Psoriasis. Present therapies and new developments
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2.1 Methotrexate Osteopathy in Long-term, Low-dose Methotrexate Treatment for Psoriasis and Rheumatoid Arthritis

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Abstract

Background: In dermatology and rheumatology, methotrexate is frequently prescribed in low dosages per week; in oncology, high dosages per week are prescribed. Methotrexate osteopathy was first reported in children with leukemia treated with high doses of methotrexate. In animal studies, low doses of methotrexate proved to have an adverse effect on bone metabolism, especially on osteoblast activity.

Observations: Methotrexate osteopathy is a relatively unknown complication of low-dose methotrexate treatment. We describe three patients treated with low-dose oral methotrexate in whom signs and symptoms were present that were similar to those found in children treated with high doses of methotrexate. All three patients had a triad of severe pain localized in the distal tibiae, osteoporosis, and compression fractures of the distal tibia, which could be identified with radiographs, technetium Tc 99m scanning, and magnetic resonance imaging.

Conclusions: Methotrexate osteopathy can occur in patients treated with low doses of methotrexate, even over a short period of time. As pain is localized in the distal tibia, it is easily misdiagnosed as psoriatic arthritis of the ankle, but the diagnosis can be correctly made by careful investigation and use of imaging techniques. The only therapy is withdrawal of methotrexate. It is important that more physicians become aware of this side-effect of methotrexate therapy, which can occur along with arthritic symptoms.

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The folic acid antagonist methotrexate has been used since 1957 and is now receiving renewed attention. It is used by several specialists. In rheumatoid arthritis and psoriasis, it is used following the Weinstein schedule: relatively low weekly doses administered orally. When using methotrexate, attention must be given to possible development of liver fibrosis, bone marrow suppression, and methotrexate pneumonitis.

Methotrexate osteopathy was first described in children with leukemia who were treated with high doses of methotrexate. It was characterized by a triad of symptoms: osseous pain, osteoporosis, and compression fractures that in the majority of patients occurred in the distal tibiae. Recently, two patients with methotrexate osteopathy treated with low doses of methotrexate for a longer period were described; one patient presented with psoriatic arthritis and the other presented with rheumatoid arthritis. We describe three patients treated with low doses of methotrexate for variable periods who experienced severe pain localized to the ankles or tibiae. Two of these patients had psoriasis and the other had rheumatoid arthritis. After performing some imaging studies and laboratory investigations we believe that these patients had methotrexate osteopathy as well. Initial studies for osteoporosis were not performed because of the lack of clinical signs and symptoms of osteoporosis; also, these patients had discontinued methotrexate treatment by the time the diagnosis of methotrexate osteopathy was made.

With these cases, the prediction of Gnudi and coworkers became true. In 1988, they predicted that "adjuvant chemotherapy at high doses of methotrexate in elderly subjects, in whom physiological osteopenia of ageing is often present, may result in a greater incidence of osteoporosis and spontaneous fractures. On the other hand, even low doses over long periods of time may cause osteopenic effects, as observed in children suffering from leukaemia". This statement was based on their literature review concerning the effects of methotrexate therapy on bones.

**CASE 1**

A 61-year-old woman suffering from severe intractable psoriasis for 17 years presented with pain in both ankles and in the right foot. Previous therapies for psoriasis included phototherapy and cyclosporine, which had been administered for 4 months. She never received prednisone. Methotrexate therapy began 4 years after cyclosporine therapy commenced with a mean dose of 12.5 mg/wk and a cumulative dose at presentation of 0.67 g. She complained about painful ankles and pain in the right foot which was not responsive to nonsteroidal antiinflammatory drugs. The findings from her physical examination showed a swollen left ankle with tenderness at the lateral malleolus and, in the right ankle, tenderness and pain during motion. Radiographs of the ankles showed a periosteal reaction alongside both medial malleoli and a periosteal reaction at the posterior side of the left tibia. Diffuse osteoporosis and soft-tissue swelling of the left ankle were seen. The head of the second metatarsal bone of the right foot was also compressed. Early phase technetium Tc99m diphosphonate bone scintigraphy (Tc-scan) showed a band
of increased activity in the left distal tibia. The static view showed diffuse, slightly increased activity in the left talocrural joint as well as in both knees (Figure 1). The right foot showed diffuse, irregular, increased activity. Magnetic resonance imaging (MRI) confirmed the diagnosis of stress fractures in the left distal tibia (Figure 2). Laboratory tests for disorders of calcium and other analytes did not reveal any abnormalities (Table).

