Reviewer No. 2 checklist for:

DMARDS Review for children

In the WHO Essential Medicines List

(1) Have all important studies that you are aware of been included?

   Yes  X  No

(2) Is there adequate evidence of efficacy for the proposed use?

   Yes  No  X

(3) Is there evidence of efficacy in diverse settings and/or populations?

   Yes  No  X

(4) Are there adverse effects of concern?

   Yes  X  No

(5) Are there special requirements or training needed for safe/effective use?

   Yes  X  No

(6) Is this product needed to meet the majority health needs of the population?

   Yes  No  X

(7) Is the proposed dosage form registered by a stringent regulatory authority?

   Yes  X  No

(8) What action do you propose for the Committee to take?

   According to the previous review, I propose the inclusion of methotrexate and hydroxychloroquine, taking into account the available evidence for rheumatic diseases in children and the more favourable side effects profile of these medicines.

(9) Additional comment, if any.

   Summarizing Dr. Peter Gowdie’s comprehensive review and adding some comments to justify or not the inclusion of DMARDs for children in the WHO Model List of Essential Medicines, taking into account the criteria based on evidence and the character of essentiality.

   The most known chronic inflammatory disorders in a paediatric setting – involving the joints and connective tissues – are juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), juvenile polymyositis (JPM), and systemic lupus erythematosus (SLE). They can present systemic clinical involvement and complications. Characteristically, these diseases present flares and a chronic relapsing and remitting course. The systemically affected patients might have worse prognosis and outcomes, with disability and increased risk of complications.

   All of these conditions are uncommon or rare diseases affecting children worldwide. Their
reported prevalence is variable, and mostly described in Caucasian population. Non-Caucasian ethnicity is associated with increased paediatric SLE disease prevalence. Non-Caucasian SLE patients were significantly younger and more likely to have nephritis. However, disease activity and damage were strongly associated with major organ disease independent of the patient’s ethnicity.1


The management of these diseases is often evaluated by non-controlled studies, with small sample size, selection bias, powerless design and no relevant clinical outcomes. Therefore the evidence of efficacy is poor. In consequence, it is difficult to estimate the global burden of these diseases and the impact of their pharmacological treatment.

As inflammatory and autoimmune diseases, their treatment includes the following pharmacological classes:

1. Non-Steroidal Antiinflammatory Medicines (NSAIMS) – frequently used for symptomatic management of musculoskeletal complaints (pain, discomfort and morning stiffness).

2. Corticosteroids – in immunosuppressive doses and added to supportive care remain the first line therapies for the management of paediatric SLE and are the mainstays of treatment of JDM.

3. Disease Modifying Agents in Rheumatoid Disorders (DMARDs) – including immunosuppressive agents (methotrexate, cyclophosphamide, azathioprine, cyclosporine, mycophenolate, leflunomide), a sulfonamide agent (sulfasalazine), and antimalarial agents (chloroquine or hydroxychloroquine). The immunosuppressive agents have not been subjected to randomised controlled trials. However they are accepted in the management of these diseases for their long-term beneficial effects in controlling disease activity. In general, they work reinforcing corticosteroid effects or reducing their dosage and the long-term exposure to them. They are generally considered early in the course of the disease if there is evidence of systemic involvement and target organ damage. They are also warrantable in patients resistant to corticotherapy, or facing unbearable associated corticoid toxic effects, or with a relapsing course of disease, or at risk of developing irreversible organ damage.

Introductory comments:

1 In this issue, the considered inflammatory and autoimmune diseases are rare or uncommon in children worldwide. As a matter of fact, this call in question the character of essentiality of medicines to be included (“Essential medicines are those that satisfy priority health care needs.”). However, these chronic diseases might cause systemic involvement, disability, and other serious complications.

2 The lack of strong evidence of DMARDs efficacy and safety in children renders difficult the decision to include these agents in the WHO Model List.

3 DMARDs are used as second- or third-line therapy in those conditions. Patients are commonly responders to corticosteroids and supportive care.

Despite these aspects, in the event that the Committee should decide for the inclusion of DMARDs, my suggestions are:
1. **Not** to include **mycophenolate mofetil** that showed no different responses over intravenous cyclophosphamide as induction treatment for lupus nephritis in adults. Both treatments showed remission in the renal system, as well as in other systems. There was no clear difference in efficacy between mycophenolate mofetil and intravenous cyclophosphamide in ameliorating either the renal or nonrenal manifestations in adults. In four children with severe lupus nephritis, who previously received short-term, low-dose intravenous cyclophosphamide plus mizoribine and corticosteroids as induction therapy, mycophenolate permitted a significant reduction in mean prednisolone dose ($P = 0.003$) in the maintenance therapy. No renal flares were observed, neither significant gastrointestinal or hematologic side effects. This promising intervention should be confirmed by a prospective randomised multicenter clinical trial. In long-term monotherapy, mycophenolate appears to have a greater risk in pregnancy and increased reports of herpes simplex and zoster infection compared to cyclosporine. I did not find reference to mycophenolate efficacy in other phases of SLE or in the other rheumatic diseases here considered.


2. **Not** to include **leflunomide** because methotrexate and leflunomide both resulted in high rates of clinical improvement of patients with polyarticular juvenile rheumatoid arthritis, but the rate was slightly greater for methotrexate. At the doses used in this study (a multinational, randomised, controlled trial, n=86, 3-17 years old), methotrexate was more effective than leflunomide. Despite the suggestion of benefit with the use of leflunomide in the paediatric population, the exact role is yet to be defined.


3. **Not** to include **sulfasalazine (SSZ)** despite the clinical benefit observed in few controlled studies performed in adults. According to the previous review, sulfasalazine does not have consistent efficacy across subtypes of JIA. On the current evidence, sulfasalazine is not effective in the management of JIA and, in fact, its use is potentially complicated by an increased and frequent risk of toxicity. A trial randomised patients with oligo- and polyarticular onset juvenile idiopathic arthritis to receive sulfasalazine (n=32) or placebo (n=29) during 24 weeks. An extension of this study evaluates whether the benefits showed with SSZ are sustained over time (median 9 years). At the final of the follow-up, 74% of the patients had active joints, and 30% showed active polyarthritis. Almost all outcome scores were better for SSZ compared with placebo. For juvenile-onset SLE, there are few randomised controlled studies with a small number of patients.
A randomised, double-blind, placebo-controlled exploratory study (n=33) demonstrated no significant difference in response rate (number of active joints as a primary outcome) in patients with juvenile onset spondyloarthropathies. Differences between groups were only significant in the doctor and patient assessments of improvement and the number of changes of concomitant treatment (2 vs. 8; *P*=0.026).2


4. **Not** to include **cyclosporine** A for JIA and JDM treatment. The role of cyclosporine in the treatment of JIA has not been clearly defined. There is little strong evidence supporting its efficacy, and there are no controlled trials. Evidence includes observational studies and case series. There are few and small retrospective studies and case series reporting the benefits of cyclosporine in patients with JDM. Cyclosporine is associated with potentially considerable toxicity and requires careful monitoring and supervision. Adverse events and lack of efficacy or flare of disease cause a high percentage of withdrawal. Most side effects are dose dependent and responsive to dose adjustment.

5. **Not** to include **azathioprine** (AZA) due to the current lack of strong evidence of efficacy for the management of rheumatic diseases in children. The evidence for the efficacy of azathioprine is based on case series, case reports and uncontrolled trials. Concerning safety, AZA is associated with higher risk of serious side effects. Besides, for those diseases there are different options more reliable and with a better toxicity profile.

AZA has been used for the management of *Systemic Lupus Erythematosus* (SLE) in children for decades. Despite this long experience, there are no controlled trials addressing its efficacy in paediatric lupus and therefore its use remains controversial. Azathioprine is used in a variety of clinical circumstances in SLE but most frequently in combination with corticosteroids. The addition of azathioprine as second line therapy may be indicated to permit steroid dose reduction in patients requiring unacceptably high doses of corticosteroids. The role of azathioprine in the management of paediatric lupus complicated by nephritis is even less well defined. On the other hand, a study of lupus nephritis in children concluded that long-term outcome was excellent with 94% survival at mean follow-up of 11 years. In this group of patients, azathioprine was the most frequently prescribed agent.1 AZA is not used routinely in the treatment of JIA.

Azathioprine is associated with potentially serious side effects in particular relating to bone marrow suppression. Sulfasalazine and azathioprine are among the most important causes of acute hepatotoxicity.2 In a cohort study, a significant proportion of rheumatologic patients on AZA had drug-related toxicity resulting in discontinuation of AZA.3


6. To include hydroxychloroquine (HCQ) due to its broad spectrum of beneficial effects and safety profile, despite the main studies supporting its use in SLE were performed in adults. Additional effects beyond immunomodulation have been recently described. A systematic review of a total of 95 articles demonstrated high levels of evidence that HCQ prevents SLE flares and increases long term survival of patients with SLE. There was moderate evidence of protection against irreversible organ damage, thrombosis and bone mass loss. Toxicity related to antimalarials is infrequent, mild and usually reversible, with HCQ having a safer profile. Recommendations are that HCQ should be given to most patients with SLE during the whole course of the disease, irrespective of its severity. HCQ is approved for the treatment of SLE and has been shown to reduce the frequency of disease flares (particularly of lupus nephritis), contribute to the maintenance of remission, prolong the onset of disease and reduce the risk of complications. Its low cost contributes to a systematic prescription in SLE patients. Hydroxychloroquine is frequently used as an adjunct to steroid therapy at the onset of treatment of juvenile SLE. However, there are no trials addressing the effectiveness of hydroxychloroquine in the paediatric population. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) recommends hydroxychloroquine for milder cases of juvenile dermatomyositis and cases mainly characterized by rash. Antimalarials have been used for the treatment of rheumatoid arthritis (RA) for several decades. Recently several trials have been published with larger sample sizes, and better design than previous studies. Hydroxychloroquine is generally considered to be a very safe medication, and it does need regular monitoring. Full blood examination is suggested on a regular basis and ophthalmology examination should occur at least yearly.


