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ORIGINAL PAPER

Effectiveness of methotrexate in moderate to severe psoriasis patients: real-world registry data from the Swiss Dermatology Network for Targeted Therapies (SDNTT)

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Abstract

Methotrexate (MTX) is a frequently used anti-psoriatic drug that is commonly recommended in international psoriasis guidelines. It is effective in treating skin lesions, nail changes and psoriatic arthritis. In 2017 a prospective, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, commonly known as the METOP trial, was published assessing the effectiveness and safety of subcutaneous administration of methotrexate. Because trial data do not always relate to real-life data with unselected patient populations, we wanted to determine whether the data obtained in the METOP-trial correspond to real-life registry data from our Swiss Dermatology Network for Targeted Therapies (SDNTT). Data of 449 patients with moderate to severe psoriasis who participated in the SDNTT registry between 2011 and 1st of July 2017 were analyzed. Only patients receiving methotrexate s.c. were included. 66 patients under MTX were included into this study. Baseline PASI was 6.3 ± 3.8 (SDNTT) compared to 15.9 ± 5.9 in the METOP trial. In our cohort, only 18% of all patients reached PASI 75 after 12 weeks, 6% showed a complete remission (PASI 100) compared to 41% and 4% in the METOP trial after 16 weeks. 22.7% of all patients showed increased liver enzymes in either study and nausea was seen in 15% (SDNTT) versus 22% (METOP) of patients. No severe adverse events were observed in our cohort. Compared to the METOP-trial, the response rates seen our real-world cohort were distinctly lower.

Keywords Methotrexate · Psoriasis · Folate acid · METOP · SDNTT · MTX

Introduction

Psoriasis is an inflammatory skin disease, which runs a chronic course and affects about 2% of the population in western countries [36]. The contribution of genetic as well as environmental factors plays an important part to the manifestation of psoriasis symptoms [4, 5]. In the last decades, increasing numbers of therapeutic options have been developed. While there is excellent evidence for new and costly therapies, few trials have investigated the effectiveness and safety of classical therapeutic agents. Methotrexate (MTX), a folate antagonist is, however, still the most frequently used anti-rheumatic agent [44, 52]. Its effectiveness in psoriasis is also well known for more than 50 years [32]. MTX is commonly recommended in international psoriasis guidelines [18, 27, 30]. While several studies have shown good effectiveness of MTX in psoriatic arthritis [12, 22, 49], no improvement of synovitis was found in a randomized placebo-controlled trial, raising the question whether it classifies as a disease-modifying psoriatic arthritis treatment [26]. In nail psoriasis, systemic [14, 15, 21, 39, 41] as well as intralesional MTX [19, 31, 42] has been reported to be efficient.

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When MTX is administrated, it docks onto intracellular folate receptors [17]. MTX and its polyglutamated derivatives act as a folate analog, competitively inhibiting dihydrofolate reductase (DHRF) leading to a decreased synthesis of pyrimidine and purine which is followed by a reduction in T-cell-induced cytokine production [17]. MTX is also reported to affect the homocysteine metabolism [17]. Mitogen-induced immunoglobulin synthesis and proliferation of peripheral blood cells is impaired via reduction of polyamine synthesis [34]. MTX is thought to inhibit the function of the 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, which leads to increased extracellular adenosine levels resulting in downregulation of inflammatory signaling [17]. In mouse models, neutrophil function is inhibited via adenosine release [13]. Adenosine itself is reported to have anti-inflammatory properties [40]. Yet, in animal models, the adenosine mediated properties of MTX have not been confirmed [3, 47]. In mouse models, MTX was shown to produce a state of anergy, where T as well as B cells were unresponsive to stimuli [16, 25]. In addition the action spectrum of MTX could be broader than expected, as an affinity of MTX for other folate-dependent enzymes like thymidylate synthase, AICAR (5-amino-imidazol-4-carboxamide ribonucleotide transformylase) and AICARFT (AICAR formyltransferase) has been reported [9, 47, 50].

