ORIGINAL ARTICLE

Current practice of methotrexate use for psoriasis: results of a worldwide survey among dermatologists

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Abstract

Background Methotrexate is one the most commonly used systemic therapies for psoriasis. Despite its widespread use in psoriasis therapy, dermatologists' practice regarding the use of methotrexate has not been investigated on global scale.

Objective To evaluate the real life use of methotrexate for psoriasis treatment in the dermatological community worldwide.

Methods A questionnaire consisting of 41 questions was designed by the Psoriasis International Network (PIN). Questions focused on safety, dosing, administration, folic acid supplementation and combination therapy aspects of methotrexate use. The anonymous web-based survey was distributed to dermatologists by the national coordinators of PIN.

Results Between 2 April and 7 August 2012, 481 dermatologists from 63 countries completed the questionnaire. Most respondents were from European and South American countries, whereas the response rate from Central America and the Near East was lowest. The majority of responders were experienced dermatologists (86% had more than 5 years of experience in psoriasis treatment). Starting and maintenance doses of 10 mg of methotrexate or lower were reported by 67% and 42% of respondents respectively. Thirty-eight per cent of respondents stop treatment at a cumulative dose of 2 g, whereas 36% did not consider cumulative dose important in this respect. The primary mode of administration was oral, and the majority of respondents administer folic acid supplementation. Almost all respondents monitored full blood count, liver and renal function tests, whereas procollagen 3 amino terminal peptide measurement and transient elastography is used by only a minority of dermatologists. There were significant differences concerning the doses, routes of administration and safety monitoring among the clinical practices in different geographical locations.

Conclusion Current clinical practice of methotrexate use in psoriasis is not uniform, depends on geographical location, and is not in full agreement with clinical guidelines.

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Conflicts of interest

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Introduction

Psoriasis is a common, chronic, multifactorial, T-cell-mediated inflammatory disease that affects 2–3% of the population.[1,2] Methotrexate is an effective, commonly used systemic therapy for moderate-to-severe psoriasis.[3,4] Despite methotrexate having been used for the treatment of psoriasis for more than 50 years, regimens for use are not uniform in clinical practice. This can be primarily attributed to the fact that methotrexate treatment has developed without randomized clinical trials and uniform recommendations on how the drug should be used were lacking.

Table 1 Baseline characteristics of survey respondents ($N = 481$)

Characteristics	*n* (%)
Sex	
Female	240 (49.9)
Male	241 (50.1)
Age	
Mean overall (SD)	48.3 (10.7)
27–40 years	134 (27.8)
41–55 years	207 (43.0)
56–80 years	137 (28.5)
Missing	3 (0.7)
Years of experience in psoriasis treatment	
Maximum 5 years	68 (14.1)
6–10 years	85 (17.7)
More than 10 years	326 (67.8)
Missing	2 (0.4)
Average weekly number of psoriasis patients consulted	
0–5	120 (24.9)
6–10	133 (27.6)
11–20	117 (24.3)
21–50	86 (17.9)
>50	25 (5.2)
Region of practice	
Africa	37 (7.7)
Near East	34 (7.1)
Europe	183 (38.0)
Asia	54 (11.1)
North America	37 (7.7)
Central America	24 (5.0)
South America	109 (22.7)
Missing or not included	3 (0.7)
Countries with at least five respondent	
Algeria	10
Argentina	38
Brazil	13
Canada	27
Chile	11
Colombia	16
Costa Rica	11
Egypt	16
France	34
Georgia	12
Honduras	7
Hungary	17
India	20
Iran	8
Israel	9
Italy	9
Korea, South	5
Lebanon	6
Mexico	11
Palestine	5
Peru	9
Portugal	5
Saudi Arabia	5
Slovenia	7
Spain	38
Taiwan (Republic of China)	17
Tunisia	5
Turkey	9
Ukraine	5
United Kingdom	24
United States of America	10
Venezuela	6

This has led to the development of several dosing, scheduling, safety monitoring and folic acid supplementation approaches.[5,6] Recently, data accumulating from a few randomized trials have led to the development of more consistent clinical recommendations.[7,8] It is not known, however, how these recommendations are translated into current dermatological practice. Whilst it seems reasonable that differences in the characteristics of dermatologists (e.g. age, gender, experience) may contribute to different treatment regimens, this has not been scientifically investigated regarding methotrexate use in psoriasis. Furthermore, although there are anecdotal reports on the differences in use of methotrexate in different geographical regions,[9] no study has been performed yet to identify these disparities.

