr>
<tr>
<td>18</td>
<td>22</td>
<td>F</td>
<td>Childhood</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>3 months</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>19</td>
<td>68</td>
<td>F</td>
<td>Adult</td>
<td>Severe</td>
<td>Face</td>
<td>15 mg</td>
<td>3 months</td>
<td>6 weeks 40%</td>
<td>40%</td>
</tr>
<tr>
<td>20</td>
<td>44</td>
<td>M</td>
<td>Childhood</td>
<td>Severe</td>
<td>Face</td>
<td>25 mg IM</td>
<td>20 months</td>
<td>3 weeks 80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

* or after stopping MTX.
Methotrexate

Because patients were treated in our unit by several dermatologists, the dose and the form of the medication varied greatly. However, the initial dose of MTX was inferior or equal to 25 mg weekly dosage. Most of the patients (14/20) started with a 25 mg IM/week. When the dose was decreased, the oral form was chosen. The initial dose for the 6 other patients was: 7.5 mg/week for 4 patients and 15 mg/week for 2 patients. Before beginning of MTX a complete clinical examination was made, including spirometry, chest X-ray and biological tests.

Concomitant therapies

All patients used emollients daily on the whole body surface. Some patients used topical treatments (corticosteroids and/or tacrolimus) before the beginning of MTX treatment. These patients were asked not to change their treatment habits during the MTX trial (except for tacrolimus which was stopped before the beginning of MTX). No other systemic therapy was allowed, including systemic corticosteroids, anti-histamines, antileucotrienes, hepatotoxic drugs and systemic immunosuppressants.

Follow-up

Patients were seen every month at consultation. Laboratory tests were performed before the treatment and every two weeks during the first three months and monthly thereafter. They included a complete blood count, serum creatinine, aspartate aminotransferase and alanine aminotransferase. The physician performed a global assessment, using a scale from 0 to 100, with a score of 0 indicating the absence of improvement and a score of 100 the absence of disease activity. The outcome of the study was judged after 3 months of MTX use or before, if the patient interrupted the treatment for any reason.

Results

Efficacy

The beginning of improvement occurred between the fourth and the eighth week of MTX initiation: the erythema and papulation became lighter, the itching acceptable, the excoriations superficial and the body surface area decreased dramatically. Fifteen patients, i.e. 75% of patients, were greatly improved (> or equal to 70% for 13 patients) by MTX within 3 months of use (table 1).

Patients n° 2 and 3 stopped the study before 3 months because of nausea. The AD lesions were unaffected by MTX treatment in 2 patients (n° 10 and 12) and got worse in one patient (n° 11).

Side effects during the first 3 months of MTX use were noted in 6 patients (n° 2, 3, 8, 13, 16, 17) and required discontinuation of MTX in 2 patients (n° 2, 3). The most frequent adverse events were nausea (4/20) and mild increase of liver enzymes (2/20).

Follow up after 3 months of MTX use

• The mean treatment duration was one year for the 15 patients who completed the 3 months initial treatment.
• No side effects were observed in these 15 patients even after several months of treatment.

Six patients (n° 1, 5, 6, 15, 16 and 20) were able to stop MTX because of a dramatic improvement of AD lesions (low disease activity with mild erythema and papulation, and a body surface area < 10%) allowing a maintenance therapy using emollients and corticosteroids or tacrolimus.

Discussion

Efficacy

The present study shows that short-term low-dose MTX is an effective treatment of adult AD. Physician’s global assessment estimated that an improvement of >70% occurred in 13 out of 20 patients (65%). These data confirm and extend the results obtained in the few previous reports suggesting that MTX could be helpful in the management of eczemas. Egan et al. used MTX to treat 5 patients with palmo-plantar pompholyx and were able to decrease or stop oral corticosteroid therapy in all patients. Shaffrali et al. used low-dose MTX in 5 elderly patients with eczema, with a satisfactory response in four and a discontinuation for the last one for other medical problems. Balasubramaniam et al. reported an AD patient intolerant to azathioprine and cyclosporine with a successful result and good tolerance of MTX [12-14; Hanifin J., personal communication].

Regimen schedule

Although the dose (7.5 to 25 mg) and the route (IM and oral) of MTX varied greatly among the patients treated in this study, there was no apparent better efficacy of the higher IM doses versus the low oral doses. Therefore, we recommend using MTX as oral tabs. This oral form does not need to follow the intermittent oral schedule of 3 doses divided over a 24-hour period each week which is used for the treatment of psoriasis because of the kinetics of proliferation of psoriatic epidermal cells.

Safety

No serious adverse event occurred in this study. We propose following the guidelines about MTX use in psoriasis. However, we insist on the necessity of checking respiratory function in AD patients using MTX because of the possibility of MTX-induced lung fibrosis, which could be more frequent in AD patients with associated asthma.

Proposal for drug dosage schedules in moderate to severe AD

According to our experience in our clinical unit and the previous guidelines, we suggest the following regimen schedule in AD in cases of no contra-indications for its prescription:
– initial weekly dosage MTX 15 mg in one single dose;
– increase of 5 mg weekly in case of inefficiency after 2 months of treatment;
– maximum dosage 25 mg;
– stop treatment after 3 months if no improvement;
– maintenance dosage between 5 and 7.5 mg.

Conclusion

Recent studies have shown that MTX was as effective as cyclosporine in the treatment of psoriasis [16]. Because the
side-effects of MTX are easily prevented by a monthly biological follow-up and because it is devoid of immuno-suppressive activity, MTX is considered as the first line systemic therapy in psoriasis.

Based on our present results suggesting that MTX is an effective and safe treatment of AD, we propose that it could be used in patients with moderate to severe AD with low response to conventional topical treatments and/or to cyclosporine. MTX, prescribed during episodes of peak disease activity, would be either tapered off when the disease subsided in response to therapy or maintained at the lowest efficient dosage or even switched to another agent. Placebo-controlled clinical trials are needed to demonstrate the effectiveness and safety of MX in AD and to define its place as a first line systemic therapy in moderate to severe AD [15, 17, 18].

References