Tocilizumab

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 29. Medicines for diseases of joints > 29.3. Medicines for juvenile joint diseases

EMLc | Codes ATC: L04AC07

Indication	Juvenile systemic arthritis Code ICD11: FA24.4
INN	Tocilizumab
Type de médicament	Biological agent
Type de liste	Liste complémentaire
Formulations	**Parenteral > General injections > IV:** 80 mg per 4 mL in vial ; 200 mg per 10 mL in vial ; 400 mg per 20 mL in vial **Parenteral > General injections > SC:** 162 mg per 0.9 mL in pre-filled syringe
Historique des statuts LME	Demande refusée en 2021 (TRS 1035) Demande refusée en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Tocilizumab
DrugBank	Tocilizumab

Recommandation du comité d'experts

The Expert Committee acknowledged that systemic-onset JIA was associated with serious morbidity in children and associated with greater morbidity than other subtypes of the disease. The Committee also noted the severe and potentially fatal complication of macrophage activation syndrome had a high mortality rate in this population. The Committee recognized that early introduction of disease modifying antirheumatic agents such as tocilizumab was proposed as safe and effective to avoid joint destruction, control systemic-onset JIA, improve quality of life and minimize long-term corticosteroid use, aiming at better physical and psychosocial function. However, as was the case in 2021, the Committee noted that only a small number of clinical studies provided comparative evidence of efficacy and safety for tocilizumab versus the antitumour necrosis factor medicines currently included on the Model List for JIA. Furthermore, the quality of evidence in these studies was rated as low or very low, and none was conducted in resource-constrained settings. The Committee acknowledged that tocilizumab should only be used in specialized care facilities and by appropriately trained clinical personnel. Its safe and effective use also required careful monitoring for adverse effects, such as infections, and tuberculosis risks and this may not be available in resource-constrained settings. The limited availability of tocilizumab in low- and middle-income countries was also a matter of concern. Therefore, the Expert Committee did not recommend the inclusion of

tocilizumab for treatment of systemic-onset JIA on the Model Lists. As was the case when these medicines were considered in 2021, the Expert Committee considered that the clinical benefits and safety of these medicines (including risk of infection) remained uncertain based on the limited available evidence. The Committee also considered that the feasibility of tocilizumab, particularly in resource-constrained settings, was unlikely given the current high price and requirements for specialized care, monitoring and management of adverse events.

Contexte

An application requesting the inclusion of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, for the treatment of children with systemic-onset JIA was evaluated by the Expert Committee in 2021. Listing was not recommended at that time because of uncertainties about the estimated clinical benefits, as well as concerns about accessibility and affordability in different settings, given the high costs of the medicine. The Committee acknowledged that management of systemic-onset JIA with disease-modifying therapy had the potential to minimize the severe side-effects of corticosteroids and noted that antitumour necrosis factor medicines were included on the Model Lists for JIA in 2019. The Committee noted that while antitumour necrosis factor medicines have proven efficacy in many subtypes of JIA, they may be less effective for patients with systemic-onset disease, and that anti-interleukin-6 receptor monoclonal antibodies such as tocilizumab are preferred as the first-line option in some guidance documents. However, the Committee considered that the comparative benefit of tocilizumab virus antitumour necrosis factor agents was uncertain because of the low quality of the evidence presented in the application. The Committee also noted that the evidence from the randomized trials presented in the application supported tocilizumab as an effective treatment for systemic-onset JIA, but that all this evidence came from trials and studies conducted in well resourced settings, and that the generalizability of the findings to resource-constrained settings was uncertain. The Committee acknowledged the multiple disease-modifying therapies being used in clinical practice for systemic-onset JIA and requested that a comprehensive evaluation of all medicines used to treat this disease be undertaken for future consideration (1).

