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GUIDELINES

Real-World Experience of Methotrexate in the Treatment of Skin Diseases: an Italian Delphi Consensus

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ABSTRACT

Background: After decades of use, methotrexate displays an established safety and efficacy profile in both in-hospital and outpatient settings. Despite its widespread use, there is surprisingly little clinical evidence to guide daily practice with methotrexate in dermatology.

Objectives: To provide guidance for clinicians in daily practice for areas in which there is limited guidance.

Methods: A Delphi consensus exercise on 23 statements was carried out on the use of methotrexate in dermatological routine settings.

The names and affiliations of the members of the "METHOD study working group" are provided in the Acknowledgements section.

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Results: Consensus was reached on statements that cover six main areas: (1) pre-screening exams and monitoring of therapy; (2) dosing and administration in patients naïve to methotrexate; (3) optimal strategy for patients in remission; (4) use of folic acid; (5) safety; and (6) predictors of toxicity and efficacy. Specific recommendations are provided for all 23 statements.

Conclusions: In order to optimize methotrexate efficacy, it is essential to optimize treatment using appropriate dosages, carrying out a rapid drug-based step-up on a treat-to-target strategy and preferably using the subcutaneous formulation. To manage safety aspects appropriately, it is essential to evaluate patients' risk factors and carry out proper monitoring during the course of treatment.

Keywords: Methotrexate; Psoriasis; Dermatology; Safety; Efficacy; Delphi-method; Dosage; Side-effects; Real-life

Key Summary Points

Methotrexate (MTX) is actual, safe and efficient to treat inflammatory dermatoses.

MTX treatment should be started at 15 mg per week, preferably subcutaneously.

Lung and liver fibrosis due to MTX are idiosyncratic non-dose-dependent rare side effects.

There is no cumulative dose threshold to consider for safety.

INTRODUCTION

Methotrexate (MTX) has been used for decades to treat a wide variety of both inflammatory and neoplastic skin diseases and still remains an important drug in the therapeutic management of psoriatic disease [1]. Nowadays, MTX is regarded as the first-line drug in patients with

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moderate-severe psoriasis who are candidates for systemic treatment, in the absence of specific contraindications [2]. In addition to psoriasis, many other diseases (e.g. pityriasis rubra pilaris, chronic spontaneous urticaria, pityriasis lichenoides, atopic dermatitis, and vasculitides or connective tissue diseases) are treated with MTX in both in-label and off-label uses (see Electronic Supplementary Table [ESM} 1) [1].

By changing the posology of MTX from daily to weekly, this drug drastically modifies its effect from anti-proliferative to immunomodulatory/anti-inflammatory by activating T-regulatory lymphocytes and preventing the biosynthesis/release of interleukin (IL)-17, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) [3]. Remarkably, MTX displays prominent anti-inflammatory activity through several mechanisms, including the inhibition of dihydrofolate reductase and aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC), thereby increasing intracellular adenosine to prevent nuclear factor-κB (NF-κB) activation, or augmenting the expression of lincRNA-p21 [3].

In over 50 years of use, MTX has demonstrated a favorable profile in terms of both safety and efficacy, as well as a therapeutic versatility in-hospital and on an outpatient basis. In this article, we summarize current overall knowledge on MTX in dermatology with the aim to shed light on the remaining dermatological areas in which its use is directed mainly by the real-life clinical management.

MATERIALS AND METHODS

Rationale

Methotrexate is widely used in both hospitals and private practices by board-certified dermatologists for different dermatoses that often do not have dedicated guidelines. Guidelines also do not often give specific recommendations for patients who differ from the ideal real-world setting. For these reasons, the aims of this study were to: (1) explore real-life data present in literature; and (2) consolidate current evidence with the clinical experience derived from a group of Italian healthcare providers and dermatologists with > 5 years of experience using MTX. We carried out a Delphi consensus exercise on 23 statements focusing on MTX in dermatology with the overall aim to provide guidance for clinicians in daily practice.

Ethical approval for this Delphi consensus was waived by the local Ethics Committees.

Delphi Technique

The Delphi technique method allows the generation of consensus through a working group of experts on a specific topic, using an interactive process of individual feedback. The method is widely used in many fields of medicine to obtain consensus when formal recommendations are lacking or for areas in which clinical evidence is insufficient [4, 5]. A scale from 1 to 10, with 1 indicating complete disagreement and 10 indicating complete agreement, was used, with a cut-off of 7 considered to indicate approval with 70% of participants voting on the summary synthesis for all rounds of voting. Discrete variables were expressed as counts (percentage), and continuous variables were expressed as means with the standard deviation or medians with the 25–75th percentiles, as appropriate. Statistical analyses were performed using IBM SPSS Statistics 25.0 for Macintosh (IBM Corp., Armonk, NY, USA).