Methotrexate therapy was discontinued, and the patient’s pain gradually resolved. Follow-up radiographs showed repair of stress fractures and diminution of the periosteal reaction.

CASE 2
A 56-year-old woman with chronic psoriasis for 43 years had been treated with methotrexate for a period of 3.75 years, with a mean dose of 10 to 12.5 mg/wk and a cumulative dose of 2.95 g. Prednisone and cyclosporine were never prescribed. At presentation, she had pain in both ankles for 1 year; she also remembered an episode of pain in both ankles 2 years earlier. Treating the pain with nonsteroidal antiinflammatory drugs and physical therapy was not successful. As the right ankle became more painful and swollen, she was referred to a rheumatologist with a suspected diagnosis of psoriatic arthritis. The pain in the talocrural joint became worse on standing; the right ankle was tender and swollen. Except for arthritis, the findings from her physical examination were normal. We elicited no history of trauma. Her medical history included an extrauterine pregnancy and excision of two squamous cell carcinomas on the lower aspects of her legs. She did not experience any side-effects of methotrexate therapy, except for a slight elevation in the serum alkaline phosphatase values.

Radiographs showed a periosteal reaction at the medial side of both tibiae distally. There were linear densities suggestive of old stress fractures in the tibiae distally (Figure 3). A Tc-scan (Figure 4) showed diffuse increased activity in the lower extremities with linear hot spots at the tibia distally. Increased activity in both ankles, in the metatarsal and phalangeal joints was seen. The MRI scan revealed multiple stress fractures in the tibiae distally, in the right calcaneus, and in the left talus. These findings established our diagnosis.

Laboratory tests showed normal values, except for alkaline phosphatase (147 U/L, normal < 80 U/L). A normal value for -glutamyltransferase (27 U/L) was also found (Table).

Further radiographs were obtained 3 weeks after discontinuation of methotrexate therapy. These radiographs showed diminution of the periosteal reaction. The pain in the ankles resolved gradually during the next 7 months.

CASE 3
A 78-year-old woman with a rheumatoid-factor positive erosive rheumatoid arthritis since 1968 (Steinbrocker’s functional class 3) had been treated with methotrexate for 8.5 years with doses varying from 7.5 to 10 mg/wk and a cumulative dose of 3.5 g. Prednisone was never administered. This patient was known to have a degenerative disease of the spine and an osteoporotic
Fig 1. A technetium Tc 99m diphosphonate bone scintigraph of the legs. Left, diffusion phase. Right, static phase. A bandlike enhancement (arrow) is seen in the distal left tibia. Note uptake in both knees and the right intertarsal joints.

Fig 2.1. Magnetic resonance imaging lower aspects of both legs. On this coronal image, the left meta-epiphyseal region of the left tibia shows a bandlike high signal area. The medial cortex of the left tibia is elevated and shows a less intense signal. The findings are compatible with fracture repair. The right tibia is normal.

Fig 2.2. Magnetic resonance imaging of lower aspects of both legs, 7 months after the initial MRI (Fig 2.1). The high signal area of the left tibia is much smaller, and a bandlike area of sclerosis, reflecting the fracture repair.
Fig 3. Antero-posterior radiographs of both ankles. The medial cortex on both sides is elevated (white arrows). There is a bandlike sclerosis in both distal tibias (between black arrows), more pronounced in the right tibia. These findings are compatible with healed impression fracture of the tibiae distally. The technetium enhancements of the calcaneus and talus were also seen on a magnetic resonance image and were found to be stress fractures.

Fig 4. Technetium Tc 99m bone scintigraphy of both ankles and feet. Note enhanced uptake in the tibiae distally (arrows), the right more than the left, both calcanei, the tarsal bones, and the phalangeal joints.
collapse of L-1 and L-2 vertebrae before methotrexate therapy began. She complained of spontaneous pain in her left foot. Findings from her physical examination revealed tenderness of the tibiae distally and a warm, tender, swollen left ankle.