7. To include methotrexate (MTX), often considered as the first choice in the treatment of rheumatic diseases such as: JIA, JDM, SLE, vasculitis, uveitis and localized scleroderma. Additionally, short and long-term data suggest that MTX is a safer drug in the paediatric population with rheumatic diseases. In JIA, methotrexate is the most frequently used second line agent and there is good evidence of its efficacy. MTX is considered the standard treatment of JIA, particularly of those subgroups with polyarticular course. JIA response and remission rates to MTX are the standard for comparison with other drug modifying anti-rheumatic drug (DMARD) and biologic agents in clinical trials. Not surprisingly, MTX is the DMARD of choice in JIA either as monotherapy drug or in combination with biologic agents. To examine the change in health-related quality of life (HRQOL) and its determinants in children with juvenile idiopathic arthritis (JIA) treated with methotrexate (MTX) 521 children were extracted from the PRINTO clinical trial. At baseline, patients with JIA showed poorer HRQOL than healthy children (P<0.01). After 6 months of treatment with standard dose MTX, there was a statistically significant improvement in all HRQOL health concepts, particularly in the physical domains. Similar improvements were observed in those who did not respond to a standard dose of MTX and were subsequently randomised
to a higher dose.²
However, a Cochrane systematic review of only two studies (n=165 JIA patients under 18 years of age) showed small to moderate effects on patients centered disability outcomes with a relative percentage improvement from 3 to 23% greater with MTX than with placebo.³
In patients with polyarticular-course juvenile idiopathic arthritis the poorer response to a 6-month MTX course was significantly associated with longer disease duration, anti-nuclear antibody negativity, higher disability and presence of wrist activity.⁴ In this condition, patients (n=133) who do not improve with MTX standard doses (8-10 mg/m²/week) were randomised to receive parenteral MTX at an intermediate dosage (15 mg/m²/week) versus a higher dosage (30 mg/m²/week) for 6 months. This study showed that the plateau of efficacy of MTX in JIA is reached with parenteral administration of 15 mg/m²/week and that a further increase in dosage is not associated with any additional therapeutic benefit. MTX should be administered for up to 9-12 months to appreciate its full therapeutic effect. There were no significant differences in the frequency of adverse events or laboratory abnormalities between the two randomised groups.⁵
In patients with JIA in remission, a 12-month vs. 6-month withdrawal of methotrexate did not reduce the relapse rate.⁶
The use of methotrexate is safe in combination with NSAIDS and corticosteroids. This medicine is well tolerated by children and adolescents. Side effects occur mainly in the form of gastro-intestinal discomfort such as nausea and vomiting or raised transaminases, which can be effectively treated with folic-acid supplementation.⁷ Most of the other side effects are mild and reversible. Children are thought to have a reduced risk of methotrexate associated hepatotoxicity compared with adults. These changes are usually transient and improve with a period of cessation. Haematological abnormalities are rare with the use of methotrexate. Malignancy due to methotrexate remains an area of controversy.
In JDM, methotrexate is the most frequently used of the immunosuppressive agents. A survey⁸ conducted among 167 American pediatric rheumatologists showed that 84% (141) prescribed corticosteroids and another medication, methotrexate being the most commonly used, for typical cases of JDM, regardless of severity. In a Brazilian registry of juvenile dermatomyositis (189 cases included), prednisone-methotrexate combination was the most indicated treatment.⁹
Methotrexate has not been subjected to a prospective randomised controlled trial and therefore evidence for its use is derived from observational studies only. There is currently an international multi-centre prospectively randomised trial co-ordinated by PRINTO (Paediatric Rheumatology International Trials Organisation) which is comparing prednisolone alone with prednisolone/methotrexate combination and prednisolone/cyclosporine combination in patients newly diagnosed with JDM. The results of this trial are eagerly awaited in order to guide the management of JDM.
MTX use requires monitoring with blood tests and close clinical supervision from a medical specialist familiar with the potential risks. It is not recommended for use if access to this supervision is unavailable. It is recommended for inclusion on the WHO complementary list of essential medicines.
3. Takken T, van der Net JJ, Holders PPJM. Methotrexate for treating juvenile idiopathic arthritis. Cochrane


