Anakinra

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

EMLc | ATC codes: L04AC03

Indication	Juvenile systemic arthritis ICD11 code: FA24.4
INN	Anakinra
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > SC:** 100 mg per 0.67 mL in pre-filled syringe
EML status history	Application rejected in 2021 (TRS 1035) Application rejected in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	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 Read more about patents.
Wikipedia	Anakinra
DrugBank	Anakinra

Expert Committee recommendation

The Expert Committee acknowledged that macrophage activation syndrome was a rare and potentially life-threatening uncontrolled cytokine storm that occurred in up to one third of patients with systemic-onset JIA, and that it was associated with a fatality rate of over 20%. The Committee noted that early detection and treatment of systemic-onset JIA was essential to improve clinical outcomes and reduce the risk of macrophage activation syndrome. The Committee noted that, as was the case in 2021, the clinical evidence for the benefit of anakinra in both systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA was limited and derived primarily from small uncontrolled studies and case series, with only one small short-term randomized trial identified in the narrative review provided with the application. The Committee also noted that anakinra did not have regulatory approval for the requested indication from national regulatory authorities and had only a weak recommendation suggesting its use in the 2013 JIA guidelines of the American College of Rheumatology. The Committee also noted that safety data for anakinra were still limited and concerns remained about the safe use of the medicine, particularly in settings with high rates of infection, especially for tuberculosis. The Committee acknowledged that anakinra for the treatment of macrophage activation syndrome should be only used in specialized tertiary care facilities by appropriately trained clinical personnel, and noted the limited availability of specialist paediatric rheumatologists in resource-limited settings. The high price and limited availability of

anakinra in low- and middle-income countries was also a concern. Therefore, the Expert Committee did not recommend the inclusion of anakinra for treatment of systemic-onset JIA with macrophage activation syndrome. As was the case when anakinra was considered for this indication in 2021, the Expert Committee considered that the clinical benefits and safety of this medicine (including risk of infection) remained uncertain based on the limited available evidence. The Committee also considered that the feasibility of use of anakinra, particularly in resource-constrained settings, was unlikely unfeasible given the current high price, limited availability, and requirements for specialized care, monitoring and management of adverse events.

Background

An application for the inclusion of anakinra, an interleukin-1 receptor antagonist, for the treatment of children with systemic onset JIA with macrophage activation syndrome was evaluated by the Expert Committee in 2021. Listing was not recommended at the time because of uncertainties about the estimates of clinical benefit and concerns about affordability and access to specialist medical services in lower-resource settings. The Committee noted that macrophage activation syndrome is a rare but serious condition involving excessive immune activation that can occur in children with systemic-onset JIA, and that it is associated with high short-term mortality, especially if untreated. The Committee noted that the application reported data only from uncontrolled cohort studies or case series, most of which enrolled only a small number of patients. The Committee considered that extrapolating clinical benefits and potential harms of anakinra and comparing anakinra with other potentially relevant therapeutic alternatives based on this type of evidence was difficult. The Committee also noted that anakinra was often highly priced, with potentially important limitations in accessibility and affordability at the country level. The Committee further acknowledged the limited availability of specialist paediatric rheumatologists in many settings (1).

Public health relevance

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 JIA 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 the disease. Systemic-onset JIA is reported to account for 4–9% of cases of JIA 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). Macrophage activation syndrome has been reported to affect about 33% of patients with systemic-onset JIA (20) and has a fatality rate of up to 23% (21).

Benefits

The application presented a review of the available evidence on the use of anakinra for systemic-onset JIA and

