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The role of Methotrexate in the treatment of Psoriasis

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DEDICATÓRIA

À minha família, por todo o apoio que me deram ao longo do meu percurso académico.

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PREFÁCIO

Este artigo de revisão será submetido à Revista da Sociedade Portuguesa de Dermatologia e Venereologia.

RESUMO

Introdução

A psoríase é uma doença sistémica, crónica e recidivante, que afeta cerca de 2-3% da população mundial. O seu tratamento é baseado na gravidade da doença e nas características do doente. Inclui tratamento tópico, fototerapia e terapêutica sistémica. Apesar da descoberta dos biológicos, o metotrexato continua a ser a principal opção sistémica na psoríase moderada a severa. O metotrexato tem sido usado ao longo do tempo na prática clínica. Contudo, a evidência científica sobre farmacocinética, mecanismo de ação, eficácia, farmacogenética, perfil de segurança, efeitos adversos e o papel da suplementação com folato, permanece insuficiente. Adicionalmente, estudos sugeriram um aumento no risco cardiovascular dos pacientes e tem sido proposto que a terapêutica sistémica possa diminuir esse risco.

Objetivos

O objetivo deste artigo é rever o papel do metotrexato no tratamento da psoríase e o seu potencial na diminuição do risco cardiovascular em doentes com psoríase.

Metodologia

A pesquisa foi realizada na plataforma PubMed, da qual resultaram 35 artigos que estavam de acordo com os critérios de inclusão.

Discussão

O mecanismo de ação do metotrexato é desconhecido, mas inclui efeitos anti-folato e anti-inflamatórios. A sua eficácia também não foi determinada, contudo, estudos demonstraram que a eficácia do metotrexato foi menor, quando comparada à dos biológicos. No futuro, o paradigma do tratamento poderá mudar. Não existem guidelines únicas sobre o metotrexato, mas muitos autores concordam que o tratamento deve ser individualizado. Apesar de comuns, a maioria dos efeitos laterais são mínimos e reversíveis, mas a monitorização é mandatória. Uma combinação de testes não-invasivos poderá substituir a biópsia hepática. A duração do tratamento com metotrexato mostrou ser curta e a razão mais comum para a sua descontinuação foi a existência de efeitos adversos, quando comparada à sua ineficácia. A associação com folato pareceu reduzir os efeitos adversos, no entanto, alguns estudos mostraram uma redução na eficácia do tratamento. Muitos estudos mostraram que o tratamento sistémico reduzia o risco cardiovascular e já foi demonstrado que o metotrexato reduz a dimensão do enfarte do miocárdio.

Conclusões

Existe uma escassez de evidência científica sobre este fármaco, apesar das tentativas para colmatar esta falha. Os dados existentes revelam algumas características do metotrexato e comparam-no aos biológicos. Uma das explicações para esta falta de evidência sobre o metotrexato na psoríase é a variabilidade inter-individual na resposta à terapêutica. Ainda existem muitas investigações por fazer, acerca do seu mecanismo de ação, do esquema de dosagem, das estratégias para prever a resposta ao tratamento, dos potenciais marcadores genéticos e do papel da suplementação com folato.

ABSTRACT

Introduction

Psoriasis is a chronic, systemic and relapsing disease that affects 2-3% of the world's population. Its treatment is based on the severity of the disease and on the characteristics of each patient. It includes topical therapy, phototherapy and systemic therapy. Despite the discovery of biological treatment and all its developments, methotrexate is still the main systemic drug used in moderate-to-severe psoriasis. Methotrexate has been used for a long time in clinical practice. However, scientific evidence on its pharmacokinetics, mechanism of action, efficacy, pharmacogenetics, safety profiling, side effects and the role of folate supplementation is too sparse. Also, studies suggested an increase in cardiovascular risk in patients with psoriasis and it has been proposed that the use of systemic treatment may reduce this risk.

Objectives

The aim of this article is to review the role of methotrexate in the treatment of psoriasis and its potential in decreasing cardiovascular risk in patients with psoriasis.

Methods

The search was performed on PubMed, from which 35 articles met all inclusion criteria.

Discussion

Methotrexate's mechanism of action is still unknown, but it includes antifolate and anti-inflammatory effects. Its efficacy is also not well established, however, studies showed lower efficacy than biologics. There are no unique guidelines on how to use methotrexate, but many authors seem to agree on individualization of dose regimen. Although common, most side effects are mild and reversible, but monitoring of psoriasis' patients is mandatory. A combination of non-invasive tests may substitute liver biopsy in the future. Drug survival of methotrexate revealed to be short and the commonest reason for treatment discontinuation is related to adverse effects. The association with folate appears to reduce its adverse effects, however, some studies showed that it also reduces treatment's efficacy. Many studies reported that systemic treatment reduces cardiovascular risk and it has already been established that methotrexate reduces the dimension of myocardial infarction.

Conclusion

Evidence about this drug is still insufficient, in spite of some efforts to achieve it. The existing data shows several aspects related to methotrexate and also compares this drug with biologics. One of the explanations for the insufficient evidence about methotrexate in the treatment of psoriasis is the inter-individual variability of treatment's response. There is still much to investigate, focus should be into its mechanism of action, dose regimen, strategies to predict treatment's response, potential genetic markers and the role of folate supplementation.

Keywords: psoriasis, dermatology, methotrexate, treatment

LIST OF ABBREVIATIONS

FA - folic acid
HLA - human leukocyte antigen
IL-18 - interleukin 18
MI - myocardial infarction
MTX - methotrexate
PASI - Psoriasis Area Severity Index
tCa - total calcium
Th1 - T helper 1
Th17 - T helper cell 17
TNF-α - tumor necrosis factor-α

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INTRODUCTION

Psoriasis is a chronic inflammatory disease, with both genetic and auto-immune components affecting the skin and/or joints.[1,2] It is one of the most common cutaneous diseases worldwide, with a prevalence of 2 to 3% of the world's population.[3-5] Clinically, it is characterized by localized or generalized erythematous and scaly plaques associated with important physical and psychological impact and decreased quality of life, mostly due to chronic disfiguration leading to a lack of self-esteem.[1,3,6,7] Additionally, over the past years, psoriasis has been associated with several comorbidities, such as cardiovascular disease and cardiometabolic risk factors.[1,3,4,6-8]

It has been suggested that treatment with therapies that modulate the inflammation and the immune system, like methotrexate (MTX), may have a cardio-protective effect and the potential to decrease cardiovascular events.[1,2,4,6,8-12]

The treatment of psoriasis is individualized and depends on many factors, such as the severity of the disease, compliance and preferences of patient, comorbidities, impact on quality of life and socioeconomic status.[3] Regarding the treatment of moderate to severe psoriasis, MTX is still the most used systemic therapy, despite the recent growth of biological treatment.[11,13,14] MTX is a folate antagonist and an immune modulator.[8,11,15] Although it is commonly prescribed, little is known about its mechanism of action, pharmacokinetics, proper administration, recommended dose regimen, monitoring, role of folic acid (FA) supplementation, security profile or even its efficacy.

OBJECTIVES

The aim of this article is to review the role of MTX in the treatment of psoriasis and its potential in decreasing cardiovascular risk in patients with psoriasis.

METHODS

A bibliographical search on PubMed that includes articles from 2006 to 2017 was conducted. This research was performed during the months of September, October and November of 2017, using different combinations of the words "psoriasis", "methotrexate" and "treatment". This review includes randomized clinical trials, bibliographic reviews, meta-analysis, retrospective studies and prospective observational studies, all of them in english.

Inclusion criteria included original studies and review articles about MTX in the treatment of psoriasis and the association between cardiovascular events and psoriasis. Articles in other languages, individual opinion articles, letters to authors and case reports were excluded.

A total of 35 articles were selected, after reading the articles that presented title and abstract according to the intended and after applying the mentioned criteria. Based on that bibliography, the relevant information was collected for this review.

DISCUSSION

Psoriasis

Psoriasis is an immune-mediated, chronic disease that affects the skin, joints or both.[1,2] It has a high prevalence, between 2 to 3% of the world's population[3-5], high impact on quality of life due to its chronicity, disfiguration and disability and it is associated with several comorbidities.[1-3,11,15]

It is equally prevalent in both genders[1,11], although a study showed that man have more severe forms of psoriasis than women.[16]

There are five types of psoriasis: guttate or eruptive psoriasis, pustular palmoplantar psoriasis, generalized pustular psoriasis, erythrodermic psoriasis and the most common form: plaque psoriasis or psoriasis vulgaris, which accounts for about 90% of the cases. Typical lesions include demarcated erythematous plaques covered by silvery lamellar scales.[1] The most common sites for the lesions are the extensor areas, like the knees, elbows or buttocks, but can appear frequently on the scalp, umbilicus and, rarely, in flexural areas. Nail involvement is also frequent.[11]

The onset of psoriasis has a bimodal distribution, with peaks being at 30-39 years and at 50-69 years.[11] Susceptibility to psoriasis is heritable. However, the disease can be triggered by mild trauma, sunburn, stress and chemical irritants.[1,3] Some drugs can exacerbate the disease, such as beta-blockers, lithium, antimalarials and non-steroidal anti-inflammatory agents. Occupational risk factors and HIV infection can also trigger psoriasis.[1,3]

The pathogenesis of psoriasis has not yet been fully comprehended, however it is now widely accepted that skin lesions of psoriasis are developed as a result of dysregulated interactions between genetics and immunity.[1,5] Immune-related genes have also been associated with the disease.[1] The three main mechanisms of psoriasis are a cross between innate and adaptive immunity and the central role of tumor necrosis factor-α (TNF-α), the axis interleukin-23/T helper cell 17 (Th17) and the effect of immune reactions on other skin cells.[1,3]

The innate immune system can develop pathogenic T cells in psoriasis. T helper 1 (Th1) and Th17 cells contribute to the pathogenesis of psoriasis by releasing inflammatory cytokines. These cytokines promote the recruitment of other immune cells, keratinocyte proliferation and sustained inflammation. T-cell mediated inflammation has a significant role in the etiology of the disease. TNF-α is a pro-inflammatory cytokine of the innate immune response. It induces the expression of intercellular adhesion molecule 1 (ICAM-1) on keratinocytes cells while also inducing the infiltration of monocytes in the dermis, which promotes the development and progression of psoriasis through hyperproliferation. Caspases play an important role in the induction of apoptosis but also in inflammatory processes. Caspase-1 belongs to the group of inflammatory caspases and it is the activating enzyme for the pro-inflammatory cytokine interleukin-1β, interleukin 18 (IL-18), a cytokine known to play an important role in psoriasis' pathogenesis. IL-18 is a pleiotropic cytokine that has costimulatory functions on Th1 cytokines. Although the role of IL-18 in psoriasis has not been fully elucidated, it is speculated that IL-18, produced by human keratinocytes, enhances interferon-γ production in inflammation and thus IL-18 seems to be a promising target in Th1-type inflammatory diseases, like psoriasis itself.[5]

Research about immunopathogenesis has resulted in highly specific therapies that target certain components of the immune system.[1,5,11,17]

Quality of life

Psoriasis affects the life of the patients directly, through their emotional status, psychological stress, self-esteem, relationships, work, social activities, financial burden and physical function (more related with psoriasis arthritis).[2,6,7,11] Emotional stress influences the development and exacerbation of psoriasis in 37-78% of patients. In addition, the adverse effects of the treatment also contribute to a decline in quality of life.[7]

In this study, the most common presenting complaint is scaling of skin and the most common exacerbation factors were seasonal weather changes, especially winter (62,2%), stress (42,9%) and irregular sleep habit (21%). The chronicity, irritation due to lesion, and disease affecting visible parts of the body are associated with psychological stress. According to the same study, combination therapy (topical plus systemic) is proven to be more effective and associated with improvement in quality of life when compared to topical treatment alone.[7]

General treatment

Psoriasis has no cure. So, the goal of management is to alleviate the disease by sustained long-term remission, while minimizing the side effects of the treatment.[3] According to the European Consensus Statement, the goal is to reduce signs and symptoms by at least 75% in Psoriasis Area Severity Index (PASI) score, as well as improve quality of life, measured by Dermatology Life Quality Index.[1]

The general therapy for psoriasis includes topical treatments, phototherapy and systemic treatments, which include conventional systemic drugs like MTX and biological drugs, like TNF-α inhibitors.[1,11,14,18] Topical therapy, like glucocorticosteroids or vitamin D derivatives, is used to treat mild disease.[1] Phototherapy may be useful in association with systemic therapy for moderate-to-severe psoriasis.[1] One study showed that the combination of MTX with narrowband ultraviolet B phototherapy offers a cheap and beneficial therapeutic option.[19] However, phototherapy and photochemotherapy are time consuming treatments, therefore only used for short-term control of the disease. Also, the carcinogenic effect associated limits the long-term use.[1]

Systemic therapies are indicated for moderate-to-severe psoriasis.[1,11,20] The conventional systemic drugs are MTX, cyclosporine and acitretin, being MTX one of the most used in clinical practice worldwide. Although they have drug-to-drug interactions and cumulative organ toxicities, with the correct monitoring, they can be used with safety and efficacy. MTX is even effective in severe cases and is a valuable component for associations with topical or biological treatment, suggesting it may be particularly useful when adjusting the patient's treatment regimen.[18]

A new era for psoriasis' treatment has emerged, with the appearance of biological treatment, like TNF-α inhibitors (etanercept, adalimumab and infliximab approved for psoriasis).[1,11] Biologics still do not show evidence of cumulative toxicity or drug-to-drug interactions, like the conventional drugs. However, long-term research in psoriasis is still sparse.[11] Biologics have a good safety profile and the only reasons why they are not on the front line of psoriasis systemic treatment is the high costs, which are about 10 times higher than conventional treatment, and that they cannot be administered orally.[1,3,11,18,21]

MTX in the treatment of psoriasis

MTX, a classic immunomodulator, is a FA antagonist that was first used in the 1950s for acute leukemia.[11,15,21] MTX has been used as an anti-inflammatory drug in psoriasis for over 50 years and is currently the front line systemic drug according to USA,

European and British guidelines. Despite the more recent discovery of biological treatment, MTX is still the cornerstone for psoriasis' treatment.[11]

The low doses used in psoriasis are considered to be effective and have a good safety profile. MTX can be used in long-term treatments, with hepatic toxicity being the most feared adverse effect. However, recent studies have suggested that liver fibrosis is not related to cumulative MTX dosing, appearing more often in people with other risk factors.[11]

MTX can be administered orally, which is often the first choice for patients because of the simplicity and lower price, or subcutaneously, route which is used if there is a lack of efficacy with oral treatment or to diminish the side effects of oral administration, mostly gastrointestinal.[18,20,21] The subcutaneous form may increase efficacy and tolerability.[18,20] Also, this form has a greater bioavailability and, therefore, the adherence to treatment may increase.[18,22]

MTX is frequently used when combined with biologics in order to increase the efficacy of biologics or to decrease the antidrug antibodies' formation.[11,13] These antibodies are related with lack/loss of response to biological treatment and increase in infliximab related infusion reactions. Therefore, this association decreases exposure to biologic drugs, decreases the costs and minimizes the side effects of MTX, which is given in a lower dose. MTX remains a valid option for patients with moderate-to-severe psoriasis, psoriatic arthritis and can be used in combination or by itself.[11]

Pharmacokinetics

MTX is absorbed in the proximal jejunum, with 79 to 80% bioavailability. This bioavailability decreases if more than 15 mg/week are taken orally due to saturation of the transporters. When MTX enters the cells, it is converted to MTX polyglutamates, which are the main anti-inflammatory agents in psoriasis. This is important because polyglutamate levels in the erythrocyte are associated with efficacy and can be used to monitor the treatment. MTX should be avoided or taken in lower doses by patients with renal impairment or patients taking simultaneously non-steroidal anti-inflammatory drugs or antibiotics.[11]

Dermal microdialysis, which consists in a semi-permeable membrane on the skin dermis that pumps to detect MTX levels in that compartment, has been tested for levels of MTX in the skin of psoriatic patients, and a pilot study showed that drug levels and bioavailability are higher in lesional skin, compared to non-lesional skin. This study has also shown that there is a large inter-individual variety, resulting from differences in

patients' pharmacogenomic profiles. Dermal microdialysis is an opportunity to evaluate MTX's levels in the blood and skin of patients.[22]

Mechanism of action

The exact mechanism of MTX is not yet fully known. However, at high doses, MTX inhibits dihydrofolate reductase and leads to a decrease in synthesis of purines and pyrimidines, components of deoxyribonucleic acid (DNA). This effect of antiproliferation is more important for cells with fast turnover, like neoplastic cells. This mechanism also explains the hematologic toxicity or mucocutaneous ulceration. Supplementation with folinic acid or FA is generally prescribed to reduce side effects and some studies demonstrate that this supplementation does not decrease efficacy, so it is likely that MTX has another mechanism besides its antifolate effect.[11]

In MTX's case, adenosine exerts its anti-inflammatory effect by binding to A2b and A3 receptors, which leads to a decrease in both concentration of leukocytes and levels of pro-inflammatory cytokines, like TNF-α. This effect of adenosine may cause hepatic steatosis and either fibrosis or cirrhosis. Additionally, when adenosine is blocked, MTX still has anti-inflammatory effects, suggesting yet another mechanism is in place. Therefore, the mechanism on MTX is very complex and further research is needed in order to understand its effects and optimize its use.[11]

MTX has also been shown to decrease caspase-1, TNF-α and IL-18, which are increased in lesional skin. Thus, MTX may also have an effect on the control of psoriasis inflammation, reducing the hyperproliferation of keratinocytes.[5]

Clinical efficacy

The evidence on MTX is sparse, although the clinical experience with this drug is extensive.[11,23] When MTX is used as a single agent, its effect takes 1 to 8 weeks to occur and, according to National Institute for Health and Care Excellence guidelines, the maximum response to treatment is usually seen at 16 to 24 weeks with 15 mg per week.[11,21] Both PASI75 response and the patient's quality of life improve significantly after initiating treatment with MTX.[21]

A study with low doses of MTX (7,5-15 mg/week), showed that a PASI75 response was achieved in 24% of patients in week 12, whereas PASI90 was achieved by 11% in week 12. Higher doses (15-25 mg/week) increase PASI75 response to 60%. Other studies evaluated the efficacy by week 16 and obtained a greater response, which suggests optimal performance around week 16 or even later. Also, doses higher than 15

mg/week are more effective than lower doses.[11] Another study, conducted through a longer period, showed 33,5% of patients achieving PASI75 by week 12, 34,9% by week 16, 44,7% by week 24 and 52,8% by week 48.[24]

The CHAMPION study compared the efficacy and safety of adalimumab, MTX and placebo in moderate-to-severe psoriasis. This study concluded that patients have significantly different responses to the same doses of MTX, related to inter-individual pharmacogenetics, and therefore that the dosing should be individualized.[3,17] Also, patients who did not respond to 20 mg/week of MTX by week 12 were unlikely to respond with higher doses. In that situation, MTX's route of administration should be subcutaneous or another therapy should be initiated, like biologics. In this study, adalimumab showed a significantly superior efficacy and improvement in treating psoriasis when compared to MTX. At week 16, 79,6% of adalimumab-treated patients achieved PASI 75, compared to 35,5% for MTX-treated patients and 18,9% for placebo. Also, the response to adalimumab was faster, with 57% improvement of mean PASI by week 4. There were no differences in rates of adverse effects in the tree groups, although adverse effects leading to discontinuation were greater for the MTX group (three patients, two related to liver enzymes elevation and the other to hepatitis). It is important to highlight that all patients received FA.[17]

A meta-analysis showed proof that the efficacy of MTX is lower than the efficacy of biologics. However, MTX's efficacy itself is very hard to find, as studies have a small sample size and, after adverse side effects, the studies were discontinued. The most common side effects, the gastrointestinal ones, are rare, only reported in 2 out of 20 trials. Limiting side effects also occur in only 3,1% of patients in 8 out of 22 studies. In terms of efficacy, the results showed 45,2% achieved PASI75 at primary endpoint (12 or 16 weeks) while on MTX therapy, compared to only 4,4% achieving PASI75 on on placebo group. In the future, with strategies to allow clinicians to prescribe the most costly drugs (biologics) instead of the conventional systemic drugs, like MTX, the paradigm may change.[23]

Due to the variability in MTX's response dependent of the patient's pharmacogenetic profile, a study suggested that pretreatment total calcium (tCa) levels may predict the treatment's response. This study found greater improvement in psoriasis by MTX in patients with relatively higher pretreatment tCa levels. Calcium has been proposed as a regulator for keratinocyte differentiation. As calcium concentration increases, keratinocytes enter the process of senescence. Studies suggest that MTX may act through a calcium-dependent mechanism. This same study found that pretreatment tCa levels had the highest correlation with MTX treatment efficacy in patients with

psoriasis. This conclusion was further supported by the synergistic effect between calcium and MTX on keratinocyte growth in vitro and psoriasis-like model mice in vivo. This significant association between pretreatment tCa levels with MTX's efficacy might be useful in predicting beneficial treatment results in psoriasis. However, larger studies are required to confirm these findings.[25]

Genetics and pharmacogenetics

Genetics may have a role on the severity of the disease, since the patients with an early onset of the disease (type I psoriasis, human leukocyte antigen (HLA)-Cw6+) have a more severe disease and a family history, while patients with late onset (type II psoriasis) have milder forms of psoriasis and no family history. Many loci have been described to have susceptibility for psoriasis. Thereby, pharmacogenetics' research is progressing on psoriasis.[1]

Although the role of HLA-Cw6 on psoriasis is already known, not much is known about its contribution in responding to different treatments. HLA-Cw6 can act like a marker for MTX's response in psoriasis and it is highly predictive of response to MTX in patients with psoriasis without arthritis. It also seems to achieve better disease control with fewer limiting adverse effects.[26]

MTX's pharmacokinetic in psoriasis is obscure. A study investigated the association of polymorphisms of genes associated with psoriasis and the response to MTX. The conclusion reinforces the link between HLA-Cw6+, early onset and preponderance to the female gender. The results also suggest that IL-4 polymorphisms are protective against psoriasis, as opposed to IL-10 polymorphisms, which are associated with an increased risk. LCE3B/3C gene deletions were associated with greater risk for psoriasis and FOXP3 acts like a disease modifying gene by predicting clinical response to MTX. Despite these conclusions, this study has limitations, such as having a small sample size and a short period of follow-up. However, the study highlighted the potential genetic markers to predict MTX response on patients with psoriasis. In the future, it might be possible to have a point-of-care testing gene chip, to predict optimal treatment response, based on genotypic profiling. If confirmed by larger studies, it may lead to an inexpensive predictive blood test, helpful for clinical decision-making.[3]

Dose regimen

There is a wide variety of dosing regimens and there are no unique guidelines on how to use MTX, such as dose-testing, the starting-dose, dose adjustments and maximum dose.[14] However, many studies and a survey of dermatologists worldwide seem to agree

on the administration of a test-dose only in frail patients (elder patients or with impaired kidney function) and on the starting-dose varying between 10-20 mg/week (lower doses in frail patients). Good-responders' dose reductions should be considered, being the maximum dose, in most studies, of 20 to 25 mg/week, with one study referring 25 to 30mg/week.[13,14,21] Every author seems to agree that the dose regimen has to be guided according to the response of the patient individually, because there are a lot of polymorphisms in relation to MTX metabolism.[11,13,14]

Safety and tolerability

MTX is considered a safe drug, while it is used at the weekly doses for psoriasis and that dose should always be the minimum necessary for the severity of the disease.[11,24] However, clinical data related to its efficacy and safety is insufficient.[27,28] Unfortunately, up to 60% of patients have side effects, the majority mild and reversible, including gastrointestinal intolerance, asthenia, arthralgias and fever. These are minimized through concomitant folinic or FA or by parenteral route. Effects like myelotoxicity can be life threatening, especially when MTX is incorrectly administrated.[11] So, the monitoring of these patients is mandatory.[11,13,21]

Shalom et al. and Dávila-Seijo et al. conducted two studies that showed a short drug survival for MTX.[29-31] None of these investigates the reasons for discontinuation, but another study focused on these reasons. This last study concluded that the average MTX drug survival rate was 18 years, which is a short period when compared to biologic treatment. Side-effects were the most common reason for discontinuation, compared with ineffectiveness, and the majority include gastrointestinal symptoms despite FA supplementation.[29] Another study endorses this conclusion, showing that the lack of efficacy as a reason to stop MTX occurs much less frequently than previously thought. Appearing in about 10% of patients, limiting adverse effects are, in fact, the most common reason to discontinue MTX.[27]

Side effects

Regarding acute side effects, the most common ones are gastrointestinal effects, like nausea, diarrhea, abdominal pain, anorexia leading to weight loss and oral ulcers. Cutaneous erosions and ulcers are best seen in patients developing acute severe toxicity. Myelotoxicity can occur and it affects all three lines of hematopoiesis, which can be lethal, and pancytopenia occurs as an idiosyncratic effect. Regarding its toxicity, MTX should be withdrawn and folinic rescue should be initiated, especially in the presence of mucocutaneous ulcers, which precedes pancytopenia. The most common neurological

effects include headache, somnolence and vertigo. Less common effects, like pericarditis and pericardial effusion, have been described and appear weeks after initiation, although cardiotoxicity is very rare and usually vanishes after withdrawal from MTX.[11] The most common side effects are dose-dependent, generally occur at initiation of therapy and can be reduced by FA supplementation.[11,21]

Regarding chronic side effects, liver fibrosis occurs in up to 25% of the patients in treatment with MTX for 5 years and may progress to cirrhosis, although the incidence of cirrhosis is very low at cumulative doses below 4g (the general dose is 1,5-2g). Recent studies suggested that liver fibrosis is not related with cumulative doses of MTX and would be more likely to occur in patients with risk factors, such as heavy alcohol intake, obesity, hyperlipidemia, diabetes, inherited liver diseases, female sex or hepatitis virus infection. The gold standard for monitoring liver fibrosis is still liver biopsy, however many non-invasive techniques have been developed. Pulmonary chronic toxicity, leading to pulmonary fibrosis may occur, but is very rare.[11,14]

Elevated transaminases in 20-30% of patients with a typical dose of MTX were found, but are consistent with other studies. Usual MTX therapy can result in abnormalities in liver enzymes, independently of cumulative dose and treatment duration. The authors suggested that hematologic toxicity can be prevented in patients with no risk factors like renal impairment, lack of FA supplementation and medical errors. According to this study, liver biopsy is not needed with the use of MTX for up to 1 year. Advanced age, duration of disease and comorbidities were not considered risk factors for adverse effects.[28]

Folate supplementation

MTX is a folate antagonist, so it would appear as the association with folate would help reduce the secondary effects of the MTX.[13] However, studies showed that folate supplementation may reduce the efficacy of treatment.[15,32] Chladek et. al. showed that folate association reduces the efficacy of treatment and, when the group stops folate, psoriasis improves quickly.[15] It also showed that the reduction in efficacy, which leads to a progression of psoriasis with MTX associated with FA, is dose-dependent.[15] However, some authors state that the different conclusions may result from polymorphisms regarding folate's and MTX's metabolism, which differs from person to person.[15,33] Studies suggest that 5-10 mg/week of FA improve the security of MTX, and that higher doses like 15 mg/week, despite reducing adverse effects, also reduce the efficacy of the treatment.[14,33] European guidelines recommend a supplementation with FA 5 mg/week, however they mentioned that the evidence is limited.[33] The uncertainty relative to folate

supplementation and the doubt that folate reduce adverse effects at the expense of reducing efficacy show the need for clinical trials with MTX with different regimens of FA association.[33]

Monitoring

Before starting MTX, the clinician must review the current medication of the patient and vaccination status and rule out risk factors for the use of MTX, like hepatotoxic factors, renal impairment, active infections or pregnancy. The absolute contraindications for MTX are chronic hepatitis B infection and seropositivity for HIV.[11]

Patients have to do a blood test before starting, 2 weeks after initiation and every 3 months to evaluate myelotoxicity and hepatotoxicity. Liver enzymes are not the best test for assess chronic liver toxicity, but an increase of five to nine-folds dispenses the biopsy. Non-invasive techniques, like procollagen III N-terminal propeptide, fibroscan, fibrotest and magnetic resonance imaging, are being developed.[11] Procollagen III for detection of hepatic fibrosis was the most validated method for monitoring, with a sensitivity of 77,3% and specificity of 91,5%.[20,21] Despite their limitations, all of these are useful tools and make the liver biopsy unnecessary.[20] The pathogenesis of MTX in the liver is related with hepatic folate depletion, so folate supplementation reduces hepatotoxicity.[21] Polymorphisms can also relate with MTX-induced hepatotoxicity.[21] Patients on MTX can develop cirrhosis or non-alcoholic fatty liver diseases like steatohepatitis, but these are associated with other risk factors, like obesity, dyslipidemia, diabetes as part of a metabolic syndrome, and may also be related to abuse in alcohol and other hepatotoxic drugs.[21] Liver biopsy is still the gold standard for evaluate the severity of disease, however it is associated with morbidity and mortality, with the risk of bleeding.[21] Fibroscan has been proven effective, however still isn't approved for use in MTX treated patients. A combination of fibrotests and fibroscans, together with measurement of the procollagen III, seem to be the ideal method for monitoring liver toxicity.[21]

Before starting MTX, a screening of latent tuberculosis, hepatitis B, hepatitis C and HIV should be done, as MTX can reactivate them.[11] MTX in pregnancy is not recommended because of the risk of inducing congenital malformations and spontaneous abortion.[11,21] The recommendation is to discontinue MTX from 3 to 6 months prior to planned pregnancy for females and, despite there being no evidence that male fertility is impaired, the recommendations are to discontinue MTX 3 months prior to conception as well.[11]

In addition, patients with psoriasis have a higher risk of non-melanoma skin cancer, so an annual screening is recommended when patients are treated with immunosuppressive drugs, like MTX.[11] When using MTX, regular monitoring for identifying MTX-related toxicity should be performed for every patient, regardless of his health status.[28]

Comorbid diseases and Cardiovascular risk in psoriasis

The comorbidities associated with psoriasis include arthritis, Crohn's disease, cancer, anxiety, depression, non-alcoholic fatty liver disease, metabolic syndrome (or its components), chronic kidney disease and cardiovascular disorders.[1,34] All these contribute to the morbidity and mortality of psoriasis. However, cardiovascular diseases seem to play the main role.[1]

Studies identified an increase in cardiovascular mortality and strokes in patients with psoriasis.[1,4,6,8] The principal theory to explain this is that psoriasis is a state of systemic inflammation, with inflammatory biomarkers and that it is associated with disease severity. This inflammation induces insulin resistance, which reduces vasodilating factors, such as nitric oxide, resulting in vascular stiffness, known as endothelial dysfunction, which leads to the expression of adhesion molecules and provides the basis for the formation of atherosclerotic plaques.[1] Additionally, T cells, macrophages and inflammatory cytokines are involved in the development of both atherosclerosis and psoriasis, which suggests a relation between the two. Further, the findings showed a dose-response association, with stronger relations for severe psoriasis when compared to mild psoriasis.[2] Another study suggested a marked increase of myocardial infarction (MI), stroke and all-cause cardiovascular mortality, only for patients with the severe form of the disease, specifically on those who need systemic therapy or hospital admissions.[6]

A meta-analysis showed that psoriasis increases significantly the risk of stroke and MI and that psoriasis is more likely to be an independent risk for cardiovascular and cerebrovascular events.[2] This study also suggests that psoriasis is linked with a 20% increase in the risk of a vascular event, like a stroke or infarction.[2] Therefore, patients must be advised of the risk and prevent such events, by assessing and treating their cardiovascular risk factors with either aggressive lifestyle modification or medical intervention.[2] However, results of a survey suggested that most physicians are not aware of the association between psoriasis and cardiovascular diseases.[4,35] Educating physicians about this association and adopting a multidisciplinary approach in the management of psoriasis' patients may lead to better outcomes.[35]

These conclusions led to the hypothesis that the use of systemic treatment for psoriasis, like MTX or biologics, will reduce the cardiovascular risk.[4,6,9] The relation of drugs that target inflammation with the decrease of cardiovascular risk is not completely established.[6]

Many studies are in course to find out whether or not MTX has a cardio-protective effect.[6,11] It is already been settled that MTX reduces the dimension of the MI and also the cardiovascular risk.[9-11] One study adds that it is the specific treatment of inflammation that may lead to a reduction of the cardiovascular risk.[9]

Many studies report that psoriasis' treatment, including MTX and TNF-α inhibitors, reduce cardiovascular risk, in addiction to improving clinical features.[4,12] When compared to MTX, TNF-α inhibitors have a lower number of major cardiovascular events, a lower hazard of major cardiovascular events and a more significant reduction in MI, stroke, transient ischemic attack and unstable angina.[12]

CONCLUSIONS

Despite MTX's mechanism of action still being unknown, it is very complex, with an antifolate effect and also anti-inflammatory effects. More studies are needed to help comprehend its mechanism and, consequently, optimize the use of the drug. Regards to route of administration, most evidence suggests starting with oral administration, mostly because it is easier, cheaper and more accepted by patients and then, if there is a lack of efficacy or gastrointestinal side effects, switch to the subcutaneous form.

Studies showed that higher doses of MTX have a more significant increase on PASI75 response, being more effective than lower doses. Also demonstrated that the PASI75 achieved better scores over time, when larger periods of follow-up were used. However, the low doses used commonly in psoriasis are considered to be effective and safe, instead larger doses, of which safety and adverse effects' rate are unknown.

MTX can be used alone or in combination with biologics. In the latter, MTX increases biologics' efficacy and decreases antidrug antibodies formation. Association therapy decreases exposure to biologic drugs, decreases costs and minimizes side effects of MTX, which is given in a lower dose.

In a study comparing a biologic drug with MTX, adalimumab showed a significantly superior efficacy, faster response and improvement in psoriasis. However, there were no differences in rates of adverse effects. Another study showed that MTX's efficacy was lower when compared to biologics. In the future, when the high costs barrier is exceeded,

clinicians may begin leaning more biological prescription rather than conventional systemic therapy, such as MTX, and the treatment paradigm may change.

In order to overcome variability in MTX's response dependent on the patient's pharmacogenetic profile, it was suggested that the treatment's response could be predicted by dosing pre-treatment tCa, which has a significant association with MTX's efficacy. However, larger studies are required to confirm these findings.

The role of HLA-Cw6 in psoriasis is already known, however its contribution in the response to different treatments is not known. HLA-Cw6 can act like a marker for MTX's response and it also seems to be related with better disease control with fewer limiting adverse effects.

It was suggested that IL-4 polymorphisms are protective against psoriasis and IL-10 polymorphisms and LCE3B/3C gene deletions are associated with an increased risk for the disease. FOXP3 acts like a disease modifying gene by predicting clinical response to MTX. This study highlighted the potential genetic markers to predict MTX response in psoriasis, but it has to be confirmed by larger studies. In the future, it might be possible to have a gene chip, to predict optimal treatment response, based on genotypic profiling, and it may lead to an inexpensive predictive blood test.

There are no unique guidelines on how to use MTX, however, many studies and a survey of dermatologists worldwide seem to agree on the administration of a test-dose only in frail patients and on the starting-dose varying between 10-20 mg/week. Good-responders should be considered into dose reductions, being the maximum dose, in most studies, of 20-25 mg/week. Every author seems to agree that the dose regimen must be individualized.

Although common, most side effects are mild and reversible. However, monitoring these patients is mandatory. They must do blood testing periodically to evaluate myelotoxicity and hepatotoxicity. Liver fibrosis occurs in up to 25% of the patients in treatment with MTX for 5 years and may progress to cirrhosis. Studies suggested that liver fibrosis is not related with cumulative doses of MTX and would be more likely to appear in patients with risk factors. Non-invasive techniques, like procollagen III N-terminal propeptide, fibroscan, fibrotest and magnetic resonance imaging, are being developed. Despite their limitations, these are useful tools and turn liver biopsy, the current gold-standard, unnecessary. A combination of these tests seems to be the ideal method for monitoring liver toxicity and may substitute the biopsy in the future.

MTX's drug survival revealed to be short and its reasons were studied. Side-effects were the most common reason for treatment' discontinuation, compared with ineffectiveness.

As MTX is a folate antagonist, its association with folate seemed to help reduce its secondary effects. However, studies showed that folate supplementation reduces the efficacy of treatment and, when the group of study stops folate, the disease improves quickly. It has also been showed that the reduction in efficacy is dose-dependent. Still, some authors state that the different conclusions of different studies may result from polymorphisms in folate's and MTX's metabolism. This uncertainty and the doubt that folate reduces adverse effects at the expense of reducing efficacy show the need for clinical trials with MTX with different regimens of FA association.

There are numerous comorbidities associated with psoriasis, but cardiovascular diseases seem to be the most important in the morbimortality rate associated with the disease. An increased risk of cardiovascular mortality and strokes in patients with psoriasis has been demonstrated. Therefore, patients must be advised of this risk and prevent cardiovascular events, through lifestyle modification or medical intervention. Nevertheless, a survey suggested that most physicians are not aware of this association. So, educating physicians and adopting a multidisciplinary approach in the management of psoriasis may lead to better outcomes.

The principal theory to justify the increased cardiovascular risk in patients suffering from is the state of systemic inflammation present, which is associated with disease severity. Regarding this hypothesis, it was suggested that the systemic treatment will reduce the cardiovascular risk. It has already been established that MTX reduces the dimension of the MI and cardiovascular risk. Many studies reported that systemic treatment reduces cardiovascular risk and, when compared to MTX, TNF-α inhibitors have a lower number of major cardiovascular events, a lower risk of major cardiovascular events and a more significant reduction in MI, stroke, transient ischemic attack and unstable angina.

One of the reasons, pointed out by many studies, which supports the sparse evidence about pharmacokinetics, pharmacogenetics, dose regimen, efficacy, and even folate supplementation, is the inter-individual variability of treatment's response. In fact, the existence of polymorphisms in genes related to psoriasis, MTX's metabolism and folate's metabolism has been mentioned several times throughout this review.

In conclusion, MTX continues to be widely used, but several features about this drug remain to be studied. This review allowed the gathering of facts that are already known by the scientific community and to emphasize the need for future studies.

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