

Modern management of juvenile idiopathic arthritis

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Many children with juvenile idiopathic arthritis (JIA) experience delays in diagnosis, but evidence suggests that treating early and aggressively leads to better long-term outcomes. This article discusses the recommended treatment options, including both traditional therapies and the newer biological agents.

Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease of childhood, with a prevalence estimated at 1 in 1000 children. It is characterised by arthritis with onset before the 16th birthday, lasting for more than six weeks, with no other cause identified. JIA is a different entity to rheumatoid arthritis, with distinct phenotypes and disease course. The current international classification identifies seven JIA subtypes based on phenotype, serology and associated features (see Table 1).¹

Arthritis is a clinical diagnosis based on history and examination. However, many paediatricians lack confidence and training in paediatric musculoskeletal assessment.² Given this, it is not surprising that children with JIA often experience protracted delays in diagnosis – nearly six months on average but many years in some.³ These delays are worrisome as they may lead to complications such as erosions, limb-length discrepancy and bony overgrowth.

Children with arthritis often present with joint pain, swelling and morning stiffness. However, presenting symptoms may also be subtle including limp, unusual posturing (such as torticollis) or overt limb preference. Diagnosis may be particularly challenging in the preverbal child, where apparent developmental regression (such as reverting from walking to crawling) may be the only sign; therefore, a high index of suspicion is warranted. The paediatric Gait Arms Legs Spine (pGALS) musculoskeletal screening tool is quick to learn and implement, and is available on the Arthritis Research UK website.⁴

The most serious extra-articular complication of JIA is anterior uveitis – ocular inflammation that is often asymptomatic but may be sight-threatening. Uveitis occurs in nearly 10 per cent of children with JIA overall,⁵ but in the oligoarticular subtype the cumulative prevalence is much higher, approaching one in three.⁶ Risk is greatest in those who are antinuclear antibody (ANA) positive and have early disease onset. There is also a



slight female preponderance. Consequently, regular ophthalmology review with slit-lamp examination represents part of the routine care of children with JIA.⁷

Principles of management

The management of JIA needs to be provided by a multidisciplinary team (MDT), including specialist doctors, nurses, physiotherapists, podiatrists and psychologists, working closely with paediatricians, community nurses and GPs.⁸ Two major trends have emerged in the drug treatment of inflammatory conditions over recent years, including in the treatment of JIA. The first is the concept of a treatment ‘window of opportunity’: literature suggests that treating inflammatory disease early and aggressively to ‘switch off’ the immune process leads to better long-term outcomes.⁹⁻¹² This is supported by evidence that children who achieve a state of inactive disease within the first five years following diagnosis accrue less disease-related damage.¹³ This has encouraged a trend towards early aggressive therapy – such as high-dose ‘pulse’ intravenous corticosteroids – instead of a slower ‘step-up’ pyramid approach.

The second important treatment principle is ‘treat-to-target’. This concept has arisen in the era of biological agents,

when treatment goals have become more ambitious and patient outcomes vastly improved. The treat-to-target approach states that tighter disease control can be achieved by formally measuring and tracking patient outcomes, with low tolerance for persistent disease activity, so that incremental gains continue to be made and patient care optimised.^{14,15} A parallel concept is that of clinical *versus* immunological remission: that there may be ongoing activity within the immune system, measurable by increasingly sensitive biochemical and radiological markers, even in the absence of clinically apparent disease. Extinguishing even this subclinical immune activity is becoming the new treatment goal.^{16,17}

Long-term outcomes for children with JIA are variable and difficult to predict. In some children, the disease resolves spontaneously, often around the time of puberty. In others, JIA represents a chronic condition requiring lifelong immunosuppression and eventual transition to an adult rheumatology service.