Pertinence pour la santé publique

JIA is the most common chronic rheumatic disease in children, with a prevalence of about 1 in 1000 children (2). In 2017, more than 2 million children younger than 16 years worldwide were estimated to have JIA, with the highest prevalence in south Asia and Africa (3). The disease is characterized by joint inflammation lasting more than 6 weeks, onset before the age of 16 years and no other identifiable cause (4–6). Untreated disease can have severe consequences, including pain, fatigue, joint damage, functional disability and impaired quality of life. JIA can also lead to anaemia, poor growth, delayed puberty and complications such as uveitis, which can cause blindness if not detected and treated (5–7). The impact of untreated JIA extends to difficulties in walking, performing daily activities and educational participation, which can result in psychosocial challenges, mental health problems and higher unemployment rates compared with healthy peers (8–10). Access to proper care for children with JIA is a major challenge, particularly in resource-constrained settings (11). The shortage of paediatricians, especially in Asia and Africa, contributes to limited access to specialist care and treatment for many children with JIA, resulting in worse clinical outcomes in these regions (7,12) Systemic-onset JIAs is the rarest subtype of the disease. It is characterized by arthritis, fever, rash and systemic inflammation, and is considered an autoinflammatory syndrome (13,14). The age at onset is typically 1–5 years (15) and it imposes a significant disease burden as patients usually require treatment for months to years after the onset of symptoms, as well as close monitoring for complications or flare-ups of disease. Systemic-onset JIA is reported to account for 4–9% of JIA cases in European countries – a population-based study in five Nordic countries reported an incidence of 0.6 per 100 000 children per year (16). Systemic-onset JIA is more common in other geographical settings, representing up to 25% and 50% of JIA cases in India and Japan, respectively (14). Uncontrolled inflammation in systemic-onset JIA carries a significant risk of high morbidity and potential mortality from macrophage activation syndrome, an uncontrolled cytokine storm (14,17,18). A study in the United Kingdom found higher mortality rates in people with systemic-onset JIA compared with people with other forms of JIA (19).

Bénéfices

The following data were also reported in the 2021 application for tocilizumab for systemic-onset JIA. Systematic reviews and meta-analyses A 2016 systematic review and meta-analysis of five placebo-controlled randomized trials (one each for anakinra, canakinumab and tocilizumab, two for rilonacept; 458 participants) aimed to define the optimal biological agent for systemic-onset JIA based on safety and efficacy data (20). The primary efficacy outcome was a 30% improvement from baseline according to the modified American College of Rheumatology Paediatric 30 response criteria (ACR Pedi 30). Outcomes were analysed by pairwise and network meta-analyses. While all treatments were more effective than placebo, there was low-quality evidence from the network meta-analysis that patients treated with rilonacept were less likely to respond than those treated with canakinumab (odds ratio (OR) 0.10, 95% confidence interval (CI) 0.02 to 0.38) or tocilizumab (OR 0.12, 95% CI 0.03 to 0.44). A 2020 meta-analysis of 19 randomized controlled trials (11 parallel trials (754 participants) and eight withdrawal trials (704 participants)) assessed the net benefit of biological agents used in JIA (abatacept, adalimumab, anakinra, canakinumab, etanercept, infliximab, rilonacept and tocilizumab) (21). The efficacy outcome was ACR Pedi 30 and the safety outcome was serious adverse events. Net benefit was determined by subtracting the risk difference of safety from the risk difference of efficacy. In systemic-onset JIA, the net benefit was 22.8% for rilonacept, 54.5% for tocilizumab and 70.3% for canakinumab in parallel trials, and 32.3% for canakinumab and 58.2% for tocilizumab in withdrawal trials. A 2017 systematic review of 25 randomized and non-randomized studies (more than 4000 participants) evaluated the efficacy of different biological therapies in JIA subtypes, including in people with systemic-onset JIA (n = 1185) (22). Over 12 weeks, systemic-onset JIA was less responsive to etanercept (ACR30 58% to 78%) compared with tocilizumab (ACR30 85%). Longer-term responses over 12 months were similar for the two treatments (ACR30 83% to 100% for etanercept versus 87% to 98% for tocilizumab). Individual randomized trials comparing tocilizumab to placebo A randomized, double-blind, placebo-controlled, withdrawal phase III trial evaluated the efficacy and safety of tocilizumab in 56 children aged 2–19 years with systemic-onset JIA not responding to disease-modifying antirheumatic drugs and biological agents (23). After an initial open-label lead-in phase where all participants were given tocilizumab (three intravenously administered doses of 8 mg/kg every 2 weeks), ACR Pedi 30, 50 and 70 responses were achieved by 51 (91%), 48 (86%) and 38 (68%) of patients, respectively. Thereafter, 43 participants who had achieved both an ACR Pedi 30 response and C-reactive protein concentrations of less than 5 mg/L were randomized to receive tocilizumab or placebo in a double-blind phase for 12 weeks (administration of placebo or tocilizumab 8 mg/kg every 2 weeks). Patients who remained on tocilizumab in the double-blind phase had sustained improvement in clinical measures of effectiveness and well-being. In contrast, most of the patients in the placebo group (18/23 patients) required rescue treatment. After the lead-in and double-blind phases, corticosteroid doses were reduced by at least 50% in most patients. Patients responding to tocilizumab and needing further treatment were then enrolled in an open-label extension phase for at least 48 weeks. By week 48 of the open-label extension phase, ACR Pedi 30, 50 and 70 responses were achieved by 47 (98%), 45 (94%) and 43 (90%) of 48 patients, respectively (24). A multicentre, randomized phase III trial evaluated the efficacy of tocilizumab compared with placebo in 112 children aged 2–17 years with persistent systemic-onset JIA of at least 6 months and inadequate response to non-steroidal anti-inflammatory drugs and glucocorticoids (25). Patients were randomized in a 2:1 ratio to either tocilizumab (12 mg/kg if weighing < 30 kg or 8 mg/kg if weighing ≥ 30 kg) or placebo intravenously every 2 weeks for 12 weeks. After 12 weeks, the primary endpoint of ACR Pedi 30 response and absence of fever was met by 85% (64/75) in the tocilizumab group and 24% (9/37) in the placebo group ($P < 0.001$). In this study, 84% of the patients in the treatment group had previously received a biological agent, including 55% who had received interleukin-1 inhibitors and 73% who had received antitumour necrosis factor agents. At week 52, ACR Pedi 70 response was achieved by 80% of the patients who received tocilizumab, including 59% who achieved ACR Pedi 90. After 52 weeks, 48% of patients treated with tocilizumab had no joints with active arthritis and 52% had discontinued oral glucocorticoids. Registry and retrospective studies A German study evaluated the efficacy and safety of treatment with etanercept, tocilizumab, and the interleukin-1 inhibitors anakinra and canakinumab in systemic-onset JIA patients using data from the German biologics register (26). Over a 5-year period, 245 patients with systemic-onset JIA exposed to biological agents were identified: 143, 71 and 60 patients received treatment with etanercept, tocilizumab and interleukin-1 inhibitors, respectively. At baseline, patients in the etanercept group had fewer systemic disease manifestations but more active joints. JIA-ACR 30, 50, 70 and 90 responses over 24

months were reached more often in the groups receiving tocilizumab and interleukin-1 inhibitor than the etanercept group. A Juvenile Disease Activity Score ≤ 1 (JADAS-remission) was achieved in 20% (etanercept), 37% (tocilizumab) and 52% (interleukin-1 inhibitors) of patients. Minimal disease activity (JADAS ≤ 3.8) was reported in 35% (etanercept), 61% (tocilizumab) and 68% (interleukin-1 inhibitors) of patients, and inactive disease in 24% (etanercept), 33% (tocilizumab) and 56% (interleukin-1 inhibitors). Another German study evaluated the clinical response rate, disease course and adverse effects of tocilizumab for systemic-onset JIA in a real-life clinical setting using data from the German-AID-registry (27). Over a 5-year period, 46 of 200 patients with systemic-onset JIA were treated with tocilizumab. A clinical response rate (defined as no symptoms and typical inflammatory markers) of 35% was reported in the first 12 weeks of treatment, and inactive disease/remission on medication (as defined in the Wallace criteria (28)) was reported in 75% of patients after 1 year. A French retrospective study using data from the Centre des Maladies Rares register: analysed the effectiveness of biological agents in achieving inactive disease or clinical remission in patients with systemic-onset JIA; described the effects of switching or discontinuing a biological agent; and assessed the proportion of patients able to maintain response without corticosteroids after withdrawing biological therapy (29). Seventy-seven patients were included with a cumulative follow-up of 245.5 patient-years. As first-line biological therapy, inactive disease was achieved in 37 patients (48%), including 33/61 (54%) patients receiving interleukin-1 inhibitors, 2/2 (100%) patients receiving tocilizumab, 1/1 (100%) patient receiving abatacept and 1/13 (8%) patients receiving antitumour necrosis factors. Switching to a second (n = 34), third (n = 18) or fourth (n = 4) line of biological treatment resulted in a further 13 patients achieving inactive disease, six with canakinumab and seven with tocilizumab. At the final follow-up, 40/77 (52%) patients were in clinical remission either on (29 patients) or off (11 patients) biological treatment.

Torts

In the 2016 meta-analysis of biological medicines versus placebo in systemic-onset JIA (20), adverse events were infrequent and likely due to the short duration of follow-up in the analysed studies. While no significant difference in serious adverse effects was found between the medications, the overall quality of evidence was considered very low. Adverse events were more common with tocilizumab than placebo or canakinumab. However, a posthoc analysis of adverse events (measured as the total number of events per total patient-days) indicated that tocilizumab did not differ significantly from placebo. Both tocilizumab and canakinumab were associated with a statistically significant increased risk of infections compared with placebo, although this significance was not maintained when evaluating events per total patient days. In the 2020 meta-analysis which assessed the net benefit of biological agents used in JIA (21), significantly more serious adverse events occurred with biological medicines compared with control groups in the parallel trials (pooled OR 2.00, 95% CI 0.94 to 4.26), including for tocilizumab (OR 4.62, 95% CI 0.56 to 38.36). In the withdrawal trials, both pooled results (OR 1.01, 95% CI 0.45 to 2.24) and results for tocilizumab (OR 1.03, 95% CI 0.25 to 4.19) did not show a significant difference. A postmarketing surveillance study in Japan evaluated the safety of tocilizumab in 417 patients with systemic-onset JIA treated in a real-world setting for 52 weeks (24). The rates of total adverse events and serious adverse events were 224.3/100 patient-years and 54.5/100 patient-years, respectively, which were higher than previously reported in clinical trials. Adverse events leading to the discontinuation of tocilizumab occurred in 4% (17/417) of patients. The most frequent adverse events were infections and infestations (69.8/100 patient-years and 18.2/100 patient-years, respectively). Notably, 74 serious infections occurred in 55 patients (18.2/100 patient-years) and 26 cases of macrophage activation syndrome occurred in 24 patients (6.4/100 patient-years). Two deaths were recorded during the 52-week period: one due to vasculitis with cardiac failure, and the other to Pseudomonas infection, interstitial lung disease and sepsis. Of the seven episodes of macrophage activation syndrome, infections were contributing factors, and in two cases, a reduced dose of corticosteroids was deemed contributory to the events. In the double-blind phase of the phase III trial in children with persistent systemic-onset JIA following inadequate response to non-steroidal anti-inflammatory drugs and glucocorticoids (25), the most common adverse events were infections, occurring in 80% (60/75; two classified as severe) of patients in the tocilizumab group compared with 41% (15/37; none severe) of patients in the placebo group. In the double-blind and extension periods combined, including patients initially assigned to placebo who made the transition to open-label tocilizumab, 39 serious adverse events occurred (equivalent to 25 per 100 patient-years), including 18 serious

infections (11 per 100 patient-years). Adverse events led to discontinuation of tocilizumab in six patients (for two because of elevated aminotransferase levels). Three episodes of macrophage activation syndrome occurred, all of which resolved. Three deaths occurred during treatment, including one from probable streptococcal sepsis. Neutropenia was reported in 17% (19/112) of patients, of whom 17 had grade 3 and two had grade 4 neutropenia. From the German study that evaluated the efficacy and safety of treatment with etanercept, tocilizumab, anakinra and canakinumab in systemic-onset JIA patients using data from the German biologics register (26), rates of adverse events were significantly higher in the tocilizumab group than the etanercept group (risk ratio (RR) 5.3, $P < 0.0001$). Rates of serious adverse events were observed more frequently with tocilizumab (RR 2.5, $P < 0.5$) and interleukin-1 inhibitors (RR 2.9, $P < 0.01$) compared with etanercept. Long-term safety of biological medicines for systemic-onset JIA was reported in another study using data from the German biologics register (30). The average follow-up duration was about 4.3 years, with a total exposure time to biological medicines of 856 exposure years and 244 exposure years for tocilizumab specifically. Safety assessments were based on adverse event reports after the first dose up to 90 days after the last dose. Rates of adverse events, serious adverse events and 25 predefined adverse events of special interest were analysed. Incidence rates were compared for each biological medicine against all other biological medicine combined using a mixed-effect Poisson model. Serious adverse events were reported with higher frequency in patients receiving canakinumab (20/100 patient-years) and tocilizumab (21/100 patient-years). Cytopenia and hepatic events occurred with higher frequency with tocilizumab and canakinumab. Medically important infections were seen more often in patients using interleukin-6 or interleukin-1 inhibitors. Macrophage activation syndrome occurred in all cohorts with a higher frequency in patients using canakinumab (3.2/100 patient-years) and tocilizumab (2.5/100 patient-years) compared with anakinra (0.83/100 patient-years) and etanercept (0.5/100 patient-years). Among the patients, 96 had received more than one biological agent. After adjustment for a number of factors (e.g. concomitant use of methotrexate and steroids, presence of systemic signs and disease duration), only an elevated risk for infections in patients treated with anakinra remained significant. Three definite malignancies were reported in patients exposed to biological agents. Two deaths occurred in patients treated with etanercept. The authors observed changes in preferred biological agents, with a shift toward tocilizumab, anakinra and canakinumab after 2013. Patients treated with tocilizumab and systemic corticosteroids had significantly higher rates of adverse events and serious adverse events compared with those treated with tocilizumab alone (127.5/100 exposure years versus 79.4/100 exposure years for adverse events, $P = 0.002$; and 28.4/100 exposure years versus 15.6/100 exposure years for serious adverse events, $P = 0.019$). Adverse events included 93 infectious events in 37 patients treated with tocilizumab (38/100 exposure years; RR 1.4, 95% CI 0.97 to 2.00). Cytopenia was reported in 22 cases, with higher rates in patients given tocilizumab (6.2/100 exposure years; RR 5.37, 95% CI 2.19 to 13.17). However, the difference in cytopenia rates did not remain significant after adjusting for a number of factors (e.g. concomitant use of methotrexate and steroids, presence of systemic signs and disease duration). In the German study that evaluated tocilizumab for systemic-onset JIA in a real-life clinical setting using data from the German-AID-registry (27), adverse events were reported in 24% (11/46) of patients, with severe adverse events in 4% (2/46) of patients (a case of Hodgkin lymphoma and one of gut perforation). No cases of macrophage activation syndrome or death were reported. Discontinuation of treatment due to adverse events was reported in 11% (5/46) of patients (three with neutropenia and two with serious adverse event). A pilot observational study compared consensus treatment plans provided by the Childhood Arthritis and Rheumatology Research Alliance in 30 newly diagnosed patients with systemic-onset JIA (31). Ten participants received tocilizumab. One grade 4 infusion reaction and one case of macrophage activation syndrome occurred with tocilizumab treatment. Grade 2 adverse events reported in tocilizumab treated patients included fever, rash, arthritis flare-up, headache, neutropenia, viral illness and infusion reaction. The application stated that children treated with tocilizumab (or any biological disease-modifying antirheumatic drug) must have access to a paediatric rheumatologist for ongoing monitoring during treatment and for urgent review should they develop complications such as infection. This is of particular importance in resource-constrained countries where up to 50% of deaths in children 5–15 years is due to infection. The trials and studies listed above all were conducted in well resourced countries. Local factors (e.g. availability of specialist services such as doctors, nurses, urgent review and access to intravenous antibiotics), as well as patient factors (e.g. health literacy rates, distance and transport to hospital, comorbid conditions, poverty and malnutrition) may significantly affect the mitigation of adverse events in resource-constrained settings.

