Triamcinolone hexacetonide

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

EMLc | ATC codes: H02AB08

Indication	Juvenile idiopathic arthritis ICD11 code: FA24.Z
INN	Triamcinolone hexacetonide
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > Locoregional injections > Intra-articular:** 20 mg per mL in vial
EML status history	Application rejected in 2021 (TRS 1035) Added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Triamcinolone hexacetonide
DrugBank	Triamcinolone hexacetonide (Triamcinolone)

Expert Committee recommendation

The Expert Committee noted that JIA was the most common chronic rheumatic disease of childhood and was associated with significant morbidity, functional disability and reduced quality of life if not appropriately treated. As was the case in 2021, the Committee considered that the available evidence was still limited, and of suboptimal quality, but accepted that use of intra-articular glucocorticoid injections with triamcinolone (hexacetonide, and to a lesser extent acetonide) may be associated with improvements in joint inflammation in oligoarticular forms of JIA and had advantages over long-term systemic corticosteroid use in terms of harms. No additional evidence was identified during the application review process and the Committee considered that it was unlikely that new evidence would be generated soon. The Committee noted that the evidence indicated that triamcinolone hexacetonide was superior to triamcinolone acetate in terms of efficacy and duration of response but that there were shortages in supply worldwide. The Committee considered that inclusion of triamcinolone hexacetonide with triamcinolone acetonide as a therapeutic alternative was appropriate and may contribute to improving access and resolving shortage problems. The Committee noted that the costs for triamcinolone hexacetonide varied across settings and other costs associated with administration must also be taken into consideration, such as analgesia and imaging. The Committee also reiterated the need for administration to be performed only by appropriately trained specialized clinical personnel. Based on these considerations, the Expert Committee recommended the inclusion of triamcinolone hexacetonide on the complementary list of the EML and EMLc for use in the treatment of JIA. Listing was recommended with a square box to indicate triamcinolone acetonide as a therapeutic alternative for national selection in situations where triamcinolone hexacetonide was not available.

Background

Triamcinolone hexacetonide was previously considered for inclusion on the Model Lists for treatment of JIA in 2021. The Expert Committee noted that the evidence presented supporting the use of intra-articular corticosteroids in JIA was limited and of suboptimal quality. Almost all studies were in high-income countries and specialized settings and the generalizability of findings to lower-income settings was uncertain. No data were included on the role and the comparative benefits and risks of triamcinolone hexacetonide compared with oral corticosteroids or disease-modifying treatments such as methotrexate. Although intra-articular steroids are considered an important tool in the treatment of JIA, the Committee noted that consensus is lacking about their efficacy and safety in different settings. The Committee noted that administration of intra-articular corticosteroids is an invasive procedure requiring specialized training and experience. It is also associated with risks of infection. Dose adjustment based on the targeted joint is an important aspect of practice, as overdose of corticosteroids might lead to joint atrophy. Laboratory tests are needed to determine disease activity and risk of progression, and to evaluate a patient's suitability for treatment. The Committee also expressed concerns about the limited availability of specialist paediatric rheumatology care in low- and middle-income settings. The Expert Committee therefore did not recommend the inclusion of triamcinolone hexacetonide on the EML or the EMLc at that time, because of the uncertain clinical benefit of triamcinolone hexacetonide given the low quality of evidence and its limited generalizability, and safety concerns associated with administration procedures (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).