Due to this very broad activity, MTX can subtly influence also concomitant low-level inflammatory states that are associated with co-morbidities. Indeed, MTX may reduce the cardiovascular risk in psoriasis patients [1, 2, 11, 20, 23, 24, 37]. Especially, when psoriasis and other risk factors for cardiac disease existed, MTX therapy was associated with a lower risk of developing cardiac events [48]. So far, no influence on hemoglobin A_{1C} and fasting glucose level was found [53].

Apart from the use as a single drug, MTX has found its use also in more complex treatment regiments for inflammatory conditions. MTX is often co-administered with biologic drugs, either to enhance their effect [7, 17] or to reduce immunogenicity decreasing the risk of auto-antibody formation or diminishing them [38]. It is even recommended to be used concomitantly with some biologicals [45, 46] in certain cases. With increasing therapeutic options concomitant treatment has become less common though.

Unfortunately, only few stringently controlled trials have been performed with this drug in psoriasis [29]. Only three trials evaluated oral MTX administration in a head-to-head comparison with modern biologics, namely with adalimumab [43], briakinumab [39] and infliximab [6]. On average, PASI 75 was reached in 39.9–42% in week 16 [6, 39].

Because MTX can be administered both orally and subcutaneously (SQ), some efforts have been made to investigate whether either route yields higher effectiveness and less side effects. Indeed, in a 6-month well-controlled trial comparing oral and SQ administration of MTX in rheumatoid arthritis clearly showed that the latter was of higher effectiveness and had a much better profile concerning side effects, especially nausea. In a prospective, randomized, controlled trial in patients with rheumatoid arthritis, SQ administration of MTX has been found significantly more effective than oral administration [8]. This has influenced our daily practice towards almost exclusively subcutaneous use of MTX in psoriasis.

Perhaps the most important study with MTX is the recently published METOP-trial, a 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluated SQ MTX in moderate-to-severe psoriasis [51].

In the METOP trial, the safety profile was not dose-dependent. Side effects included elevation of liver enzymes up 23% and leukopenia in up to 5% of all patients. Nausea was reported in 22% of all patients [51].

However, as in all controlled trials in psoriasis, we are well aware that they do not directly translate to the clinical reality that is based on unselected patient populations with all kinds of less uniform and foreseeable medical situations. Thus, we chose to use our registry data to investigate the real-life effectiveness of SQ MTX and compare the results to the METOP trial.

Methods

Patient recruitment into the Swiss Dermatology Network for Targeted

Psoriasis patients who started a new systemic therapy were included in the national non-interventional Psoriasis Registry "SDNTT" (Swiss Dermatology Network for Targeted Therapies, NCT01706692). The registry complies with a common consensus in the PsoNet network [33, 35]. It was harmonized with similar psoriasis registries. All participants sign an informed consent prior to participation. All data was collected in Swiss hospitals since 2011. Treatment decisions were based on evidence-based national and international guidelines [27, 33]. Baseline data has been previously published [10, 27]. Until 1st of June 2017 (database cut-off), 449 patients were included in SDNTT.

Inclusion/exclusion criteria for the SDNTT

Inclusion criteria included age > 18 years, clinically confirmed diagnosis of moderate to severe psoriasis, the ability to apprehend the questionnaires, being methotrexate-naïve and consent to participate in this study. Patients with incomplete data were excluded. Only patients receiving methotrexate were included in this study (Fig. 1). Prior treatment included UVB narrow band therapy ($n = 30$), fumaric acid