Delphi Round 1

A scientific committee was established comprising 19 Italian HCPs who fulfilled the following inclusion criteria: (1) board-certified dermatologist; (2) Italian as mother language; (3) > 10 years of experience managing patients with MTX; and (4) having managed/currently managing > 50 patients with MTX. The Italian Healthcare System (SSN) is a universal public healthcare system for all citizens and residents of Italy that uses a mixed public–private system administered on a regional basis; therefore, stakeholders were chosen to represent all Italian regions. The scientific committee met during the period February–May 2021 to individually draft a series of 37 open questions/summary

syntheses on specific topics in six main areas based on clinical experience. A detailed literature search was then performed in the PubMed, EMBASE and Google databases to identify and collect all relevant studies on MTX in dermatology using search terms appropriate for each question with the keywords being "methotrexate," "skin," "dermatology" and "dermatoses." After a general assessment by two dermatologists (GD and PP), all material found with the research strings was uploaded in a common cloud to allow free access to all stakeholders.

The statements were developed first individually and then discussed on June 2021 in two webinar sessions. Finally, the statements were reduced to 23 statements, considering only the most relevant, voted upon to achieve consensus and included in the present Delphi exercise.

Delphi Round 2

On September 2021, 85 dermatologists with > 5 years of experience managing MTX were invited to participate in the Delphi exercise (ESM Table 2). Of these, 69 agreed to participate. During this round, the 23 statements were presented and voted upon remotely. The steering committee then revised the statements for which agreement was not reached, which were voted upon in the next Delphi round.

Delphi Round 3

On October 2021, the eight statements for which agreement was not reached in the previous Delphi round were carefully re-assessed by the scientific committee and voted upon again. In this round, 54 dermatologists participated in the voting.

RESULTS

Pre-Delphi Exercise and Definition of Cores and Statements

A total of 23 statements were drafted that covered six areas of treatment (Table 1), including: (1) pre-screening exams and monitoring of therapy (9 statements); (2) dosing and administration in patients naïve to MTX (5 statements); (3) optimal strategy for patients in remission (2 statements); (4) use of folic acid (1 statement); (5) safety (3 statements); (6) predictors of toxicity and efficacy (3 statements). Statements in each core area are discussed in the following sections.

Pre-screening Exams and Monitoring of Therapy

The MTX monitoring regimen, in addition to the renal-function test, differs between rheumatologists and dermatologists, ultimately leading to a higher estimation of side effects by dermatologists who monitor the patient more closely with laboratory tests [6]. At the present time, sampling carried out 5–7 days after the first dose to evaluate for adverse reactions is controversial and deemed to be not highly useful. There is some disagreement over the timing of monitoring during the first 2 months of therapy with two main proposals: every 2 weeks versus only at week 2 and then once a month [7, 8]. Both proposals are derived from expert opinion and not from clinical data. The participants supported the proposal that blood counts should be monitored 2 weeks after initiation of MTX therapy (statement 1). Patients should be monitored with blood counts, hepatic function tests and creatinine level every 4 weeks for the first 2 months of MTX initiation and then every 3 months. The practice of monitoring blood parameters in the maintenance phase every 3 months is well consolidated [9, 10].

Participants were asked their opinion on how to initiate MTX in patients with latent hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Regarding the initiation of MTX for those patients with HBV, consensus was reached that the risk for viral reactivation is low and thus prophylactic therapy is not mandatory (statement 2). For those patients who are HCV positive, since the long-term effects of MTX on HCV are not known, it was held that MTX should be avoided in patients

Table 1 Questions and statements regarding use of methotrexate in daily practice

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
Pre-screening exams and monitoring of therapy				
(1) How often should monitoring for MTX tolerability be performed?	Based on expert opinion and European guidelines, complete blood count (CBC) recommended two weeks after starting treatment; CBC, liver function tests, and serum creatinine assessment should be assessed every 4 weeks for the first two months and every 3 months thereafter	> 7	6.83	8.14
(2) How should HBV(+) patients be treated?	Overall, the risk of viral reactivation for HBV seems low and thus prophylactic therapy is not mandatory. However, when safer therapeutic options are unavailable, the drug should be administered with caution and close monitoring (viral load every 6 months) is required both during therapy and after its discontinuation (6–12 months)	> 7	7.10	
(3) How should HCV(+) patients be treated?	No eradication of HCV is needed, although the long-term effects of MTX on HCV are not well known. As both HCV and MTX can cause hepatic fibrosis, there may be a synergistic effect leading to more rapid progression of the disease. MTX should be avoided in patients with hepatic fibrosis	> 7	7.80	
(4) In patients who are candidates for treatment with MTX with Mantoux/QuantiFERON-positive, is antituberculous prophylaxis safer than no prophylaxis?	There is currently no evidence to indicate the need for tuberculosis prophylaxis for patients who are Mantoux/quantiferon positive and candidates for treatment with MTX alone. There are only anecdotal cases that report on patients positive for tuberculous and undergoing treatment with MTX without prophylaxis	> 7	7.65	