Benefits

Note: the terms pauciarticular juvenile rheumatoid arthritis or juvenile chronic arthritis are used below because they are found in some older studies cited. They are equivalent to oligoarticular juvenile idiopathic arthritis. The effectiveness of steroid injections in pauciarticular juvenile rheumatoid arthritis and other forms of inflammatory arthritis was evaluated in a prospective study of 40 children who had failed therapy with non-steroidal anti-inflammatory drugs (13). Twenty-nine children had juvenile rheumatoid arthritis. Active knee joints were injected with 20–40 mg of triamcinolone hexacetonide and the effects were evaluated at 6, 12 and 24 months. A good response was defined as complete resolution of active joint inflammation and a relapse was defined as a sustained reaccumulation of joint effusion. All injected joints had a good initial response to treatment. At 6, 12 and 24 months follow-up, a good response was maintained in 67.6% (25/37), 50.0% (15/30) and 17.4% (4/23), respectively, of the joints of children with juvenile rheumatoid arthritis. No significant differences based on disease group, sex or dose were observed. Relapse was seen in eight joints. These joints were re-injected, of which five maintained a good response for 12 months. The mean dose administered was significantly higher in the relapse group than the group with a good response in the children with juvenile rheumatoid arthritis ($P < 0.01$), but the difference was not statistically significant in other types of juvenile arthritis. A retrospective study evaluated the efficacy and duration of benefit of triamcinolone hexacetonide injections in 194 children with various subgroups of juvenile chronic arthritis (14). A total of 1439 injections (including 368 reinjections) were administered and outcomes were measured after mean durations of 3, 15, 30 and 64 weeks. Significant differences in response

were seen among subgroups. Efficacy lasted for 121 weeks in early-onset pauciarticular juvenile chronic arthritis type I, 47 weeks in late-onset pauciarticular juvenile chronic arthritis type II, 105 weeks in rheumatoid factor negative polyarticular juvenile chronic arthritis, 63 weeks in rheumatoid factor positive polyarticular juvenile chronic arthritis and 36 weeks in systemic juvenile chronic arthritis. The study concluded that intra-articular triamcinolone injections were effective in treating inflammatory joint disease in all subgroups of juvenile chronic arthritis. An open-label, non-randomized, prospective study compared response rates in 85 patients with juvenile idiopathic arthritis who received triamcinolone hexacetonide and triamcinolone acetonide injections; of 130 joints, 70 received triamcinolone hexacetonide and 60 received triamcinolone acetonide (15). The response rate was evaluated using core outcome measures, including joint swelling, limitation of joint range of motion, pain on passive movement and warmth to the touch. A good response was defined as the absence of inflammation or a reduction in joint inflammation of more than 60% from baseline. Relapse was defined as the reappearance of arthritis after a period of good response. The response rate was significantly higher with triamcinolone hexacetonide than triamcinolone acetonide: 81.4% versus 53.3% (P = 0.006) at 6 months, 67.1% versus 43.3% (P = 0.006) at 12 months and 60.0% versus 33.3% (P = 0.002) at 24 months. The rate of relapse was 2.7 times higher in the triamcinolone acetate group than the triamcinolone hexacetonide group (95% confidence interval (CI) 1.6 to 4.8). A retrospective study compared the time to relapse following treatment with triamcinolone hexacetonide and triamcinolone acetonide in 85 patients with juvenile idiopathic arthritis; of 277 joints, 114 received triamcinolone hexacetonide and 112 received triamcinolone acetonide (16). The mean, standard deviation (SD), time to relapse was significantly longer in the triamcinolone hexacetonide group than the triamcinolone acetonide group (10.14, SD 0.49 months versus 7.75, SD 0.49 months, P < 0.0001). A Cox regression model analysis showed that after adjusting for sex, duration of illness or type of disease, a significant difference existed in relapse time favouring triamcinolone hexacetonide (hazard ratio (HR) 1.99, 95% CI 1.43 to 2.78). A double-blind trial compared the efficacy of triamcinolone acetonide at twice the dose of triamcinolone hexacetonide in 37 children with juvenile idiopathic arthritis (17). Children with symmetrical joints requiring injection received triamcinolone acetonide in one joint and triamcinolone hexacetonide in the other. Clinical assessments were performed at baseline, and at 3, 6, 9, 12, 18 and 24 months after injection. The response rate was assessed based on core outcome measures, including joint swelling, limitation of joint range of motion, pain on passive movement and warmth to the touch. All joints showed improvement post-injection. However, after 2–21 months of follow-up, relapse occurred more frequently in joints treated with triamcinolone acetonide (53.8%) than those treated with triamcinolone hexacetonide treated joints (15.4%). The rate of persisting or sustained response was significantly higher with triamcinolone hexacetonide than with triamcinolone acetonide at 6 months (89.7% versus 61.5%, P = 0.008), 12 months (84.6% versus 48.7%, P = 0.001) and 24 months (76.9% versus 38.5%, P = 0.001). The efficacy of intra-articular injections with triamcinolone hexacetonide and triamcinolone acetonide was compared in a retrospective single-centre chart review study of 102 patients with juvenile idiopathic arthritis (18). Of 292 included joints, 154 received triamcinolone hexacetonide and 138 received triamcinolone acetonide. The primary outcome measure for efficacy was defined as full recovery from arthritis 1 month after treatment. Rate of relapse at 3 months was also assessed. Similar efficacy was seen between treatments 1 month after injection. However, a significant difference was seen in the length of effect, with a significantly higher relapse rate at 3 months in the triamcinolone acetonide group (20.1% relapsed) compared with the triamcinolone hexacetonide group (8.8% relapsed). The significant difference persisted over time, up to 40 months. The odds ratio for relapse with triamcinolone acetonide was 2.24 (95% CI 1.39 to 3.58) compared with triamcinolone hexacetonide.