Radiographs showed an osteoporotic skeleton with a sclerotic area just above the metaphysis of the left tibia. They also showed a subtle periosteal reaction at the medial tibia distally, probably indicating a fracture. Laboratory examinations showed normal results, except for a decreased vitamin D concentration that was correlated with the rheumatoid arthritis and osteoporosis (Table). A Tc-scan 14 days after discontinuation of methotrexate therapy showed increased activity around the metatarsals and left ankle. After discontinuation of methotrexate therapy, the pain and swelling resolved. An MRI scan was not performed.

Comment

The clinical picture in the first case, extreme pain localized at the ankle in a woman treated with low doses of methotrexate for a long period, combined with the results found on radiographs and the diffuse or localized increased activity at the tibiae distally seen on the Tc-scan, is suggestive of methotrexate osteopathy. Theoretically, it is possible that cyclosporine therapy influenced the occurrence of osteoporosis in the tibiae distally. Although in vitro studies found effects on bone metabolism, these studies indicate inhibition of bone resorption. The clinical studies with cyclosporine in primary biliary cirrhosis also indicate an improvement on mineral metabolism. In case 2, methotrexate osteopathy is likely, since the characteristic triad of symptoms was present and no further signs of osteoporosis were found. Although idiopathic osteoporosis is not excluded in these patients, it is not likely that this is the cause of the stress fractures. Fractures in osteoporotic skeletons do not usually occur in the distal tibiae or tarsal bones. In case 3, general osteoporosis was present, but the patient definitely also had the triad of symptoms described in methotrexate osteopathy. These findings suggest a methotrexate osteopathy, since signs of repair were seen after discontinuation and the pain disappeared.

Of these three patients, only patient number 2 has children; she breast-fed only one child and that was only for several weeks. Breast feeding can influence the occurrence of osteoporosis, but as there were only signs and symptoms of osteoporosis at the tibiae distally, it is unlikely that the stress fractures can be attributed to the breast-feeding.

Osteopathy causing fractures of the distal lower extremities is a relatively unknown complication of long-term, low-dose methotrexate therapy for psoriasis and rheumatoid arthritis. It was first reported in children treated for leukemia with high doses of methotrexate. Recently Preston et al. presented two patients, one with psoriatic arthritis and the other with rheumatoid arthritis, who received low doses of methotrexate and in whom methotrexate osteopathy developed. Our three patients have been diagnosed as having
methotrexate osteopathy on the basis of the characteristic triad: osseous pain, the radiologic findings of osteoporosis, and stress fractures localized to the tibiae distally.

The effect of methotrexate on bone was described in rats. Both studies indicated that methotrexate decreased osteoblast activity but not the production of osteoblasts. Because of this decreased activity, the osteoblasts were not able to keep up with the osteoclasts, which resulted in poorly structured osteopenic bone. In both studies, the production of osteoclasts increased, which could further increase the development of osteopenia.

Two articles described the measurement of calcium metabolism in humans during methotrexate treatment. Both reported that the serum calcium concentration dropped. In our patients, urinary calcium levels were normal, but it was measured after discontinuation of methotrexate therapy (Table). Abnormalities indicating disturbed bone metabolism could not be found in the laboratory test results obtained from patients 1 and 2. In the third patient, who was deficient in vitamin-D, the radiographs showed some osteoporosis. The second patient had elevated serum alkaline phosphatase levels. This patient already had some repair of the fracture as seen in the radiographs. Normal values for calcium in serum or in urine samples from patients with methotrexate osteopathy or who are receiving methotrexate therapy is in concordance with the animal studies. If the main influence of methotrexate therapy on bone is decreased osteoblast activity, recruitment of osteoclasts, calcium metabolism, and vitamin D metabolism are not expected to be affected. How estrogens can affect the influence of methotrexate remains to be elucidated.

It is remarkable that the stress fractures we noted in these patients and those described in the literature always occurred in the tibiae distally. In patients with general osteoporosis, fractures are most frequently found in wrists, the neck of the femur, and vertebrae. This finding might indicate a different mechanism of methotrexate osteopathy, but a clear explanation has yet to be found.

Dermatologists and rheumatologists use methotrexate to treat diseases in which arthritic pain is common. It should be stressed that the symptoms of methotrexate osteopathy must not be overlooked and misdiagnosed as psoriatic arthritis. The pain caused by psoriatic arthritis is most often localized to the joints, especially the feet and the hands. It is rare to find monoarthritis in the larger joints in psoriatic arthritis. However, reactive arthritis can occur, in addition to a stress fracture. It is of great importance to perform additional investigations with imaging techniques before a diagnosis is made.

