

Experience with Subcutaneous Methotrexate for the Treatment of Moderate-to-Severe Psoriasis

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Abstract

Background: Clinical studies in patients with rheumatoid arthritis indicate that subcutaneous methotrexate exhibits a better pharmacokinetic profile than oral methotrexate, and this was associated with greater efficacy. Based on these findings, subcutaneous methotrexate may offer similar advantages for the treatment of psoriasis; however, this has not been previously evaluated.

Aims: To determine the effectiveness of subcutaneous methotrexate (Metoject®) in patients with moderate-to-severe psoriasis vulgaris.

Study design: Descriptive, single center case-series

Methods: The study enrolled 10 patients with moderate-to-severe psoriasis who presented at the outpatient dermatology clinic. Treatment comprised 15 mg of subcutaneous methotrexate, once weekly for 6 months. Data were obtained on demographic characteristics (Table 1), duration of psoriasis, Body Surface Area (BSA), and scores on the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI).

Results: Eight males and two females were included, with an age of between 18 and 57 years old, and a disease duration ranging from 1 to 16 years. An improvement was observed in the mean affected BSA, from 18% at baseline to 3.3% at 6 months. The mean PASI score declined from 7.0 at baseline to 2.0 at 6 months, and the mean DLQI score decreased from 8.2 at baseline to 2.1 at 6 months. None of the patients experienced clinically relevant changes in laboratory parameters or adverse events related to the gastrointestinal, respiratory or cutaneous systems.

Conclusion: Subcutaneous methotrexate was effective for the treatment of moderate-to-severe psoriasis, providing adequate disease control as well as improving quality of life.

Keywords: Psoriasis; Methotrexate; Subcutaneous; Effectiveness; Remission

Introduction

Methotrexate is an aminopterin derivative that acts via diverse and complex mechanisms to produce anti-proliferative, anti-inflammatory and immunosuppressive effects [1]. As a folic acid antagonist, methotrexate inhibits purine and pyrimidine synthesis, resulting in antineoplastic activity at high dose levels. The anti-inflammatory activity of methotrexate, which is mediated by increased adenosine release, is considered to be most important for its clinical effect on psoriasis [2,3]. In addition, the immune modulatory properties of methotrexate such as suppression of T-cell activation and altered expression of adhesion molecules are thought to be relevant [4,5].

The first clinical study of methotrexate for the treatment of psoriasis was published in 1958 [6], and, in 1972, the United States Food and Drug Administration approved the drug for this indication. Although the oral formulation of methotrexate is most widely used for the treatment of psoriasis, subcutaneous administration yields a more favorable pharmacokinetic profile [7]. Following oral administration, methotrexate is absorbed in the gastrointestinal tract, with a small proportion of each dose being susceptible to hepatic inactivation. The bioavailability of orally administered methotrexate varies between individuals, and, at doses of more than 15 mg, a decline in bioavailability is observed. By avoiding gastrointestinal absorption and hepatic inactivation, subcutaneous administration increases bioavailability [1,7]. Furthermore, a clinical study in patients with rheumatoid arthritis demonstrated that subcutaneous methotrexate was significantly more efficacious than oral methotrexate. This effect was accompanied by greater intracellular poly glutamate accumulation

after 6 months of treatment as well as fewer adverse events [8]. Subsequently, other studies have also reported an increase in poly glutamate accumulation following subcutaneous relative to oral administration of methotrexate [9].

Based on the findings in patients with rheumatoid arthritis, it may be expected that subcutaneous methotrexate is a feasible option for psoriasis; however, this prospect has not been evaluated in clinical studies. The present study was conducted to describe the effects of subcutaneous methotrexate in patients with moderate-to-severe psoriasis vulgaris.

Materials and Methods

Study, subjects and participation

This was a descriptive study of a nonconsecutive series of 10 patients who presented at the dermatology outpatient clinic of the Hospital Universitario Virgen de las Nieves (Granada, Spain) between June 2014 and January 2015.

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Methods

The study was approved by the relevant ethics committee (Comite Central de Etica de la Comunidad Autónoma de Andalucía). All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants. Inclusion criteria for patients were as follows: at least 18 years old; a diagnosis of moderate-to-severe psoriasis vulgaris refractory to topical therapy; candidate for systemic therapy and rejected phototherapy; Psoriasis Area and Severity Index (PASI) >5; and, provision of written informed consent. Exclusion criteria included: contraindications to methotrexate (anemia, thrombocytopenia, leukopenia, active infection, cardiovascular disease, hepatic disease, renal disease and alcoholism); pregnant or lactating females; and, a diagnosis of psoriatic arthritis or rheumatologic disease.

All patients were treated with subcutaneous methotrexate (Metoject[®]) at a dose of 15 mg, once weekly for 6 months. Folic acid was provided at a dose of 5 mg/week.

Data collection at baseline included demographic characteristics, duration of psoriasis and affected areas. Laboratory evaluations comprised hemograms and general biochemistry tests, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), propeptide proteoglycan III, interferon gamma release assays (IGRAs), and serum antinuclear antibodies (ANAs). ThoraxX-rays were also performed at baseline. Hemograms and general biochemistry tests were repeated at 3 and 6 months. Disease severity (Table 2) was evaluated using the Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI). Data are described as mean values, and the median (range).