Harms

The adverse event profiles of triamcinolone hexacetonide and triamcinolone acetonide are similar and most adverse events are rare (5,17,19–21). Potential adverse events include infection (septic arthritis at the injection site), subcutaneous atrophy caused by extravasation of the drug from the joint space, steroid lipodystrophy, initial post-injection pain, calcium deposition in the joint, systemic absorption and avascular necrosis in the hip joint. Proper clinical technique and accurate needle placement can greatly reduce these effects, highlighting the importance that joint injections are performed by appropriately trained clinicians (21,22). The risk of systemic

absorption of glucocorticosteroids through injections can lead to adrenal suppression and/or iatrogenic Cushing syndrome, although these adverse effects are rare (23). Diabetic children may require a temporary increase in insulin doses following intra-articular glucocorticosteroid injections (20). A prospective study evaluated the efficacy and safety of intra-articular triamcinolone hexacetonide for the treatment of coxitis in 50 patients with juvenile rheumatoid arthritis (24). Five cases of femoral head necrosis were reported among 20 children receiving triamcinolone hexacetonide and long-term systemic corticosteroids. No cases of femoral head necrosis were observed in 30 children who received triamcinolone hexacetonide without systemic corticosteroids. Triamcinolone intra-articular injections are contraindicated in active, systemic mycoses and parasitoses, herpes simplex keratitis, and acute psychoses because of the potential effect of systemic absorption of steroids. Caution should be exercised in a number of circumstances, including the presence of active infection near the affected joint, cardiac insufficiency, acute coronary artery disease, hypertension, thrombophlebitis, thromboembolism, myasthenia gravis, Cushing syndrome, diabetes mellitus, hypothyroidism, osteoporosis, gastric ulcer, diverticulitis, ulcerative colitis, recent intestinal anastomosis, exanthematous diseases, renal insufficiency, acute glomerulonephritis, chronic nephritis, cirrhosis, infections that cannot be treated with antibiotics and metastatic carcinoma. Triamcinolone hexacetonide should not be used in neonates due to the presence of benzyl alcohol as a preservative. However, a diagnosis of juvenile idiopathic arthritis in neonates is extremely rare and consultation with a paediatric rheumatologist would be necessary in such cases.

Cost / cost effectiveness

Studies on the cost–effectiveness of intra-articular corticosteroid injections for JIA are not available. The application reported that the cost per vial of triamcinolone (hexacetonide or acetonide) varies by country. The cost of treatment per child depends on the number and size of joints to be injected. The cost of untreated JIA is likely to be high for patients, their families and society (25).

WHO guidelines

WHO guidelines for the management of JIA are not currently available.

Availability

Global shortages of triamcinolone hexacetonide have been reported. Aristospan® brand of triamcinolone hexacetonide has been listed as being in short supply in the United States and has been discontinued on the United States market by the Food and Drug Administration, although it can be imported on an individual patient basis. Triamcinolone hexacetonide is not approved by the Australian Therapeutic Goods Administration but can be accessed through a special access scheme from international manufacturers. Canada has approved triamcinolone hexacetonide for inclusion in public drug formularies. Triamcinolone hexacetonide has marketing approval for intra-articular use in the United Kingdom and is included in the British National Formulary. Several European countries, including Austria, Czechia, Netherlands (Kingdom of the), Portugal, Slovenia and Spain granted marketing authorization for triamcinolone hexacetonide in 2013, before the supply problems arose. Triamcinolone acetonide has regulatory approval for intra-articular administration in Australia, New Zealand and the United States. It has marketing authorization in Canada, Sweden and Switzerland. It does not appear to have supply shortages in the same way as triamcinolone hexacetonide.

Other considerations

Joint injections are uncomfortable and analgesia with local, inhaled or general anaesthesia or sedation is recommended, especially if several joints are injected. Imaging (such as ultrasound or radiographic image intensifier) can be used to optimize the accuracy of needle placement, especially for small joints or deep joints such as the hip or subtalar joints (21,26). It is recommended that triamcinolone be administered only by appropriately trained clinical personnel experienced in using intra-articular steroids to treat active joint disease in JIA (5,21,22,27–29).

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. Allen R, Gross K, Laxer R, Malleson P, Beauchamp R, Petty R. Intraarticular triamcinolone hexacetonide in the management of chronic arthritis in children. Arthritis Rheum. 1986;29(8):997–1001.
14. Breit W, Frosch M, Meyer U, Heinecke A, Ganser G. A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol. 2000;27(11):2696–702.
15. Zulian F, Martini G, Gobber D, Agosto C, Gigante C, Zacchello F. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. Rheumatology (Oxford). 2003;42(10):1254–9.
16. Eberhard BA, Sison MC, Gottlieb BS, Ilowite NT. Comparison of the intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis. J Rheumatol. 2004;31(12):2507–12.
17. Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology (Oxford). 2004;43(10):1288–91.
18. Rubin S, Ohana O, Goldberg O, Peled O, Gendler Y, Habot-Wilner Z, et al. The efficacy and safety of intra-articular injection of triamcinolone acetonide versus triamcinolone hexacetonide for treatment of juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2022;20(1):5.
19. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA. 2005;294(13):1671–84.
20. Schiappapietra B, Varnier G, Rosina S, Consolaro A, Martini A, Ravelli A. Glucocorticoids in juvenile idiopathic arthritis. Neuroimmunomodulation. 2015;22(1-2):112–8.
21. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis Care Res (Hoboken). 2019;71(6):717–34.
22. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR standards of care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2010;49(7):1406–8.
23. 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.
24. Neidel J, Boehnke M, Küster RM. The efficacy and safety of intraarticular corticosteroid therapy for coxitis in juvenile rheumatoid arthritis. Arthritis Rheum. 2002;46(6):1620–8.
25. Moorthy LN, Peterson MG, Hassett AL, Lehman TJ. Burden of childhood-onset arthritis. Pediatr Rheumatol Online J. 2010;8:20.
26. Foster HE, Brogan PA. Paediatric rheumatology. Oxford: Oxford University Press; 2018.
27. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77(6):819–28.
28. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;63(4):465–82.
29. Lanni S, Bertamino M, Consolaro A, Pistorio A, Magni-Manzoni S, Galasso R. Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. Rheumatology. 2011;50(9):1627–34.