Materials and methods

A questionnaire consisting of 41 questions was designed by the board members of the Psoriasis International Network (PIN), a network of psoriasis professionals and patient representatives from 95 countries. Participants were asked to specify their age, how experienced they were in the treatment of psoriasis, and whether their practice was public hospital or private/office based, or both. Questions focused on the dermatologist's current practice regarding pretreatment screening tests, safety monitoring, dosing, drug administration, folic acid supplementation, efficacy assessment and combination therapy aspects of methotrexate use. The anonymous web-based survey was distributed to dermatologists by the national coordinators of PIN. The questionnaire can be viewed online following this link.

Statistical analysis was carried out using SPSS 15.0 statistical program. Pearson chi-squared, paired *t*-test test were used. *P* values of less than 0.05 were considered statistically significant.

Results

Between 2 April and 7 August 2012, 481 dermatologists from 63 countries completed the questionnaire. The questionnaires were for the most part completed in their entirety; the response rate

Table 2 Relationships of recommended methotrexate and folic acid doses with gender, age, clinical experience, geographical location and methotrexate dose increase habit of the dermatologist

	Week 1	Week 4	Maintenance	Maximum	Cumulative MTX dose (g)	Folic acid weekly dose (mg)
	Weekly MTX dose (mg)					
Total	9.7 ± 5.1	12.9 ± 4.6	12.3 ± 4.5	22.1 ± 5.3	2.5 ± 1.1	16.8 ± 11.7
Gender						
Female	9.1 ± 5.1	12.4 ± 4.5	12.2 ± 4.5	21.4 ± 5.4	2.5 ± 1.1	16.8 ± 11.7
Male	10.3 ± 5.0*	13.4 ± 4.6*	12.4 ± 4.6	22.8 ± 5.2*	2.5 ± 1.1	16.9 ± 11.7
Age						
28–40 years old	9.2 ± 4.6	12.5 ± 4.6	12.2 ± 4.8	21.5 ± 5.3*	2.3 ± 0.9*	17.6 ± 11.7
41–55 years old	10.0 ± 4.8	13.0 ± 4.4	12.5 ± 4.5	21.9 ± 4.8*	2.5 ± 1.1	17.0 ± 11.3
56–80 years old	9.9 ± 5.9	13.3 ± 4.7	12.2 ± 4.3	23.2 ± 5.9	2.7 ± 1.2	16.0 ± 12.2
Experience						
<5 years of experience	9.3 ± 4.7	12.1 ± 4.2	11.4 ± 4.7	21.0 ± 5.1	2.4 ± 1.1	18.7 ± 12.9
6–10 years of experience	9.8 ± 4.7	12.6 ± 4.9	12.4 ± 5.0	21.6 ± 5.4	2.4 ± 1.1	18.8 ± 11.5
>10 years of experience	9.8 ± 5.2	13.2 ± 4.5	12.5 ± 4.4	22.5 ± 5.3*	2.6 ± 1.1	16.0 ± 11.4*
Location						
Africa	13.4 ± 5.2†	15.3 ± 5.3†	12.8 ± 5.2‡	23.6 ± 4.2‡	2.0 ± 0.6	22.2 ± 9.9†
Near East	8.2 ± 4.7‡,†	13.4 ± 4.3†	12.4 ± 4.6‡,†	22.4 ± 4.1‡	2.8 ± 1.3‡,†	19.1 ± 11.8
Europe	9.0 ± 5.1‡,†	12.8 ± 4.2‡,†	13.1 ± 4.0‡,†	22.8 ± 4.1‡	2.7 ± 1.2‡,†	14.8 ± 11.4‡
Asia	8.6 ± 4.6‡,†	11.3 ± 4.2‡	9.3 ± 4.1†	18.2 ± 5.8†	1.9 ± 0.7	20.9 ± 11.7†
North America	8.5 ± 4.7‡,†	12.9 ± 3.6‡	14.7 ± 3.4‡	24.1 ± 5.1‡	3.0 ± 1.1‡,†	16.1 ± 11.8‡
Central America	10.5 ± 5.2‡	11.8 ± 6.4‡	10.5 ± 5.5†	20.6 ± 6.0†	2.4 ± 1.2	21.6 ± 13.0†
South America	10.9 ± 4.7‡	13.2 ± 4.7‡,†	11.9 ± 4.5‡,†	21.8 ± 6.4‡,†	2.5 ± 1.0‡,†	15.2 ± 11.1‡
Dose increase practice						
Never or rarely (n = 156)	11.5 ± 5.8	14.2 ± 5.2	12.1 ± 5.3	20.7 ± 5.6	2.4 ± 1.1	17.3 ± 11.4
Sometimes (n = 128)	9.4 ± 4.6*	12.8 ± 4.2*	12.1 ± 4.4	22.1 ± 5.0*	2.6 ± 1.2	16.9 ± 11.6
Often or always (n = 197)	8.5 ± 4.3*	12.0 ± 3.9*	12.7 ± 3.9	23.2 ± 5.1*	2.6 ± 1.0	16.4 ± 12.0