Specific therapeutic agents

NSAIDs

NSAIDs have been used in the treatment of JIA for decades, and continue to have important anti-inflammatory and analgesic

Subtype	Typical phenotype	Proportion of all JIA ⁴⁰	Gender distribution	Notable features
Oligoarticular	No more than four affected joints in the first six months of disease	27–56%	F>M	Often ANA positive. Strong association with anterior uveitis
Polyarticular – RF negative	More than four affected joints in the first six months of disease; RF negative	11–28%	F>M	Often symmetric involvement of small, medium and large joints
Polyarticular – RF positive	More than four affected joints in the first six months of disease; RF positive on two separate occasions	2–7%	F>M	Closely related to rheumatoid arthritis with similar phenotypic and prognostic features; classically affects adolescent girls
Enthesitis-related arthritis	Arthritis, enthesitis – tends to involve axial and weight-bearing joints including SIJ	3–11%	M>F	The juvenile spondyloarthropathy, often HLA-B27 positive males
Psoriatic arthritis	Arthritis, psoriasis	2–11%	F>M	Also associated with dactylitis and nail changes such as pitting, ridging, onycholysis
Systemic onset	Fever, rash, arthritis (‘Still’s disease’); may have hepatosplenomegaly, lymphadenopathy	4–17%	F>M	Can develop life-threatening immune dysregulation known as macrophage activation syndrome
Undifferentiated	Arthritis that does not meet criteria for other JIA subtypes	11–21%	–	–

M = male; F = female; RF = rheumatoid factor; SIJ = sacroiliac joint; ANA = antinuclear antibody

Table 1. Juvenile idiopathic arthritis (JIA) subtypes (International League of Associations for Rheumatology)¹

roles. They are an excellent first-line therapy in the primary care setting as they are well-tolerated, provide reasonable symptom relief and will not mask other diagnoses such as infection or malignancy.¹⁸ Naproxen (7.5mg/kg orally twice daily) is often advised first-line because it has the convenience of twice daily dosing, and also comes in a liquid formulation.

Ibuprofen is more readily available than naproxen, but when used as an anti-inflammatory agent in the treatment of JIA it should be given at higher doses than when used for antipyretic purposes. In rheumatic disease, ibuprofen should be dosed at 30–40mg/kg daily in three to four divided doses (max 2.4g per day). Alternative NSAIDs that are in common usage include piroxicam, diclofenac and indometacin.¹⁹ When used in the treatment of arthritis, NSAIDs should be given regularly to maximise the anti-inflammatory effect. All patients on regular NSAIDs should be prescribed a gastroprotective agent such as a proton-pump inhibitor or H₂-receptor antagonist.

Intra-articular steroid injections

Joint injections are safe and effective therapy for the management of JIA. The procedure is well tolerated, and usually performed under general anaesthetic for younger children, or sedation (such as nitrous oxide) for older children. The agent of choice is triamcinolone hexacetonide, which is longer acting than alternative preparations, with mean duration of response just over 12 months.^{20,21} Joint injections are used frequently for the treatment of oligoarticular disease, where they may suffice as monotherapy, thus sparing the need for regular systemic medication. They may also be used for children whose disease has a polyarticular course, to ‘mop up’ residual or flaring joints in children who have had an otherwise good response to systemic therapies. Important adverse effects include cutaneous atrophy at the injection site, and septic arthritis. When performed under sterile conditions, the risk of septic arthritis is small.²²

Disease-modifying antirheumatic drugs

The disease-modifying antirheumatic drug (DMARD) methotrexate has been used in the treatment of JIA for decades and, when dosed and monitored appropriately, remains a safe and effective mainstay of treatment.²³ It is used in children with multiple active joints, or those who have activity in joints that are not readily injectable – especially the cervical spine and temporomandibular joint. It also has a major role in the treatment of uveitis not adequately controlled by topical steroid drops. Methotrexate is dosed by body surface area at 15mg/m² and is given once per week via the subcutaneous or oral routes.

Methotrexate use in JIA is limited by two major factors. The first is efficacy – a significant minority of children show inadequate response to methotrexate, especially in the era of tight disease control.²⁴ The other is tolerability – especially nausea and vomiting, which can be debilitating and requires careful management (see Table 2). Methotrexate may also cause liver dysfunction and cytopenias. These abnormalities are usually mild and self-resolving upon temporary cessation of the drug, but its safe use requires regular blood monitoring.²⁵ The cumulative

- Increase the dose of folic acid (from weekly to daily)*
- Change from oral to subcutaneous administration of methotrexate
- Regular administration of ondansetron* pre- and post-methotrexate
- Lower the dose of methotrexate, or change to another agents (in communication with the treating rheumatologist)
- Administer the dose just prior to bedtime so that the worst of the nausea (which is usually short-lived) is slept through
- Distraction therapy – keep the child busy and preoccupied before, during and after methotrexate administration
- Refer to a play therapist or child psychologist if needle-phobia or anticipatory anxiety is prominent. This can usually be arranged via the treating team

*See Table 5 for dose and route of administration

Table 2. Strategies for the management of methotrexate-associated nausea

effect of these short treatment interruptions can limit the utility of the drug, especially if the child begins to flare in between.

