Methotrexate

Statut de médicament essentiel

Section: 29. Medicines for diseases of joints > 29.2. Disease-modifying anti-rheumatic drugs (DMARDs)

EMLc | Codes ATC: L04AX03

Indication	Rheumatoid arthritis, serology unspecified Code ICD11: FA20.Z
INN	Methotrexate
Type de médicament	Chemical agent
Type de liste	Liste complémentaire (EML) (EMLc)
Formulations	Oral > Solid > tablet: 2.5 mg (as sodium salt)
Historique des statuts LME	Ajouté pour la première fois en 1997 (TRS 882) Modifié en 2003 (TRS 920) Modifié en 2011 (TRS 965) Modifié en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Methotrexate
DrugBank	Methotrexate

Recommandation du comité d'experts

The Expert Committee acknowledged that methotrexate is one of the mainstays of treatment for chronic inflammatory autoimmune conditions. Oral methotrexate is included on the Model Lists for rheumatoid arthritis and juvenile idiopathic arthritis, and a positive recommendation for oral methotrexate for treatment of severe psoriasis has been made at this meeting. The Committee noted that data on the clinical efficacy and safety of subcutaneous methotrexate compared with oral or intramuscular formulations are limited and are based mostly on studies in patients with rheumatoid arthritis. Bioavailability data suggest higher concentration following subcutaneous administration, but only a modest effect on response or side-effects. The Committee noted that the application did not include data on discontinuation/drug survival or compliance, nor on whether subcutaneous methotrexate can delay the need for biological medicines. The Committee considered that access and affordability of methotrexate is generally acceptable, with generics available. However, the Committee noted that subcutaneous methotrexate is generally more expensive than oral formulations and prefilled syringe/autoinjector delivery systems may substantially increase the cost of treatment. The Committee noted a lack of evidence on cost–effectiveness compared with oral formulations. The Committee acknowledged that subcutaneous methotrexate may have a role only in a small subgroup of patients in whom oral treatment is suboptimal or not tolerated, however evidence supporting its use in this population is limited. Overall, the Committee considered the possible benefits of subcutaneous compared with oral methotrexate were unclear, with limited evidence suggesting only modest benefits in a small proportion of patients, at a considerably higher price. Therefore, the Expert Committee did not recommend inclusion of subcutaneous formulations of methotrexate on the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate.

Contexte

Methotrexate, in oral and parenteral formulations, is included in the EML and EMLc for use in the treatment of various cancers. Oral methotrexate is included as a disease-modifying anti-rheumatic medicine for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Biological disease-modifying medicines (adalimumab, representative of the pharmacological class of tumour necrosis factor alfa (TNFa) inhibitors) are included on the Model Lists for use in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and Crohn disease. A separate application to the 2023 Expert Committee meeting requests inclusion of oral methotrexate on the EML and EMLc for the treatment of severe psoriasis.

Pertinence pour la santé publique

Between 1986 and 2014, the mean global point prevalence of rheumatoid arthritis was reported to be 0.56%, with regional differences in prevalence: 1.46% in north America, 0.80% in Africa, 0.53% in Europe, 0.46% in South America and 0.34% in Asia (1). In the case of psoriasis, global prevalence varies widely. Prevalence in the overall population has been reported as 0.11% in east Asia, 1.58% in Australasia and 1.52% in western Europe. The estimated prevalence of psoriasis in Asian countries was reported to be much lower. Psoriasis occurs more frequently in adults than in children (2). The Global Burden of Disease study reported more than 4.6 million incident cases of psoriasis worldwide in 2019 (3). About 30% of psoriatic patients develop psoriatic arthritis (4). No information was provided in the application on the prevalence of juvenile idiopathic arthritis, psoriatic arthritis or Crohn disease. The Global Burden of Disease study reported about 4.9 million cases of inflammatory bowel disease worldwide, without differentiation between Crohn disease and ulcerative colitis (5).

Bénéfices

Rheumatoid arthritis The application presented only brief summaries of the findings of publications identified through a literature search. The following information has been elaborated by the Secretariat. A 2016 systematic review and meta-analysis (seven studies, 1335 participants) compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis (6). Subcutaneous methotrexate was associated with greater improvements at 24 weeks in the American College of Rheumatology 20% (ACR20) and 70% (ACR70) responses: ACR20 odds ratio (OR) 1.68, 95% confidence interval (CI) 1.09 to 2.61; ACR70 OR 1.52, 95% CI 1.02 to 2.26; two randomized controlled trials, 467 participants). No significant difference was found in ACR50 response between treatment groups (OR 1.68, 95% CI 0.64 to 4.44). Two studies (535 participants) evaluated pain using visual analogue scale scores. Results showed that participants treated with subcutaneous methotrexate had better pain control (mean difference (MD) –0.65, 95% CI –0.93 to –0.37). Three studies (1163 participants) reported clinical failure and found no significant difference between the subcutaneous and oral methotrexate treatment groups (OR 1.20, 95% CI 0.85 to 1.71). A randomized crossover study (47 participants) compared the relative bioavailability, safety and tolerability of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis (7). Patients were assigned to receive methotrexate 10 mg, 15 mg, 20 mg and 25 mg a week in a random sequence of three treatments: orally, subcutaneous injection into the abdomen and subcutaneous injection into the thigh. Blood samples were collected for pharmacokinetic analysis and injection sites were assessed for 24 hours after administration. Systemic exposure of oral methotrexate plateaued at doses ≥ 15 mg/week, whereas systemic exposure of subcutaneous methotrexate increased linearly and was greater than oral methotrexate at each dose. Higher systemic methotrexate exposure with subcutaneous treatment was not associated with an increase in adverse events. A randomized trial evaluated efficacy and tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients (8). Patients were randomized to receive 7.5 mg subcutaneous methotrexate (n = 52) or 8 mg oral methotrexate (n = 50) weekly for 12 weeks (part 1). Long-term (52 weeks) efficacy and safety of subcutaneous methotrexate (up to a maximum dose of 15 mg/week) was assessed in a second part of the trial. The primary efficacy endpoint was the ACR20 response rate at week 12, which was not significantly different between subcutaneous and oral treatment groups (59.6% versus 51.0%, respectively; difference 8.6, 95% CI –11.3 to 27.8). A single 6-month prospective, randomized, phase IV trial compared the efficacy and safety of subcutaneous versus oral methotrexate in 284 patients with rheumatoid arthritis (9). Patients were randomized to receive 15 mg/week orally (n = 187) or subcutaneously (n = 188) for 24 weeks. The primary outcome was ACR20 response at 24 weeks. Subcutaneous methotrexate was associated with a significantly greater proportion of patients achieving ACR20 response (78% versus 70%) and ACR70 response (41% versus 33%) than oral methotrexate. No significant difference was observed between treatment groups for ACR50 response. Treatment was well tolerated, with a similar rate of adverse events in both treatment groups. A 2016 narrative literature review identified 23 publications on the use of oral and subcutaneous methotrexate in the treatment of rheumatoid arthritis (10). Included publications were 10 systematic reviews/guidelines, six randomized trials, one prospective cohort study,

four retrospective studies, one cost-minimization analysis and one expert opinion/editorial. The review authors reported that subcutaneous methotrexate had higher and less variable bioavailability than oral methotrexate, especially at medium-to-high dosages (> 15 mg/week). Clinical response, evaluated through Disease Activity Score-28 and American College of Rheumatology Criteria, was greater with subcutaneous versus oral methotrexate, in both treatment-naïve patients and those switching from oral methotrexate because of treatment failure. Subcutaneous methotrexate was associated with fewer gastrointestinal side-effects, however other adverse effects were similar for the oral and subcutaneous routes. Evidence on the cost–effectiveness of subcutaneous versus oral methotrexate was not available, however, the review authors postulated that delaying the use of more aggressive and expensive therapies (e.g. biological disease-modifying anti-rheumatic medicines) might provide cost savings. Another 2016 narrative literature review provided an overview of a change in patient preference from oral to subcutaneous methotrexate and benefits of subcutaneous over oral therapy in patients with arthritis (11). Several studies reported better clinical response in patients treated with subcutaneous versus oral methotrexate, which has been attributed to the more stable pharmacokinetics of subcutaneous treatment. Subcutaneous methotrexate was well tolerated and caused minimal gastrointestinal disturbances at higher doses. The authors of the review acknowledged that subcutaneous methotrexate may impose a greater financial burden on patients but concluded that switching patients unresponsive to oral methotrexate to subcutaneous methotrexate might avoid the need for biologicals or other treatments, and hence result in cost savings. Furthermore, the authors concluded that most patients would prefer subcutaneous methotrexate to oral methotrexate. A 2015 narrative literature review evaluated outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis. Six studies (two systematic reviews, two randomized controlled trials, one longitudinal study and one retrospective cohort study) were included in a qualitative synthesis (12). The efficacy and toxicity of methotrexate appeared to be related to the absorbed dose rather than the route of administration. While bioavailability was greater for parenteral methotrexate, evidence was lacking that dividing oral doses was less advantageous, safer or more tolerable. The authors conceded that there may be modest benefits associated with starting patients with higher doses of methotrexate, and switching from oral to parenteral treatment when clinical response was inadequate. Additional, older literature reviews identified in the application reported findings similar to those described above (13–16). Juvenile idiopathic arthritis The application did not present any evidence for subcutaneous methotrexate for treatment of juvenile idiopathic arthritis. Psoriasis The application stated that very few data were available on the use of subcutaneous methotrexate in psoriasis. The METOP study was a prospective, randomized, double-blind, placebo-controlled, multicentre, phase III trial that examined subcutaneous methotrexate in 120 patients with moderate-to-severe plaque-type psoriasis (17). The primary efficacy endpoint (75% reduction in psoriasis area and severity index score (PASI 75) from baseline to week 16) was achieved in 37/91 (41%) patients in the methotrexate group versus 3/29 (10%) patients in the placebo group (relative risk (RR) 3.93, 95% CI 1.31 to 11.81). Subcutaneous methotrexate was reported to be generally well tolerated. The application identified other prospective (18,19) and retrospective (20) studies of subcutaneous methotrexate in chronic plaque psoriasis but did not provide any information of the evidence. Psoriatic arthritis The application did not present any evidence on subcutaneous methotrexate for psoriatic arthritis, as very limited evidence exists on the use of subcutaneous methotrexate for this condition. Crohn disease The application identified four studies that included subcutaneous methotrexate in the treatment of Crohn disease but did not provide any information of the evidence (21–24).

Torts

The application stated that comparative safety data for subcutaneous versus oral or intramuscular methotrexate were lacking. A 2016 systematic review and meta-analysis that compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis reported no significant difference between treatment groups for headache (OR 0.69, 95% CI 0.39 to 1.24), vomiting (OR 0.55, 95% CI 0.26 to 1.18) or dyspepsia (OR 0.67, 95% CI 0.37 to 1.19). Nausea was reported significantly less frequently in the subcutaneous group (OR 0.53, 95% CI 0.28 to 0.97), as was diarrhoea (OR 0.43, 95% CI 0.20 to 0.95) (6). A randomized trial that evaluated the tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients reported that any adverse events occurred 57.7% and 72.0% of patients in the subcutaneous and oral treatment groups, respectively. A trend to fewer gastrointestinal disorders, in particular nausea, was observed in the subcutaneous group. With long-term treatment, the most commonly reported adverse reactions were nausea (13.8%), stomatitis (11.9%) and increased alanine aminotransferase levels (9.2%) (8). In the METOP study in patients with psoriasis, the drop-out rate with subcutaneous methotrexate was 39% over 52 weeks, primarily due to poor efficacy and adverse events. During the placebo-controlled phase, methotrexate led to more gastrointestinal adverse events and increased liver enzyme levels compared with placebo. Gastrointestinal adverse events were usually mild to moderate, and led to permanent drug discontinuation in 3% of patients. Elevated liver enzymes occurred in 23% of

patients receiving methotrexate, leading to permanent drug discontinuation in 12% of patients (17).

Rapport coût/efficacité

The application did not present information on the comparative cost or cost–effectiveness of subcutaneous methotrexate compared with oral, intramuscular or intravenous methotrexate. In general, subcutaneous formulations of methotrexate appear to be more highly priced than oral or other parenteral forms.

Directives de l'OMS

WHO guidelines for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis or Crohn disease are not currently available.

Disponibilité

The application reported that subcutaneous methotrexate has regulatory approval and market availability in most middle- and high-income countries.

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