Gender: * $P < 0.05$ compared to females.
Age:
• Maximum weekly dose: *$P < 0.05$ compared to 56-80 years old.
• Cumulative dose: *$P < 0.05$ compared to 56-80 years old.
Experience:
• Maximum weekly dose: *$P < 0.05$ compared to <5 years of experience.
• Folic acid weekly dose: *$P < 0.05$ compared to 6–10 years of experience.
Location:
• Week 1 dose: ‡$P < 0.05$ compared to Africa, †$P < 0.05$ compared to South America.
• Week 4 dose: ‡$P < 0.05$ compared to Africa, †$P < 0.05$ compared to Asia.
• Maintenance dose: ‡$P < 0.05$ compared to Asia, †$P < 0.05$ compared to North America.
• Maximum weekly dose: ‡$P < 0.05$ compared to Asia, †$P < 0.05$ compared to North America.
• Cumulative dose: $P < 0.05$ compared to Africa, †$P < 0.05$ compared to Asia.
• Folic acid weekly dose: ‡$P < 0.05$ compared to Africa, †$P < 0.05$ compared to Europe.
Dose increase practice:
• Week 1 dose: *$P < 0.05$ compared to Never or rarely.
• Week 4 dose: *$P < 0.05$ compared to Never or rarely.
• Maximum weekly dose: *$P < 0.05$ compared to Never or rarely.

to each question was over 98% (Table 1). Most respondents were from European and South American countries (number of respondent n = 183 and 109 respectively). The number of responses received from other regions were comparable (Africa n = 37; Near East n = 34; Asia n = 54; North America n = 37 and Central America n = 24). The following participating coun-

tries were considered as Near East: Iran, Israel, Lebanon, Kuwait, Palestine and Saudi Arabia. The countries with the most participating dermatologists were Argentina, Spain and France (n = 38, 38 and 34, respectively; for the list of countries with at least five respondents, please see Table 1). As the response rate from Australia and New Zealand was very low (one respondent from each country), we did not include these two countries in our subanalysis of geographical regions. The female-to-male ratio was equal (240 vs. 241), and the majority of respondents were middle aged, experienced dermatologists (mean age was 48.3 years, 86% had more than 5 years and 68% had more than 10 years of experience in psoriasis treatment). Male respondents were somewhat older and more experienced than female respondents (data not shown). Most dermatologists saw less than 20 psoriasis patients weekly.

Methotrexate dosing and administration

The most frequent starting dose of methotrexate was 7.5 mg (n = 131, 27%), whereas 15 and 5 mg were the second and third most frequently used doses (n = 100, 21% and n = 94, 20%, respectively). Doses lower than or equal to 10 mg were recommended by two-thirds of the respondent dermatologists (n = 324, 67.4%). The mean starting dose was 9.7 ± 5.1 mg (Table 2). Respondents reported the use of increasing doses at the second, third and fourth week of methotrexate therapy, the mean doses being 11.7 ± 4.5, 12.6 ± 4.4 and 12.9 ± 4.6 mg respectively. At the second, third and fourth visits, 15 mg was the most frequently recommended dose (n = 152, 31.6%, n = 174, 36.2% and n = 191, 39.7% respectively). More than a third of the respondents (n = 188, 39.1%) recommend a maximum dose of 10 mg at week 4.