Rapport coût/efficacité

The application reported that in the United Kingdom, intravenous tocilizumab costs £102.40, £256.00 and £512.00 per vial for 80 mg, 200 mg and 400 mg vials, respectively, and subcutaneous tocilizumab costs £228.28 per 162 mg/0.9 mL prefilled pen/syringe. The manufacturer offers a confidential patient access scheme within the National Health Service that provides a discount. In Australia, the dispensed price under the Pharmaceutical Benefit Scheme for intravenous tocilizumab was reported as 82 Australian dollars (Aus$), Aus$ 203 and Aus$ 405 per vial for 80 mg, 200 mg and 400 mg, respectively. A Canadian cost–utility analysis evaluated the cost–effectiveness of tocilizumab with or without methotrexate compared with placebo plus methotrexate in the treatment of systemic-onset JIA (32). The base-case analysis focused on direct medical costs (in 2011 Canadian dollars (Can$)) from the perspective of the Canadian Ministry of Health. The incremental cost–utility ratio for tocilizumab with or without methotrexate was Can$ 69 787 per additional quality-adjusted life year (QALY) gained compared with placebo plus methotrexate. Tocilizumab treatment was the dominant treatment strategy from a societal perspective. A Finnish study compared cost–effectiveness of tocilizumab with methotrexate and anakinra (33). The incremental cost per additional QALY gained for treatment with tocilizumab was €15 181 compared with methotrexate and €14 496 compared with anakinra. Based on a willingness-to-pay threshold of €20 000 per QALY gained, tocilizumab had a 93% probability of being cost-effective compared with methotrexate and 88% compared with anakinra. This probability increased to 100% with a willingness-to-pay threshold of €27 000 per QALY. A cost–utility analysis in Thailand assessed the effect of the addition of tocilizumab to standard treatment in patients with refractory systemic-onset JIA (34). The incremental cost–effectiveness ratio of standard treatment plus tocilizumab was US$ 35 799 per QALY gained compared with standard treatment alone. The study was based on cases of refractory disease in 43 patients treated in seven tertiary hospitals in Thailand. The patients in the study had a long duration of disease and a greater overall severity. A pharmacoeconomic study evaluated the cost-efficiency of treatment with tocilizumab versus standard treatment with methotrexate and prednisolone in Russian patients with systemic-onset JIA (35). The cost–effectiveness in terms of ACR 90 and 70 was 4.4 million and 3.0 million Russian roubles (Rub), respectively, in the standard treatment group, and Rub 1.2 million and Rub 615 000, respectively, in the tocilizumab group. Pharmacotherapy was responsible for more than half of the costs in the tocilizumab group, but hospitalization costs were 12 times lower than in the standard treatment group. Annual state budget losses due to the social burden of systemic-onset JIA were almost double in the standard treatment group compared with the tocilizumab group (Rub 426 000 versus Rub 227 000).

Directives de l'OMS

WHO guidelines for the treatment of systemic-onset JIA are not currently available.

Disponibilité

Tocilizumab has regulatory approval for the treatment of systemic-onset JIA from various global regulatory agencies. The intravenous form is indicated for children aged 2 years and older, while the subcutaneous form is approved for children aged 1 year and older, weighing at least 10 kg. Recent reports indicate supply issues and shortages in some countries, mainly due to the use of tocilizumab as a novel treatment for COVID-19 and its use in clinical trials for the disease.

Autres considérations

Tocilizumab in the treatment of systemic-onset JIA should only be used by appropriately trained and experienced clinical personnel. In addition, families need to be educated on the potential side-effects of and safety concerns about tocilizumab and know when to seek health care. These principles are based on recommendations and standards of care for JIA (36,37). Intravenous tocilizumab requires specialized facilities and trained staff, including a hospital bed or clinic, cannulation equipment and expert personnel. Some patients require premedication to prevent infusion reactions, which is influenced by factors such as age, height, weight and disease activity (38). Travel distance to the hospital and transport availability can affect attendance for treatment for the child. Regular

follow-up is required for children on tocilizumab to assess treatment response and potential adverse events. Before starting tocilizumab treatment, all patients should be tested for tuberculosis due to a risk of tuberculosis reactivation. The American College of Rheumatology advises that children initially deemed at low tuberculosis risk, with a negative test, have repeated screenings if their tuberculosis risk becomes moderate or high according to regional infectious disease guidelines (39). Understanding tuberculosis risk in patients on tocilizumab and other biological disease-modifying antirheumatic medications is particularly important in resource-constrained settings with high tuberculosis rates (40).

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