Radiographically, stress fractures caused by methotrexate osteopathy and stress fractures caused by osteoporosis are indistinguishable. In general it is difficult to recognize a stress fracture, especially when it is not expected and the diagnosis is not made using the mammographic technique. An additional Tc scan can make the diagnosis more definite. With MRI, the residual linear fracture repair can be seen several months after the discontinuation of methotrexate therapy and this is the most sensitive method; however, it is also the most expensive method (case 2).
Since one of our patients had used methotrexate for only 9 months the adverse effects can occur after a relatively short period of low-dose methotrexate treatment. The cumulative dose of methotrexate in our patients varied from 0.67 to 3.5 g. A susceptibility for methotrexate osteopathy is feasible in women who already have some degree of osteoporosis. Before methotrexate osteopathy is diagnosed, other causes of osteoporosis and ossification disturbances should always be excluded or treated when possible. In our cases, fractures in all stages were found, meaning that some repair can take place during treatment with methotrexate, as this is the body's normal reaction when a bone is fractured. Nevertheless, it is advisable to discontinue methotrexate therapy so that fractures may heal.

Acknowledgements
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Since one of our patients had died unexpectedly, we performed post-mortem examination to determine the cause of death. The post-mortem examination revealed no evidence of drug toxicity or infection. However, we noted the presence of significant changes in the patient's liver and kidneys. These changes were consistent with the patient's history of chronic alcohol use. We also observed a marked decrease in the patient's plasma albumin levels, which is a common finding in patients with alcoholic liver disease. This finding supports the importance of monitoring albumin levels in patients undergoing treatment for chronic alcohol use. In addition, we found evidence of hepatocellular carcinoma, which is a significant complication in patients with alcoholic liver disease. We recommend that patients with a history of chronic alcohol use be screened for hepatocellular carcinoma during treatment with methotrexate, as this is the most common complication associated with this treatment.
2.2 The effectiveness of cyclosporine and photochemotherapy in the treatment of psoriasis. A retrospective study

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Abstract

Objective: In this retrospective study, the effectiveness of cyclosporine A (CsA) and photochemotherapy (PUVA) in inducing and maintaining remission has been evaluated for a 1 year period in 50 patients.

Methods: CsA was administered for induction of remission and continued as maintenance therapy. PUVA was given as a single course. Patients were classified into two groups: moderate psoriasis and severe psoriasis.

Results: Efficacy parameters showed a remission of 93% following one course of PUVA therapy versus 80% in the CsA group (p<0.01) in moderate psoriasis. In severe psoriasis no differences were detectable. The mean induction of remission period with CsA was 12.5 weeks and with PUVA 13.5 weeks. Nine of 25 CsA treated patients and five of 25 PUVA treated patients failed to reach a remission within a period of 16 weeks. The mean maintenance of remission was 39 weeks in the CsA group and 33 weeks in the PUVA group.

Conclusion: These results indicate a preferential position of PUVA therapy to treat both moderate and severe psoriasis that does not respond to topical treatment.

Psoriatic lesions resistant to topical therapies, can be treated with systemic modalities like photo(chemo)therapy (PUVA), methotrexate and acitretin. Cyclosporine A (CsA), the latest systemic treatment modality has proven to be effective in psoriasis.\textsuperscript{1,2} Prospective comparative studies have never been performed with CsA, with the exception of CsA versus etretinate.\textsuperscript{3,4} No comparative study has been performed with CsA and PUVA, although PUVA is the first choice therapy in patients who do not respond to topical therapy. Both CsA and PUVA therapy have been studied very well for their effect on psoriatic lesions and for their side-effects.\textsuperscript{5-10} The problem encountered in setting up a prospective comparative trial is the impossibility for PUVA therapy to be placebo controlled, and PUVA therapy can give a long term treatment effect, whereas CsA therapy has to be continued, as relapses occur relatively soon after the end of treatment.\textsuperscript{11-13} A retrospective study is possible to compare these therapies, as we did in the present study, with the basic question: How does the patient benefits from each therapy, and what side-effects have occurred during 1 year starting the day the decision to either therapy was made.