We were interested to learn how frequently respondents applied a test dose of methotrexate. We considered the first week dose to be a test dose, if it was not more than 7.5 mg and the dose was increased by a minimum of 5 mg at the next visit. Using these criteria, 102 (21.2%) dermatologists used a test dose strategy (data not shown). The mean methotrexate maintenance dose (12.3 ± 4.5 mg) was practically same as the week 4 dose, and a large proportion of dermatologists (n = 204, 42.4%) prescribe weekly doses of methotrexate at 10 mg or lower for treatment maintenance. The mean maximum weekly dose was 22.1 ± 5.3 mg. Again, a significant proportion of respondents were cautious regarding the recommended highest doses: in 103 cases (21.5%) the maximum dose prescribed did not exceed 15 mg.

Concerning the maximum cumulative dose, it should be noted that a significant number of dermatologists (n = 187, 38.9%) do not consider cumulative dose an important factor in treatment continuation. Among those who provided a numerical maximum cumulative dose, answers were almost equally distributed between 1.5 g (n = 86, 29.5%), 2.0 g (n = 82, 28.1%) and 3.0 g (n = 87, 29.8%), whereas 5 g doses were used by fewer respondents (n = 34, 11.6%). The mean maximum cumulative dose was 2.5 ± 1.1 mg.

Female dermatologists were found to be more conservative than males in their starting doses, with significantly lower doses: 9.1 ± 5.1 mg vs. 10.3 ± 5.0 mg at week 1 and 12.4 ± 4.5 mg vs. 13.4 ± 4.6 mg at week 4 respectively) (Table 2. In contrast, there was no difference in the recommended maintenance doses between female and male respondents (12.2 ± 4.5 and 12.4 ± 4.6 mg respectively). While female dermatologists prefer to apply lower maximum methotrexate doses (21.4 ± 5.4 and 22.8 ± 5.2 mg, females and males, respectively), there is no gender difference in the cumulative methotrexate dose (2.5 ± 1.1 and 2.5 ± 1.1 g). The age and clinical experience of the dermatologists did not influence the recommended starting and maintenance doses of methotrexate doses: week 1, week 4 and maintenance doses were not significantly different between the groups of 28–40 years old, 41–55 years old and 56–80 years old dermatologists, and the same applied to dermatologists with less than 5 years' experience, 6–10 years' experience and more than 10 years' experience in psoriasis treatment. In contrast, older and more experienced dermatologists tended to use higher maximum weekly and cumulative methotrexate doses (for values and significance see Table 2).

Interestingly, when the methotrexate dosing patterns in different geographical locations were analysed, relatively large differences were found. The starting (week 1) methotrexate dose was significantly higher in African countries (13.4 ± 5.2 mg) than in any other region. Dermatologists recommended rather conservative week 1 doses in the Near East (8.2 ± 4.7 mg),

Table 3 Primary mode of methotrexate administration in different geographical locations

	Oral	Intramuscular	Subcutaneous
Total (n = 481)	423 (87.9)	35 (7.3)	21 (4.4)
Gender			
Female (n = 240)	216 (90.0)	14 (5.8)	10 (4.2)
Male (n = 241)	209 (86.7)	21 (8.7)	11 (4.6)
Location			
Africa (n = 37)	24 (64.9)	13 (35.1)	0 (0.0)
Near East (n = 34)	28 (82.4)	6 (17.6)	0 (0.0)
Europe (n = 184)	157 (85.8)	9 (4.9)	18 (9.8)
Asia (n = 54)	52 (96.3)	2 (3.7)	0 (0.0)
North America (n = 37)	37 (100.0)	0 (0.0)	0 (0.0)
Central America (n = 24)	23 (95.8)	1 (4.2)	0 (0.0)
South America (n = 109)	102 (93.6)	4 (3.7)	3 (2.8)

Values within parenthesis are expressed in percentage.

North America (8.5 ± 4.7 mg), Asia (8.6 ± 4.6 mg) and Europe (9.0 ± 5.1 mg), whereas respondents from Central and South America generally use somewhat higher starting doses (10.5 ± 5.2 and 10.9 ± 4.7 mg respectively). At the 4th week, African dermatologists continue to be using the highest weekly doses (15.3 ± 5.3 mg), whereas the mean dose in Asia (11.3 ± 4.2 mg) is significantly lower than in most other regions. The dosing pattern seems to change considerably during the maintenance period, dermatologists in North America recommending significantly higher maintenance and maximum weekly doses (14.7 ± 3.4 and 24.1 ± 5.1 mg respectively) than colleagues in most other geographical regions. In Asia, mean maintenance and maximum doses (9.3 ± 4.1 and 18.2 ± 5.8 mg respectively) are significantly lower than in any other region, except for Central America. The highest and lowest cumulative doses – calculated as the weekly maintenance dose multiplied by the length of treatment (in weeks) – were reported in regions with the highest and lowest maintenance doses, namely North America and Asia (3.0 ± 1.1 and 1.9 ± 0.7 g respectively). It is, however, somewhat surprising that the cumulative dose reported by African dermatologists (2.0 ± 0.6 g) is the second lowest value. Thus, it appears that while the starting doses are high in Africa, dermatologists tend to continue methotrexate treatment for shorter periods than in other geographical regions.

