Editorial paper

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Methotrexate in rheumatoid arthritis – ongoing debate about dosage and route of administration

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Introduction

Methotrexate (MTX) acts as an antifolate by inhibiting dihydrofolate reductase and blocking DNA/RNA synthesis, but its anti-inflammatory effect in autoimmune diseases also includes increasing the release of adenosine (which suppresses inflammation) and inhibiting pro-inflammatory pathways such as nuclear factor-κB. The effects of the drug on rheumatoid arthritis (RA) were indirectly observed in 1951. Gubner et al. [1] administered aminopterin (antifolate) to patients with RA, psoriasis, and psoriatic arthritis with good results, but treatment was discontinued and disease recurrence was observed. In the following years, the drug was modified, its synthesis was facilitated, and MTX was created. For years, its effectiveness in psoriasis was studied, and it was not until the 1980s that it found wider application in rheumatology, replacing older methods of treatment such as penicillamine, sulfasalazine, and gold salts. Since then, MTX has been the basis treatment of RA and other rheumatic diseases with predominant arthritis as well as associated psoriasis. Current recommendations of the European Alliance of Associations for Rheumatology (EULAR) clearly confirm that rapid and appropriately managed MTX dose escalation not only combats the disease more effectively, but above all provides real benefits for patients in their daily lives, taking into account, for example, the drug's effect on the metabolic profile and reduction of cardiovascular risk [2]. These last 2 properties can be considered as an addition to the effective inhibition and control of the inflammatory process.

The expected goal of treatment is to achieve clinical and radiological remission. Immunological remission is not so obvious (persistence of autoantibodies), but laboratory remission with a reduction/normalisation of inflammatory parameters (erythrocyte sedimentation rate, C-reactive protein) seems fully achievable.

Early diagnosis and initiation of treatment, as well as proper escalation of the dose of the first-line drug MTX, are crucial. The dose of MTX (administered orally or subcutaneously) should be increased to a weekly dose of approximately 0.3 mg/kg, according to EULAR guidelines. Standard MTX therapy in adult patients usually starts with an initial dose of 10–15 mg/week, which is gradually increased by 5 mg every 2–4 weeks until a maximum dose of 25–30 mg/week is reached, provided that the patient tolerates the drug well [2]. In the Western hemisphere, the optimal therapeutic dose is approximately 20–25 mg per week, while in Asia, due to lower body weight and potentially different pharmacogenetics of the drug in the East Asian population, the maximum dose will be lower, e.g. 16 mg in Japan [3]. The importance of folic acid supplementation is another key aspect of MTX therapy.

The importance of rapid dose escalation

Rapid MTX dose escalation allows for faster control of disease activity, which has been confirmed in many clinical studies. A study by Gaujoux-Viala et al. [3] showed that patients treated with MTX monotherapy were more likely to achieve remission and better functional performance if the dose was rapidly escalated to a level considered optimal (≥ 20 mg/week at the start of therapy). The escalation must take into account tolerance and possible side effects. Gradual escalation allows for safe monitoring of treatment effects and possible side effects.

Maximum dose and its significance

Reaching a maximum dose of 25–30 mg/week allows for potentiation of the anti-inflammatory effect of MTX without a significant increase in the risk of toxicity, especially if the drug is administered subcutaneously with

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adequate folic acid supplementation. According to data from a meta-analysis by Visser et al. [4], patients receiving MTX doses > 20 mg/week were more likely to achieve remission compared to patients on lower doses [3]. As already mentioned, it is important to take ethnic variability into account when selecting the optimal dose [3].

The role and advantages of parenteral administration of methotrexate

Growing scientific evidence highlights the key role of parenteral (subcutaneous, *s.c.*) administration, especially at higher doses. Parenteral administration offers patients several important clinical and pharmacokinetic benefits that affect the efficacy and safety of therapy [5]. One of the important properties is better bioavailability and concentration stability with *s.c.* administration.

The American College of Rheumatology (ACR) strongly recommends MTX monotherapy over monotherapy with biologic and synthetic targeted disease-modifying antirheumatic drugs (DMARDs) in patients who have not previously received any DMARDs and who have moderate to high disease activity.

Oral administration of MTX is characterised by high variability in absorption, especially at doses above 15 mg/week. Pharmacokinetic studies have shown that subcutaneous administration of MTX allows for higher and more stable plasma concentrations of the drug, which translates into better disease control. The bioavailability of subcutaneously administered MTX is approximately 30–40% higher than that of oral administration at doses ≥ 15 mg/week. This allows for more effective dose escalation, avoiding problems with limited absorption [6–8].

A meta-analysis by Bujor et al. [9] covering 4 randomised studies showed that patients treated with subcutaneous MTX achieved a better clinical response (ACR20) than those receiving oral MTX. Subcutaneous administration increased the chances of achieving a therapeutic response and better disease control while maintaining a similar level of safety.

It has been suggested that *s.c.* administration of MTX may reduce the incidence of gastrointestinal side effects observed with oral MTX. An observational study that directly compared the severity of gastrointestinal symptoms in both forms of administration showed that they were generally more severe with oral administration [9].

Due to its better bioavailability and reduced side effects, s.c. administration allows for safe escalation of the MTX dose to levels often unattainable with oral administration. The EULAR guidelines (2022) recommend considering switching to the subcutaneous form at doses of 15 mg/week or higher to allow for further dose escalation and improved therapeutic effects. Parenteral administration is becoming the standard of care for patients requiring doses ≥ 20–25 mg/week, which is associated with greater efficacy and better disease control [1].

Benefits of methotrexate dose escalation

Faster achievement of remission

In a randomised trial by Verstappen et al. [10], patients with early RA who were treated with MTX according to an intensive dose escalation strategy achieved remission in 50% of cases after 2 years, compared with 37% in the group using a conventional treatment strategy. Intensification of MTX treatment, tailored to the individual patient's response, led to better clinical outcomes and faster remission. These results suggest that rapid MTX dose escalation may contribute to more effective suppression of inflammation and improved therapeutic outcomes in early RA treatment [10].

Limiting permanent joint damage

Uncontrolled RA leads to irreversible changes. Data from the COBRA study [11] and more recent analyses confirm that early and rapid escalation of MTX reduces the radiographic progression of joint damage even within the first 2 years of therapy.

Less need to change therapy and use biological drugs

Analysis of data from registries (e.g. NOR-DMARD, SWEFOT) shows that patients who rapidly increased their MTX dose and achieved good disease control were less likely to require biological therapy in subsequent years [12, 13]. This translates into measurable economic benefits and a reduced risk of complications associated with the use of biological drugs.

Better tolerance and safety of therapy

Studies have shown that *s.c.* administration of MTX was associated with a significantly lower incidence and severity of gastrointestinal adverse events compared to the same dose of the drug administered orally [14]. Safety is related both to the optimal selection of the drug and dose, taking into account indications and contraindications, which is obvious, but also to the proper presentation of recommendations and their observance by the patient (once a week).

The selection of the drug is related to reducing the risk of systemic complications, and a meta-analysis by Sun et al. [15] confirmed that the use of MTX is associated with a reduction in the risk of cardiovascular events in patients with RA by approximately 20% compared to patients not treated with MTX. In addition, epidemiological

studies indicate that controlling inflammation with MTX reduces the risk of developing type 2 diabetes by up to half [16] and is associated with a lower risk of dementia symptoms [17].

Folic acid supplementation (minimum 5 mg/week outside of MTX administration days) is crucial for reducing adverse effects. Liver and kidney function and blood count should be monitored during therapy. In the absence of effect or intolerance to the oral form of MTX, a rapid switch to the parenteral form is recommended.

Conclusions

Rapid and appropriate escalation of the MTX dose, including in parenteral form, brings measurable benefits to patients: faster remission, reduced joint damage, less need for biological drugs, better tolerance of therapy, and reduced risk of systemic complications. Current EULAR guidelines and ACR recommendations clearly support this approach as the standard of care in RA, emphasising its importance for improving the quality of life and health of patients.

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