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
(5) What about the utility and effectiveness of hepatic elastography in monitoring treatment with MTX?	Hepatic elastography can be a good early biomarker for patients with liver fibrosis to be performed every 3 months in patients at risk (BMI > 28 and high alcohol use (> 14 drinks per week); elastrography is recommended in non-obese patients every 1–3 years or if P3NP is not available	> 7	7.1	
(6) How should the dose of MTX be monitored in case of simultaneous and prolonged use of NSAIDs, salicylates, antibacterials, diphenildantoin?	It is advisable to evaluate the plasma levels of MTX before and after the introduction of a drug at risk of interaction and in particular in certain categories of patients (with renal insufficiency, folate deficiency, hypoalbuminemia or old age). As for NSAIDs, same-day administration should be avoided. This allows prevention of adverse reactions attributable to drug interactions	> 7	6.86	6.54
(7) How should patients who are positive for SARS-CoV-2 be managed?	From the available evidence, emerged that SARS-CoV-2 infection does not appear to contraindicate treatment with MTX	> 7	6.22	7.18
(8) Can patients with previous COVID-19 interstitial pneumonia start MTX safely?	In patients who suffered from interstitial pneumonia due to COVID-19, before undertaking therapy with MTX it is necessary to evaluate the clinical status with the routine screening for therapy with MTX, and with instrumental and laboratory tests that document the resolution of the COVID-19 pneumonia	> 7	8.36	

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
(9) In patients with a recent history of cancer, is treatment with MTX safe compared to no treatment?	MTX has been used in patients with severe psoriasis or with involvement of sensitive areas and recent history of neoplasia, in agreement with the patient's oncologist, in cases of prostate adenocarcinoma and breast tumors. There were no adverse events or relapse of neoplastic disease in any of case; therapy was effective in controlling symptoms of psoriasis and skin manifestations. Among the alternative treatments in these patients, apremilast, acitretin, and biological drugs in selected cases, in conjunction with the patient's oncologist	> 7	7.94	
Dosing and administration in patients naïve to methotrexate				
(10) In patients with moderate to severe plaque psoriasis, is initial treatment with low dose MTX (< 15 mg/week) effective and safe compared to initial treatment with high dose MTX (≥ 15 mg/week)?	In a psoriatic patient with no relative contraindications, PASI benefits from therapy at a dose of 15 mg/week	> 7	7.65	
(11) What initial dose should be used in obese patients	Obese patients may benefit from a higher dose of MTX (with weight-dependent adjustment) to achieve a good clinical response, but this may be associated with an increased risk of dose-dependent adverse events. Furthermore, considering the risk of hepatotoxicity related to the use of MTX even for low doses and a further increase in the risk of hepatic fibrosis associated only with the increase in BMI, it is advisable to not use an initial dose > 15 mg/week in psoriatic patients with obesity. These patients should undergo frequent monitoring of liver function at least in the first months of therapy	> 7	8.41	

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
(12) What is the preferred route of administration	MTX is generally administered at a dose between 7.5 mg and 20 mg per week in adult patients, preferably subcutaneously	> 7	8.54	
(13) What dose of MTX is generally used to treat psoriasis?	MTX is generally administered at doses between 7.5 mg and 20 mg per week, preferably subcutaneously. Orally it can be administered in a single dose or divided into 2 or 3 doses over a 24-h period. If PASI 50 is not achieved at 8 weeks, the dose of MTX in selected patients can be increased up to 22.5 mg per week. Further dose increases of no more than 25 mg per week can be considered only in selected patients with careful consideration of the risk/benefit profile	> 7	6.77	8.33
(14) Is it appropriate to continue taking MTX in combination with biologics in case of an inadequate response to MTX?	Although the available data are limited, in case of inadequate response to MTX, maintenance of MTX in combination with a biologic drug can be considered in terms of efficacy and safety; randomized controlled trials and long-term observational studies are however needed. Continued use of MTX can be hypothesized to reduce the antigenicity of anti-TNF agents. It may be advisable to evaluate the maintenance administration or consider a change in dose based on laboratory evaluations	> 7	6.84	6.76