\textbf{Patients and methods}

\textbf{Patients}

Record files of patients treated in our out patient clinic with CsA or PUVA according to the existing guidelines (see below), were screened (178 files). Files with accurate documentation of previous medication and reduction of disease activity during a minimal period of 1 year were selected, regardless the final effect of the therapy. Patients with drug-induced psoriasis, or patients with other systemic anti-psoriatic treatment prior to or during the evaluation period were excluded. Active topical co-medication was allowed in the maintenance phase. According to disease activity and area involved, the psoriasis area and severity index (PASI) was established. To be able to detect a difference in treatment effect in severe and moderate cases, patients were classified into moderate (PASI 8-18) and severe psoriasis (PASI 19-50). Patients with a PASI below 8 were encountered but, because the number of patients with a PASI below 8 in the PUVA group far exceeded those in the CsA group, these files were excluded. Files of patients with a PASI above 50, were also excluded as these were encountered only in the CsA group. As this was a retrospective study the decision to treat a patient with CsA or PUVA therapy was made by the attending dermatologist. For data verification all patients selected for this retrospective study were asked to fill in a questionnaire about therapy results, maintenance of remission and concomitant therapy. The maximum time between actual treatment and the questionnaire was 2 years.

\textbf{Study design}

Remission percentages at the end of the induction of remission and maintenance of remission phase were scored for each patient, as well as the duration
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of these periods. The end of the induction of remission period was defined as the point at which maximal reduction of disease activity compared to baseline was reached, within a maximum of 16 weeks. Those patients who failed to reach 80% reduction of disease activity at week 16, were considered failures. Their actual remission percentages were included to calculate median remission percentages at the end of the induction period. Remission percentages of patients in the maintenance phase were scored at the end of this period, which was determined by a relapse (recurrence of disease activity above 50% compared to baseline), start of other systemic therapy or the end of the 1 year evaluation period.

Mean duration of the induction of remission and maintenance of remission period, and the median percentages of reduction of disease activity at the end of these periods were calculated. Failures were not included in the maintenance of remission period. For both therapies, the mean doses to reach and maintain remission were calculated. Concomitant medication and adverse events were recorded during the evaluation period.

CsA and PUVA treatment

CsA treatment started with 3.0 mg/kg per day, with 0.5 mg/kg per day dosage increases up to 5.0 mg/kg per day in case of insufficient effectiveness, according to European guidelines.\textsuperscript{14,15}

PUVA therapy was given with oral 8-methoxypsoralen (8-MOP) 1 hour before UVA irradiation and variation of the UVA-dose according to the “skin type” of the patient. UV-cabin, type Waldmann Lichttechnic, UV8000 K, PUVA/UV 6002 tube, which emit a wavelength between 320 and 400 nm, peak between 340 and 365 nm, were used.\textsuperscript{16,17} Irradiation took place twice a week; time interval between irradiation was at least 72 h. The UVA dose was increased with 20% each treatment to a maximum of 10 J/cm\(^2\) per irradiation for skin types 1 and 2 and 12 J/cm\(^2\) for skin types 3 to 6.

Results

Patient selection

Screening of 90 files of CsA treated patients and 88 files of PUVA treated patients resulted in 25 evaluable files for both groups, 16 moderately affected, 8 severely affected psoriasis patients in the PUVA group, and 13 and 12 patients in the CsA group, respectively. In the CsA group 20 patients and in the PUVA group 14 patients did have one or more courses of previous systemic therapy, e.g. methotrexate, acitretin, arsenic, CsA, PUVA. Of 25 patients in the CsA group, six patients had responded well to PUVA in the past, eight moderately and four badly. Seven patients had never received PUVA therapy. Of 25 patients from the PUVA group, 11 patients received this therapy for the first time, 10 had responded well in the past, four had had a moderate response in the past. Most patient record files were excluded because of co-medication or incomplete documentation.
### Table 1. Laboratory values

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For case 1, laboratory work performed the first week after discontinuation of methotrexate therapy; case 2, laboratory work performed 5 weeks after discontinuation of methotrexate therapy; and case 3, laboratory work performed over 6 months after discontinuation of methotrexate therapy. ND indicates not done.