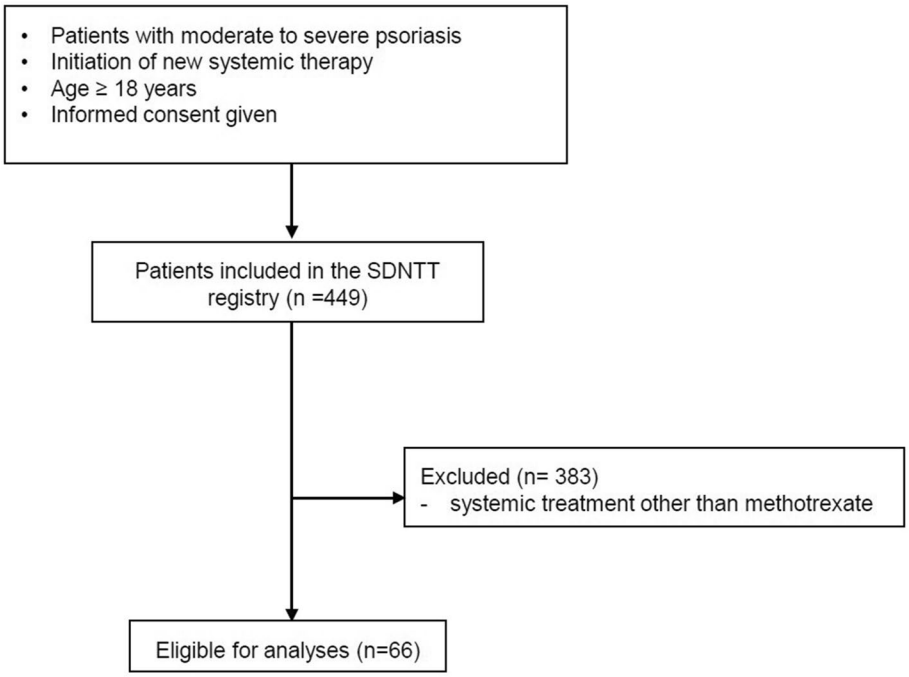

Fig. 1 Enrollment in study. Psoriasis patients with moderate to severe psoriasis who were included into the Swiss Psoriasis Registry (SDNTT) and received treatment with methotrexate were analyzed

esters ($n=3$), cyclosporine ($n=3$), PUVA-therapy ($n=3$) and oral retinoids ($n=3$). 24 patients had no prior systemic therapy before methotrexate. Concomitant topical treatment occurred in all patients.

Data acquisition

Patient characteristics like age, gender, disease severity (i.e., PASI, BSA, NAPSI) was obtained by physicians. Impairment of health-related quality of life was assessed using the patient reported Dermatology Life quality Index (DLQI). Whether the patients suffered from psoriatic arthritis was not analyzed. For this study we analyzed data obtained at week 0 and week 12. Adverse events were collected during each consultation.

Administration and dosage

In the majority of cases, patients received 7.5 mg in week 0. In week 1 10 mg and from then on 15 mg weekly. The route of administration was subcutaneous in all patients. 24 h after the injection, oral folic acid 5 mg was routinely given. Laboratory control was performed before start of therapy and for the first 3 months every 4 weeks.

Statistical analysis

After normality testing, the Mann–Whitney *U* test was used for statistical analysis.

Results

66 patients were included into this study. The mean age was 46.3, ranging from 19 to 80 years. 18 participants were women (27.3%). Most patients solely suffered from plaque psoriasis 53 (80.3%), 3 (4.5%) participants had a pustular palmoplantar psoriasis. A combination of the two types was seen in 2 (3.0%) patients. Only 1 (1.5%) patient suffered from inverse psoriasis, while 4 (6.1%) showed a combined phenotype of plaque psoriasis and inverse psoriasis. Guttate psoriasis was seen in only 1 (1.5%) patients, but 2 (3.0%) patients suffered from combined guttate and plaque psoriasis (Table 1).

At baseline (visit 1, week 0, day 0) the mean PASI was 6.3 ± 3.8 (0.9–24.5). After 12 weeks the mean PASI was reduced to 2.7 ± 2.3 (0–11.6). The majority of the patients showed improvement, which was less than PASI 50 ($n=24$; 36.3%). Only a few experienced worsening of disease ($n=3$; 4.5%) and four participants reached PASI 100 (6.1%). PASI 75 was reached by 12 (18.2%) of all patients. 46 (69.7%) of all patients reached a PASI ≤ 3, compared to 12 (18.2%) at baseline. Nail psoriasis improved from a mean NAPSI of 16.4–13.0. Additionally, life quality drastically increased and mean DLQI was reduced from 10.9 to 4.5. At baseline only 4 patients (6.9%) had a DLQI ≤ 1, while after 12 weeks this was observed in 25 (43.1%) patients (Table 1).