	Age	Gender	Evolution of psoriasis (Years)	Weight(Kg)	Height (cms)	BMI
1	18	M	1	67	178	21,15
2	23	M	2	78	176	25,18
3	34	M	1.5	80	175	26,12
4	33	M	10	78	180	24,07
5	57	M	16	69	169	24,16
6	50	F	7	65	167	23,31
7	35	M	15	78	182	23,55
8	27	M	16	83	179	25,90
9	29	M	8	89	175	29,06
10	29	F	9	68	173	22,72

Table 1: Demographic characteristics; M: Male; F: Female.

	PASI baseline	PASI 6m	BSA baseline	BSA 6m	DLQI baseline	DLQI 6m
1	5	1.5	15	4	8	2
2	9	3	22	3	9	3
3	5	1.5	14	4	8	3
4	8	2	12	3	7	3
5	6	2	17	3	8	2
6	7	2	20	3	9	1
7	7	2	18	3	7	2
8	6	1.5	18	3	8	3
9	5	1	10	2	9	1
10	12	3	32	5	9	1

Table 2: Data on disease severity at baseline and 6 months.

Results

All patients completed the 6-month follow-up period. Demographic characteristics are shown in Table 1. The study population comprised eight males and two females, with a mean age of 33.5 years (range: 18-57 years), and mean disease duration of 8.55 years (range: 1-16 years).

Data on disease severity at baseline and 6 months are presented in Table 2. At baseline, the mean PASI was 7.0 (range: 5-12), the mean affected BSA was 18% (range: 10-32%), and the mean DLQI score was 8.2(range 7-9). At 6 months, the mean PASI score was 2.0, the mean affected BSA was 3.3%, and the mean DLQI score was 2.1. All patients experienced an improvement of at least 50% from baseline in PASI, BSA, and DLQI scores, but complete disease remission was not observed. None of the patients reported skin, respiratory, gastrointestinal or joint disorders. Two patients had injection site reactions (moderate erythema with pain solved after three days). No flu-like symptoms were reported.

Biochemical tests revealed no changes in hematology, lipid and hepatic profiles.

Discussion

Psoriasis, which has an estimated prevalence of 2.3% in Spain [10], is one of the most frequent reasons for consulting a dermatologist. Approximately 70% of patients continue to be prescribed topical therapy, with alternative options not being offered [10]. Although topical therapy represents a fundamental component of the standard care for psoriasis, many patients consider topical application to be another negative aspect of the disease. Indeed, patient satisfaction with topical treatments is significantly lower than that reported with oral or parenteral treatment (injections or infusions) [11,12]. For cases in which the severity of psoriasis requires systemic therapy, three approved therapeutic options are available in Spain: methotrexate, cyclosporin and acitretin. Each of these drugs has a unique benefit-risk profile, and the optimal choice of drug depends on individual patient characteristics [11].

Results from this case series indicate that subcutaneous methotrexate was effective as a mono therapy for moderate-to-severe psoriasis. Following 6 months of treatment, disease amelioration was observed, as demonstrated by substantial changes in the main parameters used in clinical trials to measure the effectiveness of psoriasis drugs: BSA, PASI and DLQI. The therapeutic effect of methotrexate usually appears gradually, developing throughout the first 4 to 8 weeks after treatment initiation. Methotrexate may also be combined with biologic drugs, for example, to enhance efficacy or as a rescue therapy [13,14]. Methotrexate can be administered in a variety of dose regimens, including a test dose, escalating doses, continuous or intermittent therapy, or as part of a drug rotation regimen [15].

Because of the immunosuppressive action of methotrexate, hematology and virology tests must be performed to confirm the absence of hepatitis, human immunodeficiency virus and tuberculosis [12]. Furthermore, patients should be selected carefully to minimize the risk of toxicity, in particular, hepatotoxicity [16-18] and/or gastrointestinal side effects. Long-term administration of methotrexate has been linked to hepatic injury such as fibrosis and cirrhosis. Currently, levels of transaminases and aminoterminal type III procollagen peptide are considered to be adequate markers of hepatic injury, although biopsies may be used to detect structural changes. Methotrexate causes gastrointestinal toxicity in approximately 60% of patients, resulting in nausea, vomiting, dyspepsia, abdominal pain, diarrhea, anxiety and weight loss. Of note, these side effects are substantially diminished

by subcutaneous administration compared with the oral route. In the present case series, only side effects related to the delivery route were reported, with no toxicities observed.

Methotrexate was the first systemic drug for the treatment of psoriasis. With more than 50 years of experience, it remains an effective, safe and well-tolerated therapeutic option. For these reasons, methotrexate represents the standard systemic therapy for psoriasis, providing that patients are selected carefully according to individual risk profiles. In the future, pharmacogenetic studies will help to better delineate those patients for whom methotrexate is the most suitable option as well as those at greater risk of developing side effects.

For these reasons in our case series, we believe that administration of subcutaneous methotrexate is a systemic drug with excellent therapeutic results in moderate psoriasis, with few side effects and well tolerated by our patients. We emphasize its excellent safety and valid option after the prescription of biological therapy in cases where applicable.

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