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
Optimal strategy for patients in remission				
(15) What strategy should be used in patients in remission with MTX and a biologic?	In patients on biologic treatment in combination with MTX in remission, a dose step-down of MTX is generally preferred to the minimum effective dose or complete suspension of therapy over dose changes in biologic therapy, to assess whether the patient maintains the remission by continuing with the biologic alone or if a new relapse occurs	> 7	8.54	
(16) In obese patients with psoriasis on MTX therapy, is a dose step-down strategy more effective/safer than maintaining MTX dosing?	It can be reasonably concluded that according to the available literature a step-down dosing strategy in patients with obesity is safer. In obese patients with additional risk factors for hepatotoxicity (e.g. diabetes, alcohol consumption) and bone marrow aplasia, a dose step-down strategy is considered safer. There is no evidence for the most appropriate step-down strategy	> 7	7.57	
Use of folic acid				
(17) What dose of folic acid should be given to patients with psoriasis being treated with MTX?	Low doses of folic acid (5–10 mg/week) during MTX therapy are preferred and remain the gold standard to ensure prevention of side effects without loss of efficacy	> 7	8.88	
Safety				
(18) In psoriatic patients undergoing radiotherapy/chemotherapy and on therapy with MTX, is it necessary to modify the dose of MTX?	There are no indications or data regarding the need to modify or discontinue treatment with MTX during radiotherapy/chemotherapy	> 7	6.83	8.17

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
(19) What precautions should be taken in patients with psoriasis and paternity desire being treated with MTX?	It is important and appropriate to carry out counseling and guide the patient in the choice by informing him of the possible transient alterations of sperm parameters	> 7	6.74	7.7
(20) Should I suspend MTX in case of infections? (excluding TB, SARS-CoV-2, and hepatitis)	The risk of infection in patients with MTX at a non-oncological dosage is negligible and the risk of death from infectious disease is comparable to the general population. We do not recommend drug suspensions, which would only affect efficacy	> 7	6.97	7.65
Predictors of toxicity and efficacy				
(21) In patients with psoriasis treated with MTX, is male gender associated with different treatment efficacy compared to the women?	MTX is effective in the treatment of psoriasis in men and women; the available data are limited and do not allow for definition of gender-related differences in efficacy	> 7	7.84	
(22) In patients receiving MTX, is the presence of pulmonary comorbidities (COPD, interstitial disease) associated with an increase in adverse events?	Although the data in the literature are extremely scarce and refer only to patients with rheumatoid arthritis, it is possible to conclude that the presence of pulmonary comorbidities may constitute a risk factor for the onset of subacute hypersensitivity pneumonitis secondary to the use of MTX. However, this occurrence remains extremely rare. There is no evidence that the use of MTX is associated with an increased risk of developing chronic interstitial fibrotic lung disease	> 7	8.33	

Table 1 continued

Question	Statement	Mean voting score		
		First round (19 votes)	Second round (69 votes)	Third round (54 votes)
(23) Are there predisposing factors to pulmonary fibrosis (e.g. smoking) that could affect the use of MTX?	Recent reviews of the literature question the role of MTX in the onset of pulmonary interstitial disease. MTX appears to slow the progression of pulmonary fibrosis in patients with rheumatoid arthritis. Cigarette smoking is responsible for idiopathic pulmonary fibrosis. Caution is recommended but administration of MTX to smokers is not contraindicated	> 7	7.20	

BMI Body mass index, *CBC* complete blood count, *COPD* chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *MTX* methotrexate, NSAIDs non-steroidal anti-inflammatory drugs, *PASI* Psoriasis Area Severity Index, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TB* tuberculosis

with hepatic fibrosis (statement 3). Moreover, in those patients positive for tuberculosis (TBC), it was concluded that there is no need to carry out prophylaxis for TBC (statement 4); indeed, from the discussion it merged that it may even be safer not to carry out prophylaxis. There is currently no evidence to indicate the need for TBC prophylaxis for patients with latent TB infection who are candidates for treatment with MTX alone. There are only anecdotal cases that present TB disease undergoing treatment with MTX without prophylaxis [11].

Statement 5 focused on the use of hepatic elastography in monitoring patients. Monitoring patients using regular liver tests and keeping vigilant for risk factors are currently the best way to assess and limit MTX-based liver toxicity. Liver biopsy is no longer considered in any current recommendations, and there is no cumulative dose threshold [12]. Considering that the association between the cumulative dose of MTX and hepatic fibrosis is not supported by clinical evidence [13], the current trend is to prefer non-invasive monitoring (elastography and procollagen type III N-terminal peptide (P3NP)) over liver biopsy. Several studies have confirmed the long-term safety of MTX treatment in patients with immune-mediated diseases, including psoriasis. A meta-analysis of 32 randomized clinical studies involving a total of 13,177 patients with rheumatoid arthritis, psoriatic arthritis, psoriasis, and Crohn's disease (6877 patients on MTX and 6300 treated with other conventional disease-modifying anti-rheumatic drugs [DMARDs] or biologic-DMARDs or placebo) reported the absence of major hepatic events (fibrosis, liver cirrhosis or death from liver injury) in patients treated with MTX [9]. On the other hand, patients receiving MTX had a higher incidence of elevated transaminases of a different entity compared to those receiving the other treatments. A precise estimate of the incidence of MTX-related fibrosis in the dosages commonly used for psoriasis and psoriatic arthritis (< 25 mg/week) is not available and, therefore, such events can be assumed to be a rare event.

P3NP monitoring is not recommended in patients aged < 20 years and > 70 years with arthritis since its level was found to persistently

increase to > 8 mg/mL [14]. In patients who do not fall into these categories, P3NP level might be a good early biomarker for psoriatic arthritis and liver fibrosis, with monitoring to be performed every 3 months in patients at risk (body mass index [BMI] > 28 kg/m^2) and high alcohol use [> 14 drinks per week]) [15]. Thus, elastography is recommended in non-obese patients every 1–3 years or if P3NP data are not available [15].

Regarding the possibility to monitor blood levels of MTX in the case of concomitant and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, antibiotics or diphenylhydantoin, based on the scarce evidence available [16, 17, 18, 19], consensus was reached that evaluation of plasma levels of MTX is advisable before and after the introduction of a drug at risk of interaction in selected categories of patients (renal insufficiency, folate deficiency, hypoalbuminemia, elderly) (statement 6). As for NSAIDs, same-day administration with the above-mentioned agents should be avoided to prevent adverse reactions attributable to drug interactions [20].

Statements 7 and 8 concern the administration of MTX in patients who test positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and in patients with a history of interstitial pneumonia from coronavirus disease-2019 (COVID-19), respectively. Consensus was reached that there is no evidence in the literature suggesting that MTX should be contraindicated in the former group of patients [21, 22]. In those patients with history of interstitial pneumonia from COVID-19 and initiating MTX, it was noted that there is no evidence suggesting that MTX is safe in patients with interstitial lung disease, and the only relevant publication in patients with inflammatory bowel disease did not identify MTX as a risk factor for hospitalization and death due to COVID-19 [23]; this finding was confirmed in a case–control study [24]. In addition, the authors of another study reported that MTX appears to inhibit the replication of SARS-CoV-2 in vitro [25]. Given the above results, it was held that the patient's clinical status should be closely examined not only with the routine exams normally carried out, but also with instrumental and laboratory tests that confirm the resolution of COVID-19-related pneumonia. During the consensus, stakeholders agreed that only pre-existing lung fibrosis or interstitial disease may force the discontinuation MTX in patients with COVID-19. Lastly, greater knowledge of COVID-19 should be encouraged to prevent discontinuation of systemic therapies [26].

During the discussion of statement 9, many expert participants reported having administered MTX to a patient with severe psoriasis or with involvement of sensitive areas and a recent history of neoplasia (< 5 years), always in agreement with the patient's oncologist. In these cases, no adverse events or relapse of the tumor was seen, and MTX was effective in controlling symptoms of psoriasis and skin manifestations.

MTX is a drug used for the treatment of many neoplasms at much higher dosages than those used to treat psoriasis, and its use in patients with current or recent neoplasia is not contraindicated. Regarding patients with recent previous cancer, there are two cohort studies in the literature, one on women with Crohn's disease or rheumatoid arthritis with previous breast cancer [27] and one on patients with rheumatoid arthritis and previous non-melanoma skin cancer (squamous and/or basal cell tumors) [28]. In the former group, there was no increased risk of neoplastic recurrence in patients exposed to MTX in the year following cancer surgery compared to those not exposed to MTX (adjusted hazard ratio [HR] 1.07; 95% confidence interval [CI] 0.67–1.69), while in the latter group, treatment with MTX may have increased—albeit at the limits of statistical significance—the risk of recurrence of non-melanomatous skin cancer (HR 1.60; 95% CI 1.08–2.37).

In a recently published review on systemic drugs for psoriasis, only adalimumab, etanercept and infliximab (i.e. anti-TNFs) were found to have the potential to increase the risk of melanoma [29]. In the same review, it was noted that MTX does not increase the risk of melanoma.

A recent case–control study conducted in Sweden has shown that MTX therapy in

psoriatic patients does not represent a risk factor for the onset of cutaneous melanoma [30]. Even an observational study conducted on data from the PSOLAR registry (Psoriasis Longitudinal Assessment and Registry) on over 12,000 patients with psoriasis did not detect an increase in melanoma in psoriatic patients treated with MTX for > 12 months [31]. Exposure to MTX, on the other hand, can increase the risk of developing basal cell carcinoma, but not squamous cell carcinoma. More generally, regarding the alleged oncological risk of MTX, a recent cohort study of 21,699 patients with rheumatoid arthritis showed that MTX users had a lower 12-year incidence of all cancers than non-users. The protective effect was more evident in users of higher cumulative doses [32].

Dosing and Administration in Patients Naïve to Methotrexate

Regarding statement 10, on the basis of the available literature, MTX is now considered to be the traditional drug of first choice in the treatment of moderate/severe psoriasis, at the doses commonly approved in the treatment of psoriasis (7.5–25 mg/week), with a progressive clinical response associated with an acceptable level of safety for the patient [8]. The use of MTX at a reduced initial dosage of < 15 mg per week, in addition to determining a lower efficacy in terms of the Psoriasis Area Severity Index (PASI) 75 response (≥ 75% improvement in PASI from baseline) achieved at week 16 compared to the initial dosage of 15 mg/week (40% vs. 60%), does not protect the patient from adverse events [20, 33, 34].

The possibility of hepatic damage caused by iatrogenic toxicity (histologically diagnosed nonalcoholic fatty liver [NAFL] and nonalcoholic steatohepatitis [NASH]) during therapy with MTX has been reported [35, 36], although this risk was significantly linked to the patient's clinical characteristics (e.g. age > 60 years, BMI > 30 kg/m^2, type 2 diabetes, previous HBV-HCV liver disease and alcohol abuse) [37]. Therefore, in the absence of relative contraindications, the participants held that patients with psoriasis would benefit from a higher dose of MTX (≥ 15 mg/week), albeit with close monitoring.

It was also suggested that obese patients would benefit from a higher dose of MTX to obtain a good clinical response. It was noted, however, that there are some conditions that should be treated with caution. Considering the risk of hepatotoxicity related to the use of MTX even at low doses and a further increase in the risk of hepatic fibrosis in patients who are overweight, it would not be advisable to use initial doses > 15 mg/week (statement 11). Frequent monitoring of liver function should also be carried out in the first months of therapy [38, 39, 40].

MTX can be administered orally or subcutaneously. Subcutaneous administration appears to provide greater bioavailability, particularly at high doses [41, 42, 43, 44, 45, 46] (statement 12). A switch from oral to subcutaneous MTX may therefore be beneficial for patients who have suboptimal disease control. Furthermore, some studies have reported that in patients with moderate-severe psoriasis, a subcutaneous route of administration is associated with a higher response rate, more rapid onset, prolonged efficacy and fewer side effects [41, 42, 43, 44, 46, 47]. The use of a subcutaneous formulation of MTX should therefore be used as a first choice in patients starting treatment with MTX; however, the use of the subcutaneous formulation should also be attempted in patients who have not responded to the oral formulation in single or divided doses or have suspended its use due to side effects, before establishing the failure of treatment with MTX. A possible limitation is represented by its use in some patients with blenophobia.

MTX is generally administered at doses between 7.5 mg and 20 mg/week in adult patients, preferably subcutaneously [1, 20, 34]. If PASI 50 is not achieved at 8 weeks, the dose of MTX in selected patients can be increased up to 25 mg/week and carefully evaluating the risk–benefit profile (statements 12 and 13). When administered orally, it can be administered in a single dose or divided into 2 or 3 doses over a 24-h period. Further dose increases of no more than 25 mg per week can be considered

only in selected patients by carefully evaluating the risk–benefit profile (statement 13).

The last statement in this area concerned the possibility of continuing MTX in association with a biological agent in the case of inadequate response to MTX alone (statement 14). The greater efficacy of MTX in combination with a biologic agent versus biologic monotherapy was confirmed in a recent meta-analysis [48]. In a randomized trial by Zacharie et al., patients with inadequate response to MTX who started etanercept without stopping MTX achieved the therapeutic goal of "clear/almost clear" at a significantly higher percentage than that observed in patients who discontinued MTX, with a similar adverse event profile in the two groups [49]. Experience in the combination of MTX and biologics for psoriasis from clinical trials is limited and mainly related to the combination with etanercept, with the combination therapy generally found to be more effective than monotherapy [50, 51, 52, 53]. Data on the treatment of psoriatic arthritis with a combination of MTX and biological agent are limited and do not allow definitive conclusions to be drawn [54, 55, 56]. The EuroGuiDerm Guidelines on Systemic Treatment of Psoriasis Vulgaris report that treatment with anti-TNF-α and MTX may be associated and may reduce the risk of anti-drug antibodies. The most common such combination is MTX + infliximab as its use is associated with a higher risk of anti-drug antibody formation [57]. EuroGuiDerm Guidelines also hypothesize the possibility of a greater risk of infections with combined therapy, in particular with respect to monotherapy with MTX, while underlining that definitive data are lacking [20]. This was summarized in statement 14.

Optimal Strategy for Patients in Remission

Statement 15 refers to the strategy to adopt in patients who are in remission after combination treatment with MTX and a biological agent. Even if not supported by the literature, the participating experts supported the recommendation that in patients on biologic treatment in combination with MTX and in remission, a step-down dose strategy of MTX is generally preferred up to the minimum effective dose or complete suspension of therapy, instead of dose changes in biologic therapy, to evaluate whether the patient maintains the remission when continuing with the biologic alone or if a new relapse occurs.

There is a higher percentage of obesity among patients with psoriasis compared with the general population, and obese patients have a higher incidence of NAFLD and resistance to therapy. Although the incidence of hepatic fibrosis is relatively low overall, patients with obesity, diabetes and significant alcohol use have a higher incidence of hepatic fibrosis. MTX per se does not appear to cause severe fibrosis, but is an important risk factor in patients with obesity and type 2 diabetes, and can also lead to elevation of liver enzymes in patients with obesity and NAFLD. From this evidence, it was reasonably concluded that a step-down strategy in patients with obesity is likely to be safer, although the exact strategy to adopt is unclear (statement 16).

Use of Folic Acid

The statement for this subject concerned the dose of folic acid to prescribe in patients with psoriasis and being treated with MTX. Clinical studies have shown that supplementation of the MTX therapy with folic acid is safe and significantly reduces the incidence of adverse effects by improving the tolerability of MTX [58, 59]. However, in dermatological disorders, the proportion of patients in whom folate is administered during MTX therapy appears to be low, and there is a lack of specific and shared data in the literature relating to the choice of the type of folate, the recommended dose and the frequency of administration, because few clinical trials have been conducted in this area [60]. Moreover, clinical trials comparing the effectiveness of folic acid administration at 5.0–27.5 mg/week have not shown any significant difference in efficacy [60]. Given this background, the participants agreed that folic acid should be administered during therapy with MTX at a dose of 5–10 mg/week in order to

prevent side effects without loss of efficacy (statement 17).

Safety

The first statement in the area of safety considered the possibility of dose modification during radiotherapy/chemotherapy (statement 18). It was noted that there are no published data that would provide guidance for this, and the statement was based on expert opinion. If it is necessary to start chemotherapy/radiotherapy in patients with psoriasis/psoriatic arthritis currently on MTX therapy, MTX should not be interrupted/changed unless there is a clear indication from the oncologist/radiotherapist. If it is necessary to start MTX during chemotherapy/radiotherapy, the relevant oncologist/radiotherapist should be consulted.

Statement 19 addressed the question of which precautions should be taken in male patients who desire to father a child. MTX is widely used in male subjects of childbearing age with various diseases, including psoriasis. Among the reported effects at the testicular level, MTX has been associated with reversible oligospermia [61]. A rapid reduction in sperm parameters has been observed to occur after the initiation of therapy with MTX, which is attributable to interference with the final stages of spermatogenesis (transformation of spermatids into spermatozoa) [62, 63].

It should be pointed out that psoriasis, due to the effect of systemic inflammation and its comorbidities (metabolic syndrome, obesity, arterial hypertension, smoking habit, depression), may also affect spermatogenesis as well as sperm quality and number [64]. The participants agreed that before starting therapy with MTX it is important and appropriate to carry out counseling and guide the patient in the choice of therapy by informing him of the possible transient alterations of the sperm parameters. Discontinuation of MTX generally leads to a normalization of sperm parameters usually within 3 months of discontinuation, as reported in the literature (statement 19) [65]. Of note, a recent study reported that the sperm quality of patients treated with low-dose MTX is similar to that of healthy volunteers and that MTX does not increase sperm DNA fragmentation [66].

In the last statement on safety (statement 20), consensus was reached that the risk of infection, excluding TBC, SARS-CoV-2 and HBV/HCV, in patients with MTX at a non-oncological dosage is negligible and that the risk of death from infectious disease is comparable to that of the general population [67]. It was therefore not recommended to discontinue the drug in the presence of infections, other than those mentioned, as discontinuation would only affect the efficacy of the treatment.

Predictors of Toxicity and Efficacy

Considering statement 21, reviews in the literature have not found differences in the efficacy of MTX in the treatment of psoriasis by gender [34, 68]. Only one recent observational study reported that male gender is associated with clinical response to MTX treatment [69]. A systematic review of the literature on gender differences associated with response to treatment for psoriatic arthritis found no differences between men and women on long-term therapy with MTX [70]. Similarly, no gender differences were observed in another study comparing the response to MTX in psoriatic arthritis and rheumatoid arthritis [71]. Thus, statement 21 stresses the absence of evidence in the literature, albeit limited, to support the hypothesis that MTX may be more effective in male patients.

In statement 22, it was highlighted that there is scarce data in the literature on whether the presence of comorbid lung disease, such as COPD, would place the patient at higher risk of adverse events. The relevant literature refers almost exclusively to patients treated for rheumatoid arthritis. MTX is known to induce inflammatory subacute hypersensitivity pneumonitis unpredictable, which is potentially fatal [72, 73]. Risk factors include pre-existing lung diseases (patient age > 60 years, female sex, hypoalbuminemia, diabetes, previous use of DMARDs or anti-TNF-α) [74]. There is no evidence that the use of MTX is associated with an

increased risk of developing chronic interstitial fibrotic lung disease [74, 75].

