

Diagnosis and management of juvenile idiopathic arthritis

Femke H M Prince,^{1,2} Marieke H Otten,¹ Lisette W A van Suijlekom-Smit¹

EDITORIAL

by Deighton and Scott

¹Department of Paediatrics/
Paediatric Rheumatology, Erasmus
MC Sophia Children's Hospital,
Rotterdam, Netherlands

²Division of Rheumatology,
Immunology and Allergy, Brigham
and Women's Hospital, Harvard
Medical School, Boston, USA

Correspondence to: F H M Prince
f.prince@erasmusmc.nl

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Juvenile idiopathic arthritis is the most common cause of chronic arthritis in childhood; a review of 34 epidemiological studies showed that 0.07-4.01 per 1000 children worldwide are affected.^{w1} It is characterised by joint inflammation that often leads to joint destruction with physical disability and chronic pain that affects daily life.¹ During the past decade, increased understanding of the disease has improved treatment, particularly through earlier diagnosis and new treatments that help to prevent long term damage to joints. Earlier this year, the British Society for Paediatric and Adolescent Rheumatology published standards of care for children and young people with juvenile idiopathic arthritis, which outlined the importance of involving different disciplines within healthcare.² We review recent advances in the diagnosis and management of juvenile idiopathic arthritis, focusing on evidence from randomised controlled trials, cohort studies, systematic reviews, and current guidelines.

What is juvenile idiopathic arthritis and who gets it?

Juvenile idiopathic arthritis (formerly juvenile chronic arthritis in Europe and juvenile rheumatoid arthritis in North America) covers a heterogeneous group of conditions more accurately described as subtypes.^{w2-w4} The disease encompasses all forms of arthritis that begin before the age of 16 years, persist for more than six weeks, and are of unknown cause.³ It is thought to be a multifactorial autoimmune disease with environmental and genetic contributory factors.⁴ The heterogeneity of the subtypes and changes in terminology and classification make it difficult to interpret studies on the role of the environment.⁵ The most common risk factors are infections in combination with genetic susceptibility. Many other factors, such as stress and maternal smoking, are thought to contribute

to the pathogenesis. Juvenile idiopathic arthritis is a complex genetic disease with multiple genes involved. Individual cohort studies have confirmed and replicated several associations between juvenile idiopathic arthritis and variants in the histocompatibility (HLA) genes but the strength of the associations differ for each disease

Box 1 | Differential diagnosis of joint problems in children⁸

Arthritis*

Infective and reactive: Lyme disease, viral infection, mycoplasma infection, post-streptococcal reactive arthritis
Juvenile idiopathic arthritis

Connective tissues disorders: systemic lupus erythematosus, dermatomyositis, systemic sclerosis

Systemic vasculitis: Henoch-Schönlein purpura, Kawasaki's disease, polyarteritis nodosa

Other: haemophilia, immunodeficiency (including periodic fever syndromes), sarcoidosis, inflammatory bowel disease

Mechanical and degenerative causes†

Trauma: accidental and non-accidental

Hypermobility

Avascular necrosis including Perthes' disease, Osgood-Schlatter's disease, Scheuermann's disease

Slipped upper femoral epiphyses

Anterior knee pain including chondromalacia patallae

Non-organic causes‡

Idiopathic pain syndromes: diffuse or localised (reflex sympathetic dystrophy)

Benign nocturnal idiopathic limb pains (growing pains)

Psychogenic causes

Miscellaneous causes‡

Osteomyelitis

Tumours: malignant (leukaemia, neuroblastoma) or benign (osteoid osteoma, pigment villonodular synovitis)

Endocrine and metabolic abnormalities: rickets, diabetes, hypophosphataemic rickets, hypothyroidism or hyperthyroidism

Genetic disorders: skeletal dysplasias, mucopolysaccharidoses, collagen disorders (Ehlers-Danlos syndrome, Stickler's syndrome)

*Joint(s) show (or mimic) signs of inflammation: redness, swelling, heat, pain, loss of function

†Most likely cause in otherwise well patients with joint pain but no swelling (except for trauma)

‡Most likely cause in patients with overall malaise in addition to joint problems

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▶ A personal view from the parent of a young patient with rheumatoid arthritis is available online (*BMJ* 2011;**342**:c7450)

SUMMARY POINTS

Early recognition and early aggressive treatment of juvenile idiopathic arthritis prevent joint damage and allow for normal development and growth

The disease is heterogeneous and complex, so patients benefit from regular review and management by experts in a multidisciplinary team

The disease currently has no cure, but clinical remission is a realistic treatment goal

Biological disease modifying antirheumatic drugs are a new and effective treatment for severe disease, but they increase the risk of infection; more data on long term adverse events need to be obtained from registries

Trials need to determine the optimal treatment strategies with synthetic and biological disease modifying antirheumatic drugs

Table 1 | Juvenile idiopathic arthritis subtypes^{3 6 w6}

Categories	Characteristics	% of total	Onset age	Sex ratio (F:M)	Relative risