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This publication discusses the evidence supporting the use of subcutaneous methotrexate, supplied in a prefilled syringe (Trexject®). Subcutaneous methotrexate is indicated in the management of severe, recalcitrant, active rheumatoid arthritis (RA) in adults not responding to, or intolerant of, an adequate trial of non-steroidal anti-inflammatory drugs and one or more disease-modifying drugs.[1] Subcutaneous methotrexate may also be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment.[1] Subcutaneous methotrexate was first included in the Australian Register of Therapeutic Goods on 25 August 2015 and has been listed on the Pharmaceutical Benefits Scheme since 1 April 2018.

Independent commentary by Phillip Vecchio

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Introduction

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune condition associated with persistent synovitis, systemic inflammation and the presence of autoantibodies.[2] Persistent inflammation of the joints can lead to the development of bony erosions, cartilage and tendon degradation, and deformity of the joints.[2] In many patients, inflammation can also occur at other sites, for example the lungs, heart and kidneys.[2]

Approximately 2% of the Australian population (over 400,000 people) have RA.[3] The prevalence of the disease is slightly higher for women than men.[3] The onset of RA is usually between 35 and 60 years, however most people with RA are aged over 65 years.[3] In data reported by the Australian Institute of Health and Welfare, 18% of people with RA stated they had poor health compared with 4% of people without RA.[3] RA has the potential to lead to disability and, in Australia, there has been a 72% increase in hospitalisations for people with RA in the past 10 years.[3]

The goal of RA management is to maximise long-term quality of life.[2] This may be achieved by controlling symptoms, normalising physical function, enabling participation in social and work-related activities, preventing joint damage and minimising cardiovascular complications.[2] Therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) is typically used to induce clinical remission of RA and prevent joint damage.[4] The initial induction strategy typically uses csDMARD monotherapy, or a combination of csDMARDs with or without a corticosteroid.[2] Methotrexate is the csDMARD of choice for most patients and usually forms the backbone of regimens when combination therapy is needed.[2]

Once disease control has been achieved and maintained with csDMARD therapy, and any corticosteroid therapy has been completely tapered, the csDMARD dose is usually reduced to that which maintains disease control.[2] If remission is not achieved, or there is a persistence of significant disease activity, treatment with a biological DMARD or a targeted synthetic DMARD may be considered.[2]

Methotrexate monotherapy has been shown to reduce disease progression and improve quality of life.[5] It is considered the "gold standard" csDMARD to treat RA by the Australian Rheumatology Association, and is the recommended first choice for monotherapy in the guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[6,7] In patients with RA, several lines of evidence indicate that subcutaneous administration of methotrexate may be associated with optimised methotrexate treatment, improved outcomes and better treatment compliance compared to oral administration of methotrexate.[8]

Psoriasis

Psoriasis is a chronic immune-mediated skin disease that is characterised by the eruption of reddish, silvery-scaled plaques, predominantly on the elbows, knees, scalp and trunk. Clinical manifestations of psoriatic skin lesions and coexisting comorbidities can have a substantial negative impact on quality of life.[9] The prevalence of psoriasis in Australia varies across studies and has been estimated at between 2% and 7%.[10] Guidelines recommend phototherapy or non-biologic systemic therapy as initial treatment for severe psoriasis.[11] Non-biologic therapies recommended include methotrexate, cyclosporin and acitretin.[11]

Subcutaneous methotrexate

This section summarises subcutaneous methotrexate injection as a prefilled syringe. Detailed information can be found in the Trexject® Product Information.

Pharmacological properties

Methotrexate is a cytotoxic agent that competitively inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid.[8] This inhibition interferes with DNA synthesis and cellular reproduction.[8] Tissues with high rates of cellular proliferation are generally more sensitive to the anti-inflammatory effects of methotrexate.[1] In RA and psoriasis, these anti-inflammatory effects are thought to result from several mechanisms, including modification of the cellular redox state, inhibition of polyamines and accumulation of anti-inflammatory molecules.[8]

In patients with RA, methotrexate can reduce articular swelling and tenderness within 3 to 6 weeks.[1] Although methotrexate improves symptoms of inflammation, there is no evidence that it reduces remission of RA or has a beneficial effect on bone erosion or other radiological changes that result in impaired joint use, functional disability and deformity.[1] While most studies of methotrexate in patients with RA are relatively short-term (3 to 6 months), data from long-term studies indicate that initial clinical improvements in the symptoms of inflammation (pain, swelling, stiffness) are maintained for at least 2 years with continued therapy.[1]

In patients with psoriasis, the rate of epithelial cell proliferation in the skin is much greater than that in normal skin.[1] This difference in proliferative rates provides the basis for use of methotrexate to control the psoriatic process.[1]

Studies in adult patients with RA comparing oral methotrexate at doses of 7.5 to 30 mg/week with equivalent doses administered intramuscularly or subcutaneously have generally shown lower area under the plasma concentration time curves with oral therapy versus parenteral administration for doses of methotrexate as low as 10 mg.[1]

Dosage and administration

In patients with RA or psoriasis, the recommended initial dose of subcutaneous methotrexate is 7.5 mg once weekly.[1] Depending on the individual activity of the disease and tolerability of the patient, the initial dose may be increased gradually by 2.5 mg per week.[1] A weekly dose of 25 mg should not be exceeded.[1]

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

Contraindications

Methotrexate is contraindicated in patients with:[1]

- Hypersensitivity to methotrexate or to any of the excipients
- Alcoholism or hepatic disorders, including alcoholic liver disease or other chronic liver disease
- Severe renal impairment (creatinine clearance less than 20 mL/min)
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia
- Serious, acute or chronic infections, such as tuberculosis, HIV or with overt or laboratory evidence of other immunodeficiency syndromes
- Patients with peptic ulcer disease or ulcerative colitis and ulcers of the oral cavity
- Poor nutritional status
- Concurrent vaccination with live vaccines

Methotrexate is also contraindicated in pregnancy and breast-feeding, on the day of a surgery with anaesthesia and in combination with retinoids, such as acitretin.[1]

Interactions with other medicines

Methotrexate may interact with:[1]

- Alcohol, hepatotoxic medicinal products and haematotoxic medicinal products
- Leflunomide
- Medicinal products with high plasma protein binding
- Antibiotics
- Products containing folic acid or folinic acid
- Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents
- Proton-pump inhibitors
- Allopurinol
- Medicinal products that cause folate deficiency
- Medicinal products with adverse reactions on the bone marrow
- Other antirheumatic medicinal products
- Sulfasalazine
- Amiodarone
- Theophylline
- Mercaptopurine
- Psoralen and ultraviolet A therapy
- Vaccines
- Caffeine- or theophylline-containing beverages

Safety profile of oral versus subcutaneous methotrexate

In head-to-head studies comparing oral to subcutaneous methotrexate in methotrexate-treatment naïve RA patients, the safety profiles associated with the two routes of administration were generally similar, with some studies reporting a reduced incidence of gastrointestinal adverse events with subcutaneous methotrexate.[8,12-15] Similar safety findings were observed in studies investigating patients switching from oral to subcutaneous methotrexate.[16-18] For instance, in an observational study of 70 patients with RA receiving 7.5 or 15 mg/week oral methotrexate, switching to subcutaneous methotrexate at the same dose resulted in a significant decrease in nausea and abdominal pain, and a complete cessation of vomiting and diarrhoea.[18]

Subcutaneous methotrexate is also generally well tolerated in patients with psoriasis, with serious adverse events reported for only 3% of patients in the methotrexate group of one particular randomised, double-blind, placebo-controlled, phase 3 study.[19]

Expert commentary:

It is difficult to imagine treatment of any inflammatory arthritis without methotrexate, particularly now that we are so comfortable with its indications, dosing, escalation and monitoring.

Tolerability and effectiveness of this indispensable drug when taken orally are bugbears of management, both of which may be practically improved by parenteral administration. There are some people who just do not absorb it and most clinicians familiar with the power of methotrexate can vouch for "amazing" differences in clinical outcome when switched from oral to subcutaneous. Nausea, headaches and fogginess frequently, but not always, reduce in intensity.

Until the availability of the pre-filled syringes, attempts to convert the intolerant or non-responders to parenteral methotrexate may have been thwarted by several factors. These include the awkward and impractical need to draw up the solution from ampoules, the need to separately obtain suitable syringes, the need for it to be drawn up in chemotherapeutic conditions, the requirement for the disposal of vials of unspent drug in an approved manner and finally administration (often) by a healthcare professional. The pre-filled syringe does much to allay concerns and improve independence and self-administration.

Key trials and expert commentary on the use of methotrexate injection

Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial[13]

Summary: Subcutaneous administration of methotrexate was significantly more effective than oral administration in patients with active RA, with no difference in tolerability.

Methods: This multicentre, randomised, double-blind, controlled, phase 4 study randomised patients 1:1 to 15 mg/week methotrexate administered either orally (two 7.5 mg tablets plus a dummy prefilled syringe) or subcutaneously (prefilled syringe containing 10 mg/mL plus two dummy tablets) for 24 weeks. Patients who did not meet the American College of Rheumatology criteria for 20% improvement (ACR20) at week 16 remained blinded and were switched from 15 mg oral to 15 mg subcutaneous methotrexate and from 15 mg subcutaneous methotrexate to 20 mg of subcutaneous methotrexate for the remainder of the study. Eligible patients had active RA, as defined by a Disease Activity Score in 28 joints (DAS28) ≥4, and had not previously taken methotrexate or biologic agents, and had not taken DMARDs 2 weeks prior to randomisation. The primary outcome was ACR20 response at 24 weeks. Key secondary endpoints included ACR50 and ACR70 responses and safety.

Results: A total of 375 patients were randomised and analysed for efficacy. At week 24, the proportion of patients with an ACR20 response was significantly higher in the subcutaneous methotrexate group than in the oral methotrexate group (78% vs. 70%). The proportion of patients achieving an ACR70 response at week 24 was also significantly higher in the subcutaneous group than in the oral group (41% vs. 33%). No statistically significant difference was found between groups in the proportion of patients achieving an ACR50 response. Patients with a disease duration ≥12 months had higher ACR20 response rates (89% for subcutaneous vs. 63% for oral). Treatment was switched at week 16 for 14% of the ACR20 non-responders. Switching from oral to subcutaneous methotrexate and from 15 mg to 20 mg subcutaneous methotrexate resulted in 30% and 23% ACR20 response rates, respectively.

Methotrexate was well tolerated. The proportion of patients with adverse events over 24 weeks was similar amongst treatment groups. Similar proportions of patients had serious adverse events in the two groups (5.7% for subcutaneous vs. 4.3% for oral). With the exception of one case of pneumonitis in the subcutaneous group, all other serious adverse events were unrelated to study drug. No life-threatening adverse events and no deaths occurred. More patients in the subcutaneous group than in the oral group withdrew due to adverse events. Moderate or severe adverse events reported at ≥3% incidence and higher in one group than the other were diarrhoea (2.6% for subcutaneous vs. 6.9% for oral) and loss of appetite (7.3% for subcutaneous vs. 3.2% for oral).

Expert commentary:

These results relating to better effectiveness of subcutaneous methotrexate reflect practice, as does tolerability of this formulation and the similarity of side-effects. I would predict there is no difference in the incidence of the rare pneumonitis between oral and subcutaneous.

Tolerability and patient/physician satisfaction with subcutaneously administered methotrexate provided in two formulations of different drug concentrations in patients with rheumatoid arthritis[20]

Summary: Patients with RA receiving subcutaneous methotrexate preferred a smaller volume of administered drug and the improved usability of a pre-attached needle in combination with a smaller prefilled syringe.

Methods: This open-label, comparative, within-patient controlled, multicentre study enrolled RA patients who had previously received oral methotrexate and required intensified therapy. Patients received 20 mg/week subcutaneous methotrexate with a medium-concentration formulation (2 mL of a 10 mg/mL solution) for 3 weeks followed by a high-concentration formulation (0.4 mL of a 50 mg/mL solution) for 3 weeks. The first methotrexate injection for each syringe type was administered by a physician or nurse and the patients self-injected the remaining doses. Questionnaires and visual analogue scales were used to document satisfaction, usability and local tolerability. The aim of the study was to assess the preference of RA patients for continuous subcutaneous methotrexate treatment with either a medium- or high-concentration formulation.

Results: A total of 132 patients were enrolled. At the end of the study, 93% of patients preferred the high- over the medium-concentration methotrexate formulation. A total of 91% of patients assessed the high-concentration formulation as "good" or "very good" compared with 34% for the medium-concentration. Physicians and patients statistically significantly favoured syringe usability with the high- compared to the medium-concentration formulation. Nurses' and investigators' overall assessment was 19% "good" and 81% "very good" for the high-concentration formulation, and 31% "good" and 13% "very good" for the medium-concentration formulation. A total of 50% of nurses and investigators had no preference for one formulation over the other.

Most adverse events were mild or moderate in intensity. The most frequent adverse events were gastrointestinal disorders (6%), investigations (4%) and general disorders and administration site conditions (3%). There were no relevant differences in adverse events between the two methotrexate formulations with the exception of increased liver enzymes in the high- compared to the medium-concentration group (5 patients vs. 0 patients). Three patients discontinued the study due to the adverse events of coughing, dizziness and nausea/sicca symptoms/pain. Physicians' assessment of the injection site showed significantly less erythema with the high- compared to the low-concentration formulation (20% vs. 29%).

Expert commentary:

It stands to reason, as well as reflecting the results of this open-label study, that smaller volumes are preferred by all.

Preference, satisfaction and usability of subcutaneously administered methotrexate for rheumatoid arthritis or psoriatic arthritis: results of a postmarketing surveillance study with a high-concentration formulation[21]

Summary: In patients with rheumatoid or psoriatic arthritis, there was a high acceptance by patients (88%) and healthcare professionals (93%) of a prefilled syringe with a pre-attached needle for subcutaneous self-administration of a high concentration (50 mg/mL) of methotrexate.

Methods: This post-marketing surveillance study enrolled patients with rheumatoid or psoriatic arthritis. Patients received six methotrexate 50 mg/mL injections over 5 weeks. The first methotrexate injection was administered by a physician or nurse and the patients self-injected the remaining doses. The physicians recorded patient histories, previous and concomitant methotrexate therapy and the methotrexate dose administered. They also used questionnaires to document physicians', nurses' and patients' assessments of usability, preference and tolerability at each respective visit. Adverse events were also collected. The aim of the study was to assess preference, satisfaction and usability of subcutaneous self-administration of a ready-to-use 50 mg/mL methotrexate formulation in patients with rheumatoid or psoriatic arthritis.

Results: A total of 403 patients were enrolled; 77% had RA and 15% had psoriatic arthritis. The remainder had other rheumatic diseases or arthritis, or had no information available. A total of 55% of patients had previously received methotrexate treatment and, of these, 42% had previously self-administered methotrexate as a subcutaneous injection. The most common reasons that patients wanted to change to subcutaneous self-administration of a high concentration of methotrexate were improved bioavailability (43%), improved usability (25%) and a dislike of methotrexate tablets (14%).

At 5 weeks, the overall assessment of self-administration of 50 mg/mL of methotrexate was "very good" and "good" in 88% of patients compared with 3% who gave a "poor" or "very poor" assessment. Overall, 93% of physicians and nurses provided an assessment of "very good" and "good" compared with 1% who gave a "poor" or "very poor" assessment. Availability and use of a pre-attached needle was considered advantageous by 92% of patients, physicians and nurses overall. A total of 96% of patients described the feeling of the injection as comfortable or tolerable, and severe pain was reported only once. A total of 84% of patients reported improved quality of life and 89% reported a feeling of more independence. Of patients who had previously self-administered low concentration methotrexate as a subcutaneous injection, 95% would prefer a high concentration in future. Physicians considered 96% of patients suitable for subcutaneous self-administration of methotrexate. The treatment was well-tolerated and no serious adverse events were reported.

Expert commentary:

This research verifies that the methotrexate injection is not uncomfortable and that there is frequent perceived value in switching. Many clinicians are able to recall patients where clinical control was poor to moderate, then experiencing clinically valuable improvements on subcutaneous therapy, even drug-induced remissions. Not everyone easily accepts a weekly injection as compatible with their concept and tolerability for treatment, but improvements in outcome and tolerability, as well as demonstrated ease of administration, are reinforcing incentives.

Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration[22]

Summary: In patients with RA, systemic exposure with subcutaneous methotrexate demonstrated linear increases at doses of 10, 15, 20 and 25 mg/week whereas systemic exposure with oral methotrexate plateaued at doses ≥15 mg/week.

Methods: This randomised, multicentre, open-label, three-way crossover, phase 2 study assigned patients with RA undergoing treatment with methotrexate for ≥3 months to receive methotrexate 10, 15, 20 and 25 mg/week in a random sequence of three treatments: oral, subcutaneous into the abdomen and subcutaneous into the thigh. Investigators selected the dose based on the patients' then-current oral methotrexate regimen. The study was conducted for 8 weeks. The primary objectives were to compare the relative bioavailability of oral methotrexate to that of subcutaneous methotrexate and to determine whether the two injection sites provided bioequivalent drug exposure. Secondary objectives were to compare other pharmacokinetic parameters for the three modes of administration and safety.