The most common adverse event was an elevation of the liver enzymes. 11% of patients newly developed liver transaminase levels above the upper limit. No leukopenia was reported in our cohort. No severe adverse events were recorded in this cohort over the given time (Table 1).

Table 1 Demographics, baseline data and data at month 3

	Baseline	Month 3	
N	66	66	
Age (mean, SD, range)	46.3 ± 15.5 (19–80)		
Sex (w)	18 (27.3%)		*p* value
Weight (mean, SD, range in kg)	81.2 ± 18.4 (43–115)	–	
Psoriasis type			
Plaque psoriasis (PP) alone	53 (80.3%)		
Pustular palmoplantar psoriasis	3 (4.5%)		
PP + PPP	2 (3.0%)		
Psoriasis inversa (PI)	1 (1.5%)		
PP + PI	4 (6.1%)		
Guttate psoriasis (GP)	1 (1.5%)		
PP + GP	2 (3.0%)		
Baseline visit 1—week 0–day 0			
PASI			
Mean (SD, range)	6.3 ± 3.8 (0.9–24.5)	2.7 ± 2.3 (0–11.6)	$p < 0.0001$
*Q*1	3.45	1.2	
Median	6.1	2.05	
*Q*3	8	3.35	
Average PASI reduction (%)		53.6 ± 32.8 (−70 to 100)	
Worsening (*n*, %)		3 (4.5%)	
PASI0-50 (*n*, %)		24 (36.4%)	
PASI50 (*n*, %)		19 (28.8%)	
PASI75 (*n*, %)		12 (18.2%)	
PASI90 (*n*, %)		4 (6.1%)	
PASI100 (*n*, %)		4 (6.1%)	
PASI *n* = 66			
PASI ≤ 3	12 (18.2%)	46 (69.7%)	
PASI ≤ 2	5 (7.6%)	33 (50.0%)	
PASI ≤ 1	2 (3.0%)	13 (19.7%)	
BSA	7.3 ± 5.5 (0.6–29.5)	3.2 ± 4.0 (0–25.4)	$p < 0.0001$
DLQI (*n* = 58) (mean, SD, range)	10.9 ± 7.2 (0–25)	4.5 ± 5.4 (0–19)	$p < 0.0001$
DLQI *n* = 58			
DLQI ≤ 3	9 (15.5%)	36 (62.0%)	
DLQI ≤ 2	7 (12.0%)	32 (55.2%)	
DLQI ≤ 1	4 (6.9%)	25 (43.1%)	
NAPSI (*n* = 42) (mean, SD, range)	16.4 ± 22.2 (0–75)	13.0 ± 17.0 (0–60)	ns
Adverse events			
Increased liver enzymes (*n*, %)	8 (12.1%)	15 (22.7%)	
Fatigue		4 (6.1%)	
Increased sweating		1 (1.5%)	
Loss of weight		1 (1.5%)	
Vertigo		1 (1.5%)	
Stomach ache		2 (3%)	
Nausea		10 (15.2%)	
Infections		0 (0%)	
SAE		0 (0%)	
Previous therapies			
UVB narrow band	30 (45.5%)		
Fumaric acid esters	3 (4.5%)		
Cyclosporine	3 (4.5%)		
PUVA	3 (4.5%)		
Vitamin A derivates	3 (4.5%)		

ns not significant

When analyzing patients' preceding therapies, most frequently, UVB narrow band therapy ($n=30$, 45.5%) had been performed prior to MTX treatment (Table 1).

Discussion

Despite the fact that MTX is a traditional drug, its effectiveness has only recently been shown in several randomized controlled trials [6, 28, 43]. Because trial data do not always correspond to real-life data with unselected patient populations, we wanted to determine whether the data obtained in the METOP-trial correspond to real-life registry data. Compared to the METOP-trial, the response rates seen our cohort were distinctly lower. Indeed, only 18% of all MTX-treated patients in our registry reached PASI 75. Several explanations contributed to this lower-than-expected effectiveness (Fig. 2).