Statement 23 considers predisposing factors for pulmonary fibrosis, such as smoking, that would limit the prescribing of MTX. Recent reviews have questioned the role of MTX in the onset of pulmonary interstitial disease [74, 75]. On the other hand, MTX appears to slow the progression of pulmonary fibrosis in patients with rheumatoid arthritis. Cigarette smoking is responsible for idiopathic pulmonary fibrosis. Caution was recommended when prescribing MTX to smokers, but smoking should not be considered as a contraindication.

In recent years, the safety profile has been the subject of new re-analyses, which have led to the realization that the actual risks of MTX treatment for patients are lower than previously believed, especially regarding hepatic and pulmonary safety and infectious risk [9, 67, 76]. The safety profile can be further optimized through individual risk assessment and adequate monitoring of treated patients. An important advantage of MTX over other systemic treatments for psoriasis lies in the effects that the drug has on the main comorbidities that can frequently occur in the psoriatic patient. MTX is, in fact, effective in the treatment of psoriatic arthropathy and can also be useful in the case of inflammatory bowel disease, being indicated in the treatment of Crohn's disease [77]. In addition, in patients with high levels of systemic inflammation and therefore at high cardiovascular risk, such as in patients with psoriasis, MTX has been shown to reduce cardiovascular risk, mainly thanks to its anti-inflammatory action [78]. Indeed, a systematic review and meta-analysis of patients with immune-mediated inflammatory diseases, including psoriasis, who were treated with MTX demonstrated that the incidence of major adverse cardiovascular events (stroke, myocardial infarction, coronary artery disease and sudden cardiac death) was significantly reduced (21%) compared to that of patients undergoing other treatments; the risk of myocardial infarction was also 18% lower [79].

Despite its widespread use, there is surprisingly little clinical evidence to guide daily practice with MTX in dermatology. Although generally considered to be safe and efficacious, in dermatological conditions MTX is used at lower doses compared to those used in rheumatology. The more confident use of MTX in rheumatology, with higher dosages and less fear of safety aspects, allows for better outcomes in terms of efficacy and compliance. Indeed, in a retrospective follow-up study, patients with psoriatic arthritis managed by rheumatologists were generally treated with higher doses of MTX and underwent fewer liver enzyme monitoring controls than patients managed by dermatologists [80]. Patients managed by dermatologists also reported a higher rate of discontinuation, increased liver enzymes, loss of response and drug intolerance. These findings may be explained by the high use of oral versus subcutaneous MTX, with an increased prevalence of nausea associated with the former, and heterogenous interpretation of data on transaminases, often leading to a discontinuation of MTX or a decrease in MTX dose that limits drug efficacy. The clinical relevance of hepatic alterations has been overestimated by dermatologists, while in reality clinically relevant adverse hepatic events did not differ between the two groups. Moreover, the optimal starting dose has not been established in clinical studies, and only a handful of researchers have investigated the use of different doses of MTX for psoriasis [81, 82]. Despite some recommendations having been made on initial dose and treatment escalation, summarized in a recent international Delphi procedure [83], several aspects that impact daily practice in patients with psoriasis are far from being fully elucidated.

CONCLUSIONS

Many patients with moderate-severe psoriasis are still not treated, and among those being treated, some are still not adequately treated with systemic agents, although guidelines recommend the use of such agents to manage the systemic inflammation generated by this immune-mediated disease. Current guidelines for the management of patients with moderate-to-severe psoriasis recommend first-line use

of MTX, cyclosporine or acitretin, while biologics should be considered if there is no response, intolerance or contraindication to first-line medications [20, 33, 34]. It should be noted that in Italy, the EuroGuiDerm Guidelines for psoriasis [20] were adapted but it was not reported that biologics may be considered the "first choice in severe disease when success can not be expected with conventional drugs" [85].

MTX is an effective and safe treatment for patients with moderate to severe psoriasis in the long term. Due to the chronicity of psoriasis, it is essential to consider that patients need to be treated systematically for many years, and thus more demanding treatments regarding safety and efficacy should be taken into consideration only when the first-line treatments are no longer sufficient to manage the disease. To obtain better efficacy from MTX, it is essential to optimize the treatment using appropriate dosages, carrying out a rapid step-up of the drug based on a treat-to-target strategy and preferably using the subcutaneous formulation. The latter allows improvement of patient compliance due to a better gastrointestinal tolerability and higher efficacy. To manage safety aspects appropriately, it is essential to evaluate the patient's risk factors and carry out proper monitoring during the course of treatment [84].

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