The mechanism of action of methotrexate in arthritis is poorly understood, but is postulated to work by modulating lymphocyte function or by modifying adenosine levels.²⁶ It is known to disrupt folate metabolism so is usually co-administered with folic acid to reduce side-effects. Folic acid may be given daily, or weekly, but is traditionally not administered on the same day as methotrexate due to a theoretical risk of reducing methotrexate efficacy.

Other DMARDs used in the treatment of JIA include sulfasalazine (especially for enthesitis-related arthritis, the juvenile spondyloarthropathy), leflunomide, ciclosporin and hydroxychloroquine. While it was standard in the past for children to switch between DMARDs, most children who fail methotrexate therapy now escalate directly to a biological agent.²⁷ In fact, as safety data grows, some children with severe disease are beginning biological therapy as first-line.²⁸

As with methotrexate, all DMARDs require routine blood tests, monitoring for cytopenias, hepatic and renal dysfunction. Many DMARDs are teratogenic and should be prescribed cautiously in females of childbearing age. Adolescent patients should be warned to avoid alcohol while on most DMARDs, given the potential for hepatotoxicity. National British Society for Paediatric and Adolescent Rheumatology (BSPAR) guidelines exist to direct safe prescribing of many DMARDs, including methotrexate. These are freely available on the BSPAR website.²⁹

Biological agents

Biological agents, or ‘biologics’, have revolutionised the treatment of JIA and JIA-uveitis, vastly improving patient outcomes and raising the bar on disease control. These represent a new class of drug that uses monoclonal antibodies or other recombinant proteins to specifically target cells and cytokines that are driving the inflammatory process. Biologics are a great triumph of ‘bench-to-bedside’ medicine, where laboratory understanding of disease pathogenesis has allowed the development of targeted effective therapies. A number of biological DMARDs (bDMARDs) have now entered the market, each with slightly different indications and utility (see Table 3). In clinical trials,

Drug	Mechanism	Target molecule or pathway	Route of administration	Dose and frequency
Etanercept	Soluble TNF alpha receptor	TNF alpha	Subcutaneous	0.4mg/kg twice weekly, or 0.8mg/kg weekly
Adalimumab	Monoclonal antibody to TNF alpha	TNF alpha	Subcutaneous	Age <13 years: 24mg/m ² fortnightly (max 20mg if aged 2–4 years, max. 40mg if aged 4–12 years) Age ≥13 years: 40mg fortnightly
Infliximab	Monoclonal antibody to TNF alpha	TNF alpha	IV Infusion	Hospital-based infusion Usually given at week 0, 2, 6 then 6–8 weekly thereafter
Tocilizumab	Monoclonal antibody to soluble IL-6 receptor	IL-6	IV Infusion	Hospital-based infusion Usually given 2–4 weekly
Abatacept	CTLA4-Ig fusion protein	T cell co-stimulatory molecule (interferes with T cell activation)	IV Infusion	Hospital based infusion Usually given at 0, 2, 4 weeks then 4 weekly thereafter
Anakinra	IL-1 receptor antagonist	IL-1	Subcutaneous	Usual starting dose 2mg/kg daily (max. 100mg daily) Dose may be titrated up as tolerated
Canakinumab	Monoclonal antibody to IL-1	IL-1	Subcutaneous	Prescribed through specialist clinic only
Rituximab	Monoclonal antibody to CD20	CD20 (B cells)	IV infusion	Hospital-based infusion. Usually given as 2 doses, 2 weeks apart. May be repeated months/years later

TNF = tumour necrosis factor; IL = interleukin; CTLA-4 = cytotoxic T lymphocyte antigen 4; CD = cluster of differentiation

Table 3. Biological agents used in the treatment of juvenile idiopathic arthritis (JIA) (NB. Doses listed here are provided as a guide only; these medications should only be prescribed through a specialist paediatric rheumatology service. Please refer to NICE guidelines for further guidance on dosing³⁰)