For instance, in the METOP trial, patients had a PASI at baseline 15.9, compared to 6.3 in our trial. The lower average PASI levels correspond well to the real-life situation in Switzerland. Additionally, the trial lasted longer and the PASI 75 was evaluated at 16 weeks, instead of 12. Therefore, in the METOP trial, patients had more time to reach this threshold than in our analysis of the SDNTT registry. Lastly, all patients in our cohort used MTX 15 mg s.c. weekly and no dose-escalation had been performed. In the METOP trial, patients were allowed to administer a dose of 25 per week in comparison. Furthermore, our cohort was smaller than the METOP trial and no placebo-group existed. Additionally,

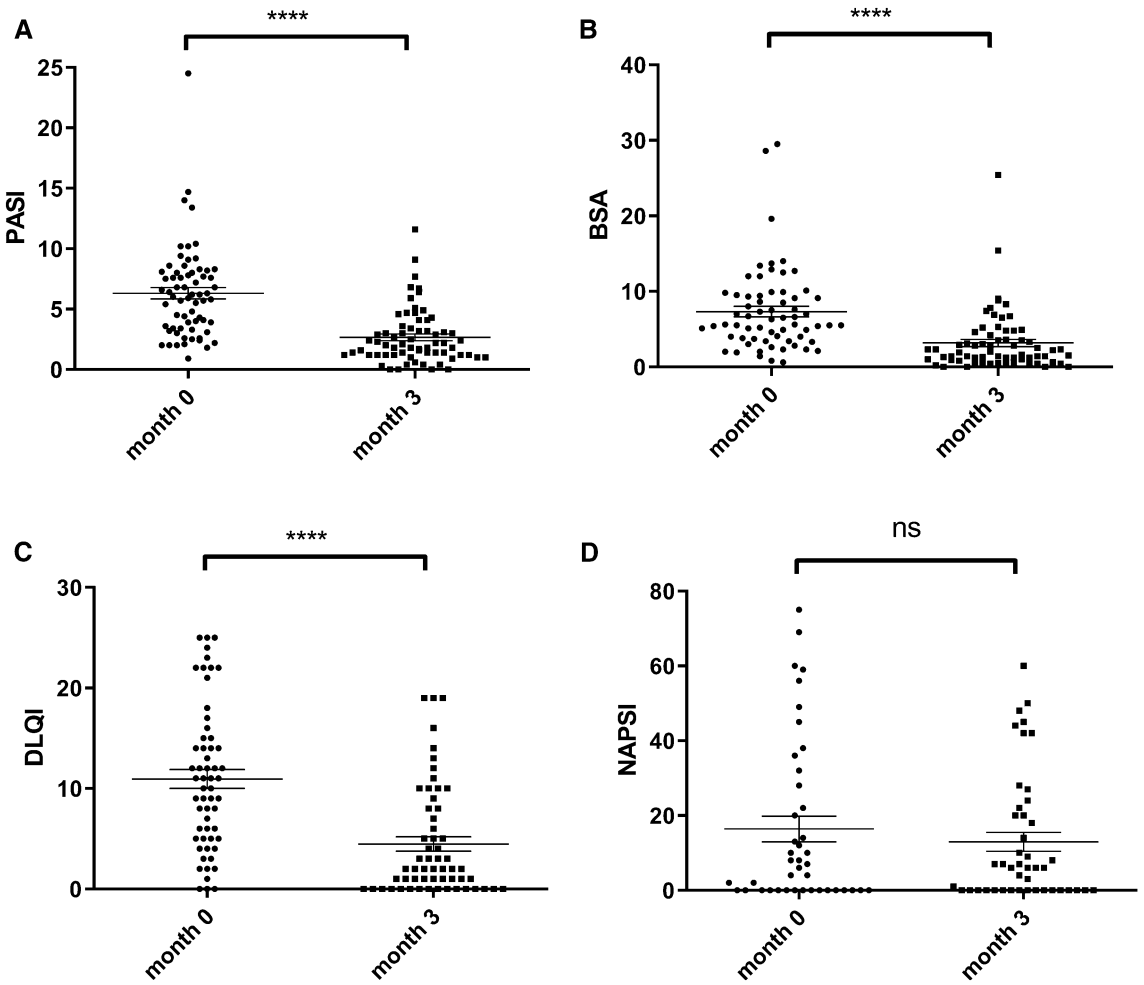

Fig. 2 **a** Psoriasis Activity and Severity Index (PASI). The mean PASI at baseline was 6.3 ± 3.8 (0.9–24.5) and after 12 weeks 2.7 ± 2.3 (0–11.6). This reduction was statistically highly significant ($p<0.0001$). **b** Body surface area (BSA). The BSA covered with psoriasis efflorescences at baseline accounted for 7.3% ± 5.5 (0.6–29.5) of the whole integument. After treatment with subcutaneous methotrexate 15 mg once weekly for 3 months, this number was significantly ($p<0.0001$) reduced to 3.2% ± 4.0 (0–25.4). **c** Dermatology Life Quality Index (DLQI). Significant $p<0.0001$ reduction of DLQI from 10.9 ± 7.2 (0–25) to 4.5 ± 5.4 (0–19) was seen after 3 months of MTX therapy. **d** Nail Psoriasis Severity Index (NAPSI). An absolute reduction of NAPSI from 16.4 ± 22.2 (0–75) to 13.0 ± 17.0 (0–60) was seen. Statistically, this did not reach significance

our analysis stopped after 3 months, while the METOP trial continued until week 52. While in the METOP trial only plaque-type psoriasis patients were included, in our cohort different kinds of psoriasis types were included.

Additionally, these differences could explain for the lower number of adverse events reported in our real-life cohort. No case of major cardiovascular event, neoplasm or death was reported in our study, nor did we observe a case of neutropenia. In other studies, relevant drop-out rates were seen with MTX [51], which we did not observe in the 12 weeks of analysis. Another possible explanation is underreporting in real-world setting.