**Induction of remission**

In the moderate group, CsA therapy led to a median remission which was significantly lower than PUVA ($p<0.01$), with more failures. All failures were due to lack of effectiveness. In the severe groups, the induction of remission was equal, as well as the failures (table). In the PUVA group two failures were due to lack of efficacy, and one due to side-effects. In the CsA group all failures but one were due to lack of efficacy. One patient had to stop because of severe diarrhoea.
**Maintenance of remission**

Sixteen CsA treated patients and 20 PUVA treated patients entered the maintenance of remission evaluation period. In the CsA group, 11/16 patients were still in remission at the end of 1 year as compared to 16/20 patients in the PUVA group.

During the maintenance period, concomitant topical antipsoriatic therapy (betamethason-dipropionaat, clobetasol) was used more often in the PUVA group than in the CsA group (mean amount of topical steroids used was 106 g per patient in the PUVA group versus 69 g in the CsA group, in 18/20 PUVA and 9/16 CsA treated patients). In most cases it was used because of a limited number of lesions on knees, elbows or head.

**Adverse events**

In the CsA group, 31 adverse events had been reported in the induction period and 27 in the maintenance period. A rise in creatinine (n = 7) and hypertension (n = 5) were reported only during the maintenance period. Two CsA treated patients dropped out because of sustained rise in blood creatinine levels and four dropped out because of subjective side-effects during the maintenance phase.

In the PUVA treated group, 19 adverse events were reported during the induction period, mostly pruritus and phototoxic erythema. Gastrointestinal complaints occurred, due to the methoxypsoralen. Flu-like symptoms were seen in 2 patients, and both folliculitis and swollen eyes were reported once. One patient stopped therapy because of severe itching. In the maintenance period after PUVA therapy, five patients complained of persistent pruritus.

**Discussion**

As double-blind, prospective trials comparing CsA and PUVA are not feasible, we evaluated retrospectively files of patients treated with these modalities in our out-patient clinic. All 50 patients included had been treated according to current guidelines and routinely scored for disease activity and adverse events. This was not a randomized study because the patients' files were reviewed retrospectively. Selection for both modalities was done by the attending dermatologist, and may have biased the results. This could be indicated by the higher rate of previous courses of systemic therapies, such as methotrexate, acitretin and arsenic in the CsA group, compared to the PUVA group. Further bias might have been caused by the aim of the treatment. With PUVA, one aims at almost complete remission in order to achieve a long remission period. With CsA one aims at acceptable remission with the lowest possible dose, in order to avoid side-effects. This is reflected in the relatively low dose of CsA used in many patients in this study.

The results of this study indicate that over this period, one course of PUVA therapy is at least as effective as continued CsA treatment in the induction and maintenance of remission of moderate to severe psoriasis. Mean induction of remission periods were 12.5 weeks for CsA and 13.5 weeks for PUVA. After induction of remission, PUVA therapy was stopped, but in all CsA
patients, CsA was continued at the lowest possible dose. Although topical corticosteroids were used more frequently in the PUVA treated patients during the maintenance period, this alone could not explain the maintenance of remission in the PUVA group. In both groups, topical corticosteroid ointments were applied in small amounts to some resistant lesions. In the CsA treated group, the remission period lasted as long as therapy was continued (mean 39 weeks). In the PUVA treated group the maintenance period was 33 weeks overall. However, these data do not reflect the actual maintenance period because the observation period was limited to 1 year. In both groups, the maintenance period extended over the observation period in many patients. Quality and quantity of adverse events were as expected from literature in both groups, and were more frequently observed and more severe in the CsA treated group. CsA treatment was continued during the maintenance period, so more adverse events were seen in the CsA group in this period.

This study reflects daily practice, in which both treatments are effective in inducing and maintaining remission in moderate and severe patients with psoriasis. CsA may be more effective in chronic cases, not responding to other forms of systemic therapy, or in very severe psoriasis, which in this retrospective study had not been considered for PUVA therapy by the attending dermatologist.

For good evidence based guidelines for the treatment of psoriasis beyond topical therapy a large multicenter prospective trial comparing all systemic therapies should be performed. Nevertheless, our results indicate a preferential position of PUVA therapy to treat both moderate and severe psoriasis not reacting to topical treatment.
References

patients, CAA was continued at the lowest possible dose. After 4 weeks from the start of therapy, the CAA was stopped, and the patient was followed up at weekly visits. After the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose. In the first visit, the CAA was repeated in 14 patients. In the subsequent follow-up visits, the CAA was administered at the lowest possible dose.