Results: A total of 47 patients completed the study. Subcutaneous methotrexate exhibited a linear, dose-proportional increase in systemic exposure with no plateau at each dose. In contrast, systemic exposure of oral methotrexate plateaued at doses ≥15 mg/week. Subcutaneous administration also resulted in higher methotrexate exposure than the comparable oral dose at each dose level investigated. The maximum observed concentration of methotrexate was comparable across routes of methotrexate administration. The treatments in both the oral methotrexate and subcutaneous methotrexate groups were generally safe and well tolerated, with no new treatment-related safety signals identified.

Expert commentary:
There is a well-known saturation of effect with oral methotrexate attributed to its variable and unpredictable gastrointestinal absorption. There is some evidence for "saturable" gastrointestinal receptors and minimal additional available drug in doses greater than 15 mg. This has long been considered to be the key to the improved responsiveness from parenteral therapy.

Utilization of subcutaneous methotrexate in rheumatoid arthritis patients after failure or intolerance to oral methotrexate: a multicenter cohort study[17]

Summary: In patients with active RA who started subcutaneous methotrexate after failure or intolerance to oral methotrexate, the extrapolated median duration of subcutaneous methotrexate using an exponential model was 8.9 years, with a mean dose of 18.4 mg.

Methods: This non-interventional, non-comparative, multicentre cohort study retrospectively collected data from the clinical records of patients with active RA. Non-parametric and parametric methods were used to determine treatment duration. The aim of this study was to determine the median duration of subcutaneous methotrexate treatment in adult patients with active RA.

Results: A total of 50 patients were included in the study. At baseline, the mean duration of oral methotrexate was 4.7 years with a mean dose of 14.3 mg. A total of 32 patients at baseline had discontinued oral methotrexate due to lack of efficacy and 13 patients due to adverse events. The probability of discontinuing subcutaneous methotrexate after 1, 2 and 3 years of treatment was predicted to be 6.1%, 8.5% and 23.2%, respectively. The median duration of subcutaneous methotrexate treatment based on exponential modelling was 8.9 years. The mean dose of subcutaneous methotrexate was 18.4 mg. A total of 9 patients discontinued subcutaneous methotrexate during the observation period; 6 patients due to adverse events and 3 patients due to lack of efficacy.

Expert commentary:
Again, this suggests that failure of/intolerance to oral methotrexate is well worth a switch to subcutaneous methotrexate for all the reasons that make this drug such a valuable medication in remission-seeking therapy.

Psoriasis

While few studies have investigated subcutaneous methotrexate in psoriasis,[8] a favourable efficacy and safety profile for oral methotrexate has been established in clinical studies as well as in clinical experience.[1] For the treatment of psoriasis, methotrexate is usually given once weekly either orally, intramuscularly or subcutaneously.[1] The start-dose of methotrexate in randomised controlled trials has varied from 5 to 25 mg/week, and was most commonly either 7.5 mg or 15 mg/week.[1] Guidelines vary from 5 to 15 mg/week.[1] The majority of studies have demonstrated a remission or an improvement in skin condition within 16 to 24 weeks after initiating methotrexate treatment.[1] A higher starting dose (15 mg/week) in two studies has contributed to an achievement of maximum response after 8 to 12 weeks of treatment.[1]

Expert commentary:
There is no reason why other diseases outside the inflammatory arthritis arena should also not be equally benefitted from consideration of parenteral methotrexate for indications of improved effectiveness or tolerability.

Conclusions

Subcutaneous methotrexate injection is an effective treatment option for patients with RA or psoriasis.[8,13,21,23] Studies show that subcutaneous methotrexate can benefit patients who have failed to achieve required response rates or shown unacceptable intolerance to oral methotrexate.[17,22] In addition, subcutaneous methotrexate may delay the need to treat with biological DMARDs, and could be associated with higher persistence rates and improved adherence compared with oral methotrexate.[8]

Expert's concluding comments

Treating our patients with optimum therapeutic tools, which aim for remission with the least intolerance, healthcare consumption and cost, is the coveted goal in practice. Subcutaneously administered methotrexate is not only a useful alternative to its oral cousin when it is deemed to be ineffective or poorly-tolerated, it is a valuable agent in the quest for remission. Pre-filled methotrexate syringes assist the patient's journey with improved prescription, comfort and ease of administration.

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