<ul style="list-style-type: none"> • Slowing of growth in height and pubertal development • Cushingoid facies • Disruption of sleep • Increased appetite with associated weight gain • Reduction in bone mineral density • Acne • Striae • Mood lability and behavioural disruption including hyperactivity and teariness • Hypertension • Impaired glucose tolerance/diabetes • Hirsutism • Adrenal crisis

Table 4. Corticosteroid side-effects in children

many show efficacy in over 50 per cent of children, but longer-term efficacy data are awaited. NICE guidelines now exist to direct the safe prescribing of several biological agents in JIA, including their indications, safety data and dosing guidance.³⁰

Etanercept was the first biological agent to be approved for use in JIA. It is a soluble receptor protein that targets tumour necrosis factor (TNF) alpha, a critical proinflammatory cytokine. Subcutaneous therapy with etanercept (given twice weekly at 0.4mg/kg, or weekly at 0.8mg/kg body weight) may be administered via prefilled pens, prefilled syringes or vials, depending on the drug and the dose required. Parents should receive education and support for these injections from specialist nursing teams.

Biologics are new therapies with limited long-term safety data. There is some evidence that they may increase the risk of malignancy, especially lymphoproliferative malignancy.³¹ Concerns have also been raised regarding an increased risk of demyelinating disease.³² Biologic registries have been

developed to gather answers to these important questions. Nonetheless, it is undeniable that biologics have opened up entirely new treatment pathways for JIA, and in doing so have improved patient and disease outcomes.

Antidrug antibodies (ADAs) are a well-recognised complication of biologic use. These occur when the patient mounts an immune response to the drug itself, and may result in reduced treatment efficacy and infusion reactions.³³ Co-administration of methotrexate or another DMARD appears to reduce ADA development,³⁴ hence many children may be prescribed a DMARD and a bDMARD simultaneously.

Systemic corticosteroid therapy

Corticosteroids continue to play an important role in the management of JIA, despite their significant side-effect profile (see Table 4). They are powerful and fast-acting anti-inflammatory agents, and are often used in JIA induction therapy or in the management of disease flares. Systemic corticosteroids (often

given as a high-dose 'pulse' of 30mg/kg daily intravenous methylprednisolone for three days followed by a weaning course of oral prednisolone starting between 1–2mg/kg daily) are primarily used in the treatment of children with polyarticular or systemic disease; oligoarticular disease can usually be managed with targeted joint injections.

Corticosteroids provide rapid relief of symptoms and control of inflammation, hence their role is largely as a temporising measure while awaiting the effect of a DMARD or bDMARD. Biological therapies have had a dramatic role as steroid-sparing agents and steroids are now rarely used as maintenance therapy. Long-term steroids should not be stopped abruptly due to the risk of adrenal suppression.

Ancillary medications

GPs and community paediatricians have a key role in monitoring the growth, wellbeing and disease sequelae of JIA and its treatment, including drug-related side-effects. There are a

Drug	Dose	Utility in JIA
Proton-pump inhibitors / H ₂ -receptor antagonists	Lansoprazole: 0.5–1mg/kg daily (max. dose 15mg if <30kg, max. 30mg if >30kg) Ranitidine: age-dependent dosing. Refer to <i>BNF</i>	Prevention of gastritis and gastrointestinal upset secondary to NSAID and/or steroid use
Folic acid	5mg orally once weekly (or 1mg daily for 6 days per week); not given on same day as methotrexate	Used concomitantly with methotrexate to reduce methotrexate-related side-effects
Calcium/vitamin D supplementation	Various combined formulations available: usually one tablet daily	Used to ameliorate the adverse effects on bone density of steroid use, immobility and chronic inflammatory disease
Antiemetics, eg ondansetron	Ondansetron: 0.1–0.2mg/kg orally (max. 8mg) given one hour before methotrexate	Used in the treatment of methotrexate-associated nausea and vomiting
Contraception	N/A	Prevention of pregnancy in sexually active females on teratogenic medications, including methotrexate
Immunisation (of the patient and household)	N/A	Only killed vaccines should be administered to immunosuppressed patients Influenza vaccine (IM, not intranasal) should be administered to immunosuppressed children annually Varicella zoster infection can be catastrophic in immunosuppressed patients, hence strong consideration should be given to immunising the child's household (but not the immunosuppressed child as VZV is a live vaccine)
Eye drops, most commonly dexamethasone steroid drops; also antimuscarinic/ antiglaucoma agents	Titrated by ophthalmologist	Initiated and overseen by an ophthalmologist for the treatment of JIA-associated uveitis and associated glaucoma

Table 5. Other medications commonly used in juvenile idiopathic arthritis (JIA)

number of other medications that are commonly prescribed in children with JIA; many are employed to reduce treatment adverse effects (see Table 5).