We next analysed the relationship between the applied methotrexate doses and the dermatologists' tendency to increase the dose in case of non-satisfactory clinical improvement. Although a large proportion of dermatologists (n = 197, 41.0%) always or frequently (in more than 75% of cases) increase the dose in case of inadequate therapeutic response, a significant portion (n = 156, 32.4%) reported to either never or rarely do so in patients with inadequate response. Interestingly, those who never or rarely increase the dose prescribe significantly higher first and fourth week doses of methotrexate than those who are more likely to raise the dose (Table 2). On the other hand, while there was no difference in the recommended maintenance and cumulative doses between the groups, the maximum doses were significantly lower among those who generally do not increase the methotrexate dose in case of suboptimal therapeutic result (Table 2).

Methotrexate administration

Most of the participating dermatologists (n = 423, 87.9%) primarily prescribe oral methotrexate (Table 3); intramuscular and subcutaneous administration is used considerably less frequently (n = 35, 7.3% and n = 21, 4.4% respectively). Whilst the choice of primary mode of methotrexate administration is not influenced by the gender of the prescribing dermatologist, it is heavily dependent on the geographical location. More than one-third of African dermatologists (n = 13, 35.1%) principally prescribe methotrexate in the form of intramuscular injection, whereas subcutaneous use is almost exclusively limited to European countries. A relatively small portion of respondents switch from oral to intramuscular or subcutaneous administration always or frequently (in more than 75% of cases) in case of inadequate therapeutic response (n = 100, 20.8%) or gastrointestinal side effects (n = 155, 32.2%). A number of respondents never or rarely consider transitioning from oral to injectable methotrexate (because of inadequate efficacy (n = 268, 55.7%) or gastrointestinal adverse events (n = 222, 46.2%).

Folic acid supplementation

Most of the participating dermatologists (n = 392, 81.5%) prescribe folic acid supplementation during methotrexate treatment in more than 75% of the cases (data not shown). On the other hand, only 7 (1.5%) and 30 (6.2%) respondents reported that

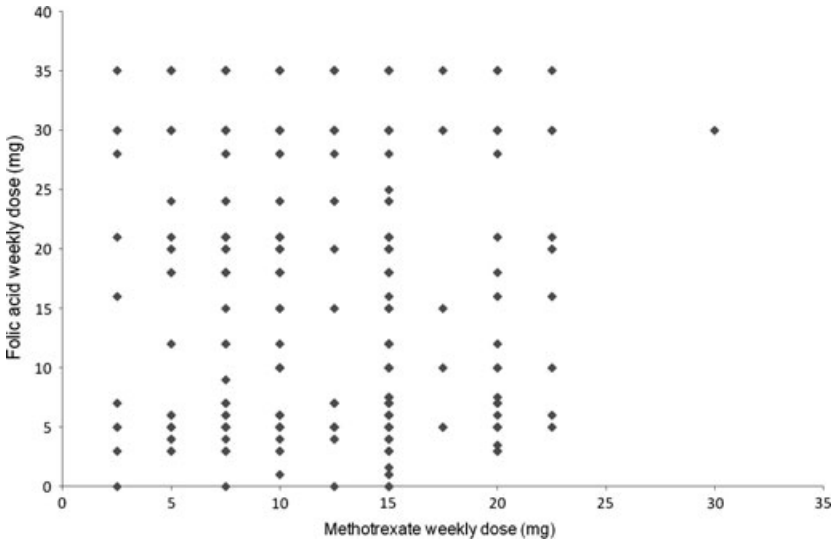

Figure 1 Folic acid and methotrexate weekly maintenance doses recommended by the respondent dermatologist (n = 481). Each dot represents one respondent. No correlation was observed between the applied weekly methotrexate and recommended weekly folic acid doses.

Table 4 Frequency of examinations recommended by respondent dermatologists before and during methotrexate therapy of psoriasis

	Pretreatment	1st month	2nd–3rd months	After 3 months
CBC	474 (98.5)	473 (98.3)	467 (97.1)	467 (97.1)
Liver function tests	475 (98.8)	460 (95.6)	472 (98.1)	471 (97.9)
Renal function tests	417 (86.7)	314 (65.0)	325 (67.6)	342 (71.1)
Hepatitis B serology	314 (65.3)	20 (4.2)	11 (2.3)	10 (2.1)
Hepatitis C serology	303 (63.0)	18 (3.7)	10 (2.1)	11 (2.3)
Albumin level	205 (42.6)	129 (26.8)	136 (28.3)	147 (30.6)
Prothrombin level	77 (16.0)	68 (14.1)	65 (13.5)	73 (15.2)
HIV serology	213 (44.3)	13 (2.7)	5 (1.0)	5 (1.0)
Chest X-ray	214 (44.5)	25 (5.2)	27 (5.6)	28 (5.8)
Mantoux test	94 (19.5)	6 (1.2)	5 (1.0)	7 (1.5)
Quantiferon test	34 (7.1)	2 (0.4)	5 (1.0)	4 (0.8)
ANA screen	43 (8.9)	9 (1.9)	7 (1.5)	7 (1.5)
Procollagen	56 (11.6)	8 (1.7)	20 (4.2)	44 (9.1)
Transient elastography	19 (4.0)	3 (0.6)	4 (0.8)	6 (1.2)

Values within parenthesis are expressed in percentage.

they never or very rarely (in less than 25% of cases) supplement methotrexate treatment with folic acid. The two most frequently prescribed weekly doses were 30 mg and 5 mg (n = 97, 24.7% and n = 84, 21.4% respectively). The mean weekly folic acid dose was 16.8 ± 11.7 mg, and it was not influenced significantly by the gender, age and dose increasing habit of the dermatologist (Table 2). On the other hand, physicians with less than 10 years of experience in psoriasis treatment tended to recommend higher doses than more experienced colleagues. Similarly, geographical location of the respondent significantly influenced the quantity of the recommended folic acid, as African dermatologists reported at least 50% higher doses than Europeans (22.2 ± 9.9 and 14.8 ± 11.4 mg respectively). No correlation between the recommended folic acid dose and the prescribed weekly maintenance dose of methotrexate was found (Fig. 1).

Pretreatment work-up and safety monitoring

Complete blood count (CBC) and liver function tests (LFT) were recommended by almost all participants before prescribing methotrexate, while somewhat fewer, but still a significant portion of dermatologists recommend renal function tests (RFT) (Table 4). Hepatitis B and C serology tests are recommended by approximately two-thirds of the respondents. While chest X-ray films are used for tuberculosis screening relatively frequently

Table 5 Frequency of investigations recommended by respondent dermatologists in different geographical regions before methotrexate therapy and for the monitoring of long-term liver toxicity during methotrexate treatment