macrophage activation syndrome in systemic-onset JIA. It asserted that the most important way to treat macrophage activation syndrome in systemic-onset JIA was to control the underlying inflammation caused by the disease. Anakinra in systemic-onset JIA Randomized trials A multicentre, randomized, double-blind trial compared the efficacy of 1-month treatment with anakinra (2 mg/kg daily, up to a maximum of 100 mg) versus placebo in 24 patients with systemic-onset JIA (22). Response was defined as a 30% improvement in the paediatric American College of Rheumatology criteria for JIA (ACRpedi 30), absence of disease-related fever and a decrease of at least 50% of both C-reactive protein and erythrocyte sedimentation rate compared with baseline. After 1 month, a response was observed in 67% (8/12) of patients in the anakinra arm and 8% (1/12) of patients in the placebo arm ($P = 0.003$). An open-label treatment period followed the first part of the trial, in which all patients received anakinra for up to 12 months. Two patients from the placebo group stopped treatment during the first month of treatment due to injection pain and withdrew from the trial. Nine of the remaining 10 patients who switched to anakinra had responded at month 2. Seventeen patients continued in the trial until month 6, of whom six responded. Sixteen patients continued in the trial for 12 months, of whom seven responded. The authors concluded that anakinra treatment was effective in the treatment of systemic-onset JIA, at least in the short term. Non-randomized trials A 5-year follow-up, single-centre, prospective study in the Netherlands (Kingdom of the) evaluated anakinra as first-line monotherapy in 42 patients (age range 3.9–11.8 years) with active systemic-onset JIA (23). The median time to achieve clinically inactive disease was 33 days. For children who had inactive disease at 3 months, anakinra was tapered and ultimately stopped. At 1 year, 76% of all the children had inactive disease, and 52% of the children who had stopped receiving medication earlier continued to have inactive disease. Factors positively associated with inactive disease at 1 year included high neutrophil count at baseline and complete response after 1 month of anakinra treatment. After 5 years of follow-up, 96% of all the patients had inactive disease, and 75% continued to have inactive disease while not receiving medication. Articular or extra-articular damage was reported in < 5% of patients and only 33% received glucocorticoids. Treatment with anakinra was equally effective in systemic-onset JIA patients without arthritis at disease onset. The authors concluded that “treatment to target” (where disease activity is accurately monitored and clinical remission is actively pursued by regular adjustment of therapy, starting with first-line, short-course monotherapy with anakinra) is a highly effective strategy to induce and sustain inactive disease and to prevent damage from the disease and glucocorticoids. A single-centre retrospective study in Italy evaluated 25 patients with systemic-onset JIA treated with anakinra for at least 6 months (24). The median age at disease onset was 5.8 years and the median age at start of treatment was 7.3 years. Of note, 14 patients were receiving concomitant glucocorticoids, nine patients were receiving concomitant disease-modifying antirheumatic drugs (methotrexate or ciclosporin) and six patients had previously received biological agents (etanercept, abatacept and infliximab). After 6 months of anakinra treatment, 14 (56%) patients had clinically inactive disease (defined as the absence or rash, fever and active arthritis), which was reached at a median of 2.1 months after the start of treatment. Clinically inactive disease was maintained in all 14 patients at median follow-up of 2.8 years. Nine patients were able to withdraw from anakinra and five continued with anakinra monotherapy. No cases of macrophage activation syndrome were observed during anakinra treatment. Demographic characteristics and clinical and laboratory features at baseline were also compared in responders and non-responders: no differences were observed in the number of active joints before starting anakinra or concomitant glucocorticoid treatment. The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome. An international multicentre series assessed the use of anakinra as first-line disease-modifying therapy in 46 children with systemic-onset JIA (25). Among the 46 children studied, 10 received anakinra monotherapy, 21 received anakinra plus corticosteroids, five received anakinra plus disease-modifying antirheumatic drugs and 10 received anakinra plus corticosteroids and disease-modifying antirheumatic drugs. Outcomes were evaluated after a median follow-up of 14.5 months. Fever and rash resolved within 1 month in more than 95% of patients, while C-reactive protein and ferritin normalized within this time in more than 80% of patients. Active arthritis persisted in 39% of patients at 1 month, in 27% of patients at 3 months and in 11% of patients at more than 6 months of follow-up. Almost 60% of patients, including eight of 10 receiving anakinra monotherapy, attained a complete response without escalation of therapy. Disease characteristics and treatment were similar in partial and complete responders, except that partial responders were markedly younger at onset of the disease (median age 5.2 years

versus 10.2 years, P = 0.004). Eleven episodes of macrophage activation syndrome (in nine patients) were observed, six episodes at presentation and five episodes after starting anakinra during the study. Anakinra effectively managed five out of the six cases of macrophage activation syndrome at presentation; increasing doses of anakinra and additional agents such as steroids and ciclosporin A were used to control these episodes. A retrospective case series in the United States evaluated the effect of anakinra on disease activity and corticosteroid dose in 33 patients with systemic-onset JIA (26). The median duration of systemic-onset JIA before treatment was 29 months and most patients had used more than one other medication before starting anakinra: prednisone (94%), methotrexate (76%), tumour necrosis factor inhibitors (61%), ciclosporin (36%) and cyclophosphamide (6%). Anakinra treatment was associated with a reduction in corticosteroid dosage and erythrocyte sedimentation rate and increases in haemoglobin and albumin, all indicators of response to therapy. Large joint arthritis counts decreased after 3–4 months but not small joint counts. More significant decreases in erythrocyte sedimentation rates from pre- to post-treatment (1–2 months) were seen in patients on high doses of anakinra than those on low doses, implying a dose–response effect. Fever and rash, present in seven cases before treatment, resolved in all cases. Eight patients had periods of arthritis, one developed macrophage activation syndrome and another Epstein–Barr virus infection. A single-centre series in Germany reported on four patients who received anakinra as first-line therapy for systemic-onset JIA (27). The median age of the patients was 4.6 years (range 2.75–9.25 years). The mean follow-up time was 13.5 months (range 2–50 months). Anakinra was started at doses from 1.5 to 4 mg/kg for a median duration of 3 (range 3–18) months. Two patients responded to anakinra monotherapy and two cases required corticosteroids. Normalized body temperature and the absence of evanescent rashes were achieved after a median of 4 (range 2–10) days. Macrophage activation syndrome in systemic-onset JIA A single-centre study in Türkiye evaluated the use of anakinra to treat macrophage activation syndrome in 15 hospitalized paediatric patients, 13 with systemic-onset JIA and two with other autoinflammatory diseases (28). Nineteen episodes of macrophage activation syndrome were observed in the 15 patients. Anakinra (2 mg/kg a day) was started within a median of 1 day of admission. Clinical symptoms resolved within a median (range) of 2 (1–4) days of the introduction of anakinra and laboratory findings normalized within a median of 6 (4–9) days. Corticosteroid treatment was stopped within a median of 10 (4–13) weeks of starting anakinra. Patients were followed for a median of 13 (6–24) months. Two patients developed recurrent macrophage activation syndrome episodes when the anakinra dose was reduced, while the other patients achieved remission. A retrospective case series in Canada reported on the use of anakinra in 12 children with macrophage activation syndrome related to paediatric rheumatic disease (eight due to systemic onset JIA) in whom treatment with corticosteroids and other immunosuppressants had provided only limited benefit (29). Five patients required intensive care. Anakinra 2 mg/kg/day was added to pre-existing therapy. All patients achieved remission of macrophage activation syndrome within a median of 13 (range 2–19) days. Corticosteroids were discontinued within 6 weeks for seven patients. Over a median follow-up of 22 (range 2–40) months, all patients remained in remission from macrophage activation syndrome at the final follow-up and had effective control of their underlying rheumatic disease.

Harms

Adverse effects associated with anakinra include gastrointestinal disturbances (nausea, vomiting and diarrhoea), headache, abdominal pain, upper respiratory and urinary tract infections, and neutropenia (30). In the multicentre, randomized trial of anakinra, 14 adverse events were reported in patients receiving anakinra in the double-blind phase, with injection pain being the most common adverse event, followed by post-injection erythema and infections. No serious adverse events were reported. During the open-label phase, 89 adverse events were reported, of which five were considered serious. The most common adverse events were infections, followed by injection pain and post-injection erythema. Six patients discontinued treatment: two due to adverse events; two due to lack of efficacy; and two due to a disease flare (22). In the international multicentre series of anakinra as first-line treatment of systemic-onset JIA in 46 children, adverse events included injection site reactions (20 cases), serious infections (three cases), elevated liver enzymes (two cases), hepatitis (one case) and mild asymptomatic neutropenia (one case) (25). In the single-centre case series in Germany that assessed the efficacy and safety of first-line anakinra treatment no reported treatment-related adverse reactions were observed other

than local injection-site inflammation (27). Similarly, the Canadian case series on the effect of anakinra in 12 children with macrophage activation syndrome, no adverse effects were reported from anakinra administration (29). A prospective, open-label, single-centre, clinical cohort study from the United States investigated the long-term safety of anakinra treatment for up to 5 years in 43 patients with cryopyrin-associated periodic syndromes (31). Safety was evaluated using adverse event reports, laboratory assessments, vital signs and diary reports. In total, 1233 adverse events were reported during the study, with a yearly rate of 7.7 adverse events per patient. The event rate decreased over time and dose escalation during the study did not affect the frequency of adverse events. Anakinra had similar safety profiles in adults and children. The most frequently reported adverse events were typical symptoms of cryopyrin-associated periodic syndrome such as headache and arthralgia. Injection site reactions occurred mainly during the first month of treatment. A total of 24 serious adverse events were reported in 14 patients, which all resolved during the study period. The most commonly reported serious adverse events were infections (pneumonia and gastroenteritis). Other serious adverse events included post-lumbar puncture headaches and one episode of macrophage activation syndrome triggered by infection (which was alleviated with temporary corticosteroid therapy). No permanent treatment discontinuation occurred due to adverse events.

Cost / cost effectiveness

No comparative cost–effectiveness studies of anakinra for the treatment of macrophage activation syndrome in systemic-onset JIA were identified in the application. The application described the unit cost of anakinra 100 mg subcutaneous injection as Aus$ 53.00 in Australia, Can$ 41.10 in Canada, £26.23 in the United Kingdom and US$ 142.50 in the United States. Corresponding annual drug treatment costs for a 50 kg child would be Aus$ 19 345–38 690, Can$ 15 001–60 006, £9574–38 296 and US$ 52 013–208 050.

WHO guidelines

WHO guidelines for the treatment of systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA are not currently available.

Availability

Anakinra has regulatory approval as a treatment for systemic-onset JIA in Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czechia, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands (Kingdom of the), Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, United Kingdom and the United States of America. Anakinra does not yet have regulatory approval as a treatment for macrophage activation syndrome. Anakinra is not widely available globally and there are reports of recent supply issues stemming from its use in clinical trials for the treatment of complications related to COVID-19 that are similar to macrophage activation syndrome (cytokine storm).

Other considerations

Diagnosis, monitoring and use The diagnosis of macrophage activation syndrome in systemic-onset JIA is based on defined criteria (18) validated in clinical practice (32,33). Macrophage activation syndrome is a life-threatening cytokine storm (34), often triggered by infection, which is of particular concern in resource-constrained settings, where access to specialist paediatric rheumatologists, multidisciplinary teams and treatments are challenges. Such inequity further contributes to the burden of disease and long-term disability (35). The diagnosis of macrophage activation syndrome, evaluation of its severity and monitoring of response to treatment are assessed using blood markers of inflammation (C-reactive protein and full blood counts) as well as specific markers of macrophage activation syndrome (ferritin, triglycerides, liver function tests and clotting profiles) (32,33). Monitoring of anakinra treatment follows the routine monitoring of systemic-onset JIA in acute disease flare-up, concomitant infection or where macrophage activation syndrome is suspected (32,33). Use of anakinra in acute macrophage activation syndrome in systemic-onset JIA is limited to highly specialized care in tertiary facilities. Its use in systemic-onset JIA outside of the hospital setting requires specialized training of caregivers and adequate storage conditions. The medication must be stored in cold temperatures (2–8 °C), and parents and caregivers

need training in administration and to have suitable cold storage facilities available. Tuberculosis risk Awareness of the risk of tuberculosis in patients with JIA receiving treatment with anakinra or other biological disease-modifying antirheumatic drugs is of particular importance in resource-constrained settings with high rates of tuberculosis (35). Patients starting immunosuppressive treatments should undergo tuberculosis testing, although this might not be feasible during acute presentations of macrophage activation syndrome. The American College of Rheumatology suggests that low-risk children with negative initial tuberculosis screening should be retested if their tuberculosis risk changes (36). It is also recommended that patients with JIA with a positive tuberculosis test receive appropriate prophylaxis for tuberculosis (as per current national and/or international guidelines): at the start of biological therapy; during biological therapy; when a previously negative purified protein derivative test converts to positive at the mandatory annual tuberculosis screening; and if the patient has a new exposure to tuberculosis (35).

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).
2. Harris JG, Kessler EA, Verbsky JW. Update on the treatment of juvenile idiopathic arthritis. Curr Allergy Asthma Rep. 2013;13(4):337–46.
3. Dave M, Rankin J, Pearce M, Foster HE. Global prevalence estimates of three chronic musculoskeletal conditions: club foot, juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. Pediatr Rheumatol Online J. 2020;18(1):49.
4. Petty R, Southwood T, Baum J, Bhettay E, Glass D, Manners P. Revision of the proposed classification criteria for juvenile idiopathic arthritis. J Rheumatol. 1997;1998;25(10):1991–4.
5. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther. 2016;3(2):187–207.
6. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767–78.
7. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. Lancet Child Adolesc Health. 2019;3(4):255–63.
8. Gutiérrez-Suárez R, Pistorio A, Cespedes Cruz A, Norambuena X, Flato B, Rumba I. Health-related quality of life of patients with juvenile idiopathic arthritis coming from 3 different geographic areas. The PRINTO multinational quality of life cohort study. Rheumatology. 2006;46(2):314–20.
9. Oen K, Guzman J, Dufault B, Tucker LB, Shiff NJ, Duffy KW. Health-related quality of life in an inception cohort of children with juvenile idiopathic arthritis: a longitudinal analysis. Arthritis Care Res (Hoboken). 2018;70(1):134–44.
10. Foster HE, Marshall N, Myers A, Dunkley P, Griffiths ID. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. Arthritis Rheum. 2003;48(3):767–75.
11. Chausset A, Pereira B, Echaubard S, Merlin E, Freychet C. Access to paediatric rheumatology care in juvenile idiopathic arthritis: what do we know? A systematic review. Rheumatology (Oxford). 2020;59(12):3633–44.
12. Harper BD, Waceke Nganga RA, Forsyth KD, Ham HP, Keenan WJ, Russ CM. Where are the paediatricians? An international survey to understand the global paediatric workforce. BMJ Paediatr Open. 2019;3(1).
13. Katsicas MM, Russo RAG. Systemic-onset juvenile idiopathic arthritis. Cham: Springer International Publishing; 2020.
14. De Benedetti F, Schneider R. Systemic juvenile idiopathic arthritis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. Textbook of pediatric rheumatology. Seventh edition. Philadelphia: Elsevier; 2016:205–16.
15. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). J Rheumatol. 2008;35(2):343–8.
16. Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol. 2003;30(10):2275–82.
17. Dewoolkar M, Cimaz R, Chickermane PR, Khubchandani RP. Course, outcome and complications in children with systemic onset juvenile idiopathic arthritis. Indian J Pediatr. 2017;84(4):294–8.
18. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun. 2012;13(4):289–98.
19. Davies R, Southwood T, Kearsley-Fleet L, Lunt M, Baildam E, Beresford MW, et al. Mortality rates are increased in patients with systemic juvenile idiopathic arthritis. Arch Dis Child. 2017;102(2):206–7.
20. Cakan M, Karadag SG, Tanatar A, Ayaz NA. The frequency of macrophage activation syndrome and disease course in systemic juvenile idiopathic arthritis. Mod Rheumatol. 2020;30(5):900–4.
21. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol. 2018;10:117–28.
22. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011;70(5):747–54.
23. Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. Arthritis Rheumatol. 2019;71(7):1163–73.
24. Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, et al. Anakinra in systemic juvenile idiop

athic arthritis: a single-center experience. J Rheumatol. 2015;42(8):1523–7.
25. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63(2):545–55.
26. Zeft A, Hollister R, LaFleur B, Sampath P, Soep J, McNally B, et al. Anakinra for systemic juvenile arthritis: the Rocky Mountain experience. J Clin Rheumatol. 2009;15(4):161–4.
27. Hedrich CM, Bruck N, Fiebig B, Gahr M. Anakinra: a safe and effective first-line treatment in systemic onset juvenile idiopathic arthritis (SoJIA). Rheumatol Int. 2012;32(11):3525–30.
28. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. Clin Rheumatol. 2018;37(12):3329–35.
29. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology (Oxford). 2011;50(2):417–9.
30. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J. 2021;19(1):135.
31. Kullenberg T, Löfqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology (Oxford). 2016;55(8):1499–506.
32. Minoia F, Bovis F, Davi S, Horne A, Fischbach M, Frosch M. Development and initial validation of the MS score for diagnosis of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Ann Rheum Dis. 2019;78(10):1357–62.
33. Shimizu M, Mizuta M, Yasumi T, Iwata N, Okura Y, Kinjo N, et al. Validation of classification criteria of macrophage activation syndrome in Japanese patients with systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2018;70(9):1412–5.
34. Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2015;13:55.
35. Scott C, Chan M, Slamang W, Okong'o L, Petty R, Laxer RM, et al. Juvenile arthritis management in less resourced countries (JAMLess): consensus recommendations from the Cradle of Humankind. Clin Rheumatol. 2019;38(2):563–75.
36. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65(10):2499–512.