Managing the immunosuppressed child

JIA is an autoimmune disease, hence most therapeutics used in its management are immunosuppressive. This places children being treated for JIA at increased risk of infection, including disseminated infection or infection with unusual organisms.

Children who are immunosuppressed and develop fever or signs of infection must be seen by a doctor as a matter of urgency, and close physical examination undertaken. Importantly, some immunosuppressive agents prevent a child from developing a fever, or raised inflammatory markers, even in the presence of significant or overwhelming infection. Hence the absence of pyrexia is not always reassuring. If there is any clinical doubt, the child should be referred to their local emergency department and consideration given to admission.

Chickenpox infection is of particular note in the management of immunosuppressed children. Management of varicella exposures varies depending on the level of immunosuppression and the child's pre-existing varicella immunity. It may involve close observation, passive immunisation with varicella immunoglobulin, or hospital admission for antiviral therapy.

Tuberculosis exposures in children on biological therapies are also potentially high risk, especially in children who are on anti-TNF therapy. TNF alpha has an important role in granuloma formation, and therefore in the immune response to tuberculosis.³⁵ All children should be screened for tuberculosis before commencing biological therapy^{36,37} and the treating team should be notified of any significant tuberculosis exposure as a matter of urgency.

Clinicians involved in the care of children with JIA should also be vigilant to the possibility of malignancy, especially in children who have been on a DMARD or biological agent.^{31,38,39}

School and social life

Modern management aims to keep children with JIA out of hospital, attending full-time school and participating in sport and peer activities, wherever possible. Visits to hospital may mean missed school time and require the understanding and co-operation of school staff to ensure children are not excluded from activities due to their JIA. Good communication between all MDT members, school and primary care providers ensures smooth arrangements for drug prescribing and monitoring as well as full integration into school life.

Conclusion

Therapeutics in the treatment of JIA have progressed rapidly over the last decade, and so too have our expectations of disease control. Treatment now aims for minimal disease activity and quality of life approaching that of any other child. While biological therapies have largely been responsible for these gains, we are also using traditional therapies in more effective ways. In particular, there has been a movement to

early aggressive therapy and closer disease monitoring as we 'treat-to-target'. With the shift to personalised, targeted therapies we can expect biomarkers and pharmacogenomics to play an increasing role in JIA treatment choices in the future.

Helpful online resources

Arthritis Research UK. <http://www.arthritisresearchuk.org/arthritis-information/young-people.aspx>
 British Society for Paediatric and Adolescent Rheumatology. <http://www.bspar.org.uk/>
 Pediatric Rheumatology International Trials Organisation (PRINTO). <https://www.printo.it/>
 Arthritis Care. <https://www.arthritiscare.org.uk/what-is-arthritis/types-of-arthritis/656-juvenile-idiopathic-arthritis-jia>