Taken together, MTX is a cost-effective and popular treatment among our patients, but real-world data does not show it to be a competitive treatment in contrast to newer drugs.

Almost 70% of all patients reached a PASI ≤ 3 and 43.1% a DLQI ≤ 1. From our experience, the majority of patients is satisfied when a PASI ≤ 3 is reached. This is in concordance with the DLQI scores seen (62% reached a DLQI ≤ 3).

Therefore, we will continue using methotrexate as a first-line treatment in patients with moderate to severe psoriasis due to good experience and high patient satisfaction. In terms of effectiveness, our study points out that the real-world PASI 75 might significantly differ from the PASI 75 measured in clinical trials. In fact, we believe that the term "real-world PASI 75" would give clinicians a better understanding of what therapeutic success can be expected in daily routine.

Compliance with ethical standards

Conflict of interest Mathias Drach has no conflict of interest. Karolina Papageorgiou has no conflict of interest. Julia-Tatjana Maul is an employee of USZ and holds a "Filling the GAP" scholarship. Vahid Djamei has no conflict of interest. Nikhil Yawalkar has received honoraria for consulting and advisory board attendance from Abbvie, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Gebro, Janssen, Leo, Novartis, MSD and Pfizer. Peter Häusermann has received honoraria for consulting and advisory board attendance from Abbvie, Almirall, Celgene, Eli Lilly, Galderma, Janssen, Leo and Novartis. Florian Anzengruber is an employee of the University Hospital Zurich. He has received honoraria from Abbvie, Celgene, Leo Pharma, Galderma, Eli Lilly, Almirall, Janssen—Cilag and Novartis, but has no financial interest, nor holds any shares of any pharmaceutical company. Alexander A. Navarini is on the advisory board of AbbVie, Pfizer, Novartis, Celgene, MSD, Galderma, Sanofi, Boehringer-Ingelheim, Lilly.

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