	Africa	Near East	Europe	Asia	North America	Central America	South America
Predose workup							
CBC	36 (97.3)	33 (97.1)	180 (98.4)	54 (100.0)	37 (100.0)	24 (100.0)	108 (99.1)
Liver function tests	36 (97.3)	33 (97.1)	181 (98.9	54 (100.0)	37 (100.0)	23 (95.8)	109 (100.0)
Renal function tests	29 (78.4)	28 (82.4)	163 (89.1)	44 (81.5)	34 (91.9)	18 (75.0)	99 (90.8)
Hepatitis B serology	20 (54.1)	16 (47.1)	139 (76.0)	35 (64.8)	22 (59.5)	8 (33.3)	73 (67.0)
Hepatitis C serology	21 (56.8)	16 (47.1)	137 (74.9)	29 (53.7)	21 (56.8)	8 (33.3)	70 (64.2)
Albumin level	13 (35.1)	14 (41.2)	92 (50.3)	17 (31.5)	14 (37.8)	7 (29.2)	46 (42.2)
Prothrombin level	4 (10.8)	3 (8.8)	25 (13.7)	4 (7.4)	3 (8.1)	5 (20.8)	33 (30.3)
HIV serology	13 (35.1)	5 (14.7)	94 (51.4)	18 (33.3)	11 (29.7)	6 (25.0)	66 (60.6)
Chest X-ray	13 (35.1)	9 (26.5)	86 (47.0)	28 (51.9)	14 (37.8)	6 (25.0)	58 (53.2)
Mantoux test	1 (2.7)	8 (23.5)	27 (14.8)	7 (13.0)	4 (10.8)	3 (12.5)	44 (40.4)
Quantiferon test	1 (2.7)	2 (5.9)	21 (11.5)	2 (3.7)	4 (10.8)	1 (4.2)	3 (2.8)
ANA screen	0 (0.0)	1 (2.9)	15 (8.2)	1 (1.9)	0 (0.0)	4 (16.7)	18 (16.5)
Procollagen	3 (8.1)	1 (2.9)	45 (24.6)	1 (1.9)	0 (0.0)	1 (4.2)	4 (3.7)
Transient elastography	1 (2.7)	1 (2.9)	13 (7.1)	0 (0.0)	1 (2.7)	1 (4.2)	2 (1.8)
Long-term liver toxicity workup							
Transient elastography	2 (5.4)	7 (20.6)	57 (31.1)	4 (7.4)	9 (24.3)	2 (8.3)	11 (10.1)
Procollagen	13 (35.1)	7 (20.6)	85 (46.4)	6 (11.1)	0 (0.0)	2 (8.3)	12 (11.0)
Liver biopsy	6 (16.2)	14 (41.2)	13 (7.1)	9 (16.7)	13 (35.1)	4 (16.7)	23 (21.1)

Highest frequencies are marked with dark grey shading, whereas lowest frequencies are marked with white shading.
Values within parenthesis are expressed in percentage.

(n = 214, 44.5%), Mantoux and interferon release tests are not as widespread (n = 94, 19.5% and n = 34, 7.1% respectively). Similarly, the use of procollagen 3 amino terminal peptide (PIIIP) and transient elastography examinations, as well as antinuclear antibody (ANA) determinations, is limited (n = 56, 11.6%; n = 19, 4.0%; n = 43, 8.9%, respectively). Almost half of the dermatologists recommended HIV screening and albumin level determination before starting methotrexate therapy (n = 213, 44.3% and n = 205, 42.6% respectively). While the frequency of dermatologists recommending CBC, LFT and RFT continues to be high during subsequent visits, only a few participant order viral hepatitis and HIV serology, chest X-ray, Mantoux test, interferon release assay or serum ANA titres. The percentages of respondents performing serum albumin and prothrombin level examinations on follow-up visits remained almost constant (Table 4).

Next, we subdivided the workup results according to the geographical location of the respondent dermatologists (Table 5). CBC, LFT and RFT were uniformly frequently recommended in the pretreatment workup. Hepatitis B and C serologic tests are part of routine examinations in Europe, as approximately three-quarters of dermatologists perform the test; these tests are rarely ordered in Central America (n = 8, 33.3% for both tests). Interestingly, HIV testing, chest X-ray and Mantoux testing is most frequently ordered in South America, whereas interferon release assays, PIIIP measurement, and transient elastography examinations are performed mostly in Europe. It is also somewhat surprising that the use of ANA screening, PIIIP and transient elastography was rarely reported from North America.

Regarding the long-term monitoring of liver toxicity, transient elastography and PIIIP examinations were most popular among European dermatologists (n = 57, 31.1% and n = 85, 46.4%, respectively). Interestingly, while PIIIP determinations are not performed in North America, liver biopsy is relatively frequently recommended there and in the Near East (n = 14, 41.2% and n = 13, 35.1%, respectively). Liver biopsy is only performed occasionally in Europe (n = 13, 7.1%).

Discussion

Although the number of respondents in this survey was high, their geographical distribution was not uniform. As the idea of this survey originated in Europe, it is not surprising that the contribution from European countries was highest. While in other regions the response rate was lower, we may still consider the results to be representative for the given area. It is likely that dermatologists with an interest in methotrexate treatment are probably overrepresented in this survey, and thus, the use of methotrexate in the total dermatological community is perhaps lower than calculated here. Nevertheless, despite all the drawbacks of the online survey approach, our results are the first to provide a global snapshot of methotrexate prescribing for psoriasis.

Several of the survey results were surprising. Generally, methotrexate doses were lower than those recommended by current guidelines.[7,8] Approximately two-thirds of the dermatologists start with doses lower than or equal to 10 mg, and more than 40% of respondents prescribe 10 mg or lower doses for maintenance treatment. Interestingly, female dermatologists were found to be more conservative in choosing their starting dose; however, their maintenance strategy did not differ from that of male colleagues. A substantial portion of dermatologists (n = 187, 38.9%) do not consider cumulative dose an important factor in the decision of treatment continuation, suggesting that new tools for hepatotoxicity monitoring may change our approach to methotrexate treatment.

Perhaps the most interesting findings relate to the differences between geographical regions. It seems that the administration schedules are quite diverse. In Africa dermatologists start with high doses but maintenance doses are not as high in some geographical regions, and they tend to continue methotrexate treatment for shorter periods of time. North American based dermatologists recommend the highest maintenance and maximum weekly doses, as well as the highest maximum cumulative doses. The opposite occurs in Asia, where doses are at least 25% lower in every category. This may perhaps be due to a greater incidence of adverse effects in the Asian population: according to a recent report, more than 50% of patients treated with methotrexate in a psoriasis centre in Malaysia developed deranged liver transaminases, and almost 10% required MTX withdrawal due to hepatotoxicity.[10] Consequently, Asian-based dermatologists use increased caution when prescribing methotrexate. Another important factor to consider would be higher body mass index (BMI) in the USA and Europe compared to Asia (the average male BMI in the USA, France and Japan are 29, 25.55 and 23.7 respectively). Moreover, regulatory differences may also affect clinical practice in different regions. In any case, these results indicate that extrapolation of data from clinical trials performed in one geographical area to another carries significant risk. It is also interesting to note that more than one-third of African dermatologists principally prescribe intramuscular methotrexate, whereas subcutaneous use is almost exclusively limited to European countries.

According to our results, folic acid is generally prescribed by dermatologists in association with methotrexate therapy; however, dosing and scheduling are far from being uniform, as reported previously.[11–13] Weekly doses of folic acid are not dependent on the prescribed weekly maintenance dose of methotrexate. On the other hand, geography is again an important factor, as African dermatologists reported the use of significantly higher doses than colleagues from other regions.

While there are some common themes in predosing and follow-up workup examinations, such as liver and RFT and CBC, there are major differences as well. The relatively high frequency

of HIV testing, chest X-ray and Mantoux testing in Africa is probably due to the high prevalence of HIV and tuberculosis in this region. However, the use of interferon release assays, PIIIP and transient elastography examinations is limited by cost. It is also somewhat surprising that use of ANA screening, PIIIP and transient elastography was practically unreported in North America. Regarding the long-term monitoring of liver toxicity, the use of transient elastography and PIIIP examinations in Europe seem to provide enough data to avoid liver biopsy, as suggested by a report from a recent consensus conference.[14] Interestingly, in North America, liver biopsy is still relatively frequently recommended.

According to our findings, the use of methotrexate in clinical practice appears to differ substantially from guideline recommendations in several aspects, particularly dosing. It should be noted, however, that there is limited evidence from randomized controlled trials regarding methotrexate dosing in psoriasis, and evidence-based data is mostly derived from European and North-American clinical trials. As this forms the foundation for currently available guidelines, it is not surprising that European and North-American survey respondents seem to be more compliant with guidelines than dermatologists from other regions. As referred to earlier, these deviations may stem from regulatory variances, differences in the physiological aspects of the populations or simply prescribing tradition. Therefore, we suggest that the aetiology of these geographical differences should be investigated. There may be various underlying reasons, e.g. population differences in liver enzyme function or weight. If, however, this is not the case, the reason of deviation from the guidelines (e.g. local regulations, common myths in the dermatologic community, etc.) should be ascertained and corrected.

The results of this study are limited by several factors. Surveys generally provide lower quality information; however, this is usually balanced by the robustness of data due to the large sample size of the studied population. In addition, it is likely that dermatologists with more experience in methotrexate therapy are overrepresented in this study; therefore, the conclusions may not necessarily reflect the clinical practice of the entire dermatological community. Furthermore, the geographical distribution of respondents was uneven, thus, some countries or continents are underrepresented in the study.

In conclusion, while survey methodology might provide less accurate data than other methods, our study provides substantial new information regarding the use of methotrexate for psoriasis treatment. There is a need to harmonize methotrexate use in psoriasis, taking into account geographical and potential ethnic differences in drug efficacy and safety.

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