References

1. Petty RE, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31(2):390–2.
2. Myers A, et al. More 'cries from the joints': assessment of the musculoskeletal system is poorly documented in routine paediatric clerking. *Rheumatology* 2004;43(8):1045–9.
3. Foster HE, et al. Delay in access to appropriate care for children presenting with musculoskeletal symptoms and ultimately diagnosed with juvenile idiopathic arthritis. *Arthritis Rheum* 2007;57(6):921–7.
4. Arthritis Research UK. Paediatric gait arms legs spine (pGALS) videos. <http://www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx>
5. Carvounis PE, et al. Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Arch Clin Exp Ophthalmol* 2006;244(3):281–90.
6. Heiligenhaus A, et al. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocular Immunology Inflammation* 2013;21(3):180–91.
7. Royal College of Ophthalmologists, British Society for Paediatric and Adolescent Rheumatology. *Guidelines for screening for uveitis in juvenile idiopathic arthritis (JIA)*. Updated 7 June 2006. [https://www.bspar.org.uk/DocStore/FileLibrary/PDFs/BSPAR Guidelines for Eye Screening 2006.pdf](https://www.bspar.org.uk/DocStore/FileLibrary/PDFs/BSPAR%20Guidelines%20for%20Eye%20Screening%202006.pdf)
8. Davies K, et al. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. *Rheumatology* 2010;49(7):1406–8.
9. Wallace CA, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheumatism* 2012;64(6):2012–21.
10. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum* 2003;48(7):1771–4.
11. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin Exp Rheumatol* 2003;21(5, Suppl. 31):S154–7.
12. Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? *Arthritis Rheumatol* 2014;66(6):1405–13.
13. Magnani A, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2009;36(3):628–34.
14. Smolen JS, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheumatic Dis* 2010;69(4):631–7.
15. Smolen JS, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann*

Rheumatic Dis 2016;75(1):3–15.

16. Consolaro A, et al. Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2012;30(4, Suppl 73):S157–62.
17. Vastert S, Prakken B. Update on research and clinical translation on specific clinical areas: From bench to bedside: How insight in immune pathogenesis can lead to precision medicine of severe juvenile idiopathic arthritis. *Best Practice Res Clin Rheumatol* 2014;28(2):229–46.
18. Sobel RE, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the Phase 4 registry. *Pediatr Rheumatol* (Online J) 2014;12:29.
19. Litalien C, et al. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs* 2001;3(11):817–58.
20. Bloom BJ, et al. Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. *Rheumatol Int* 2011;31(6):749–56.
21. Zulian F, et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. *Rheumatology* 2004;43(10):1288–91.
22. Seror P, et al. Frequency of sepsis after local corticosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in France). *Rheumatology* 1999;38(12):1272–4.
23. British Society for Paediatric and Adolescent Rheumatology. *Methotrexate use in paediatric rheumatology - Information for health professionals*. 2013. https://www.bspar.org.uk/DocStore/FileLibrary/PDFs/BSPAR_Guideline_for_Methotrexate_2013.pdf
24. Ruperto N, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004;50(7):2191–201.
25. van Dijkhuizen EH, Wulffraat NM. Prediction of methotrexate efficacy and adverse events in patients with juvenile idiopathic arthritis: a systematic literature review. *Pediatr Rheumatol* (Online J) 2014;12:51.
26. Cutolo M, et al. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. *Ann Rheumatic Dis* 2001;60(8):729–35.
27. NHS England. *Clinical Commissioning Policy Statement: Biologic therapies for the treatment of juvenile idiopathic arthritis (JIA)*. October 2015. <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e03pd-bio-therapies-jia-oct15.pdf>
28. Ringold S, 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 Care Res* 2013;65(10):1551–63.
29. British Society for Paediatric and Adolescent Rheumatology. *BSPAR clinical guidelines – medication guidelines*. <http://www.bspar.org.uk/clinical-guidelines>
30. NICE. *Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis*. TA373. December 2015. <https://www.nice.org.uk/guidance/ta373>

[nice.org.uk/guidance/ta373](https://www.nice.org.uk/guidance/ta373)

31. Ruperto N, Martini A. Juvenile idiopathic arthritis and malignancy. *Rheumatology* 2014;53(6):968–74.
32. Magnano MD, et al. Demyelination and inhibition of tumor necrosis factor (TNF). *Clin Exp Rheumatol* 2004;22(5, Suppl. 35):S134–40.
33. Hsu L, Armstrong AW. Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response. *Expert Rev Clin Immunol* 2013;9(10):949–58.
34. Jani M, et al. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology* 2014;53(2):213–22.
35. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin Exp Immunol* 2010;161(1):1–9.
36. Beukelman T, 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* 2011;63(4):465–82.
37. Ringold S, 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.
38. Simard JF, et al. Juvenile idiopathic arthritis and risk of cancer: a nationwide cohort study. *Arthritis Rheum* 2010;62(12):3776–82.
39. Nordstrom BL, et al. Risk of malignancy in children with juvenile idiopathic arthritis not treated with biologic agents. *Arthritis Care Res* 2012;64(9):1357–64.
40. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369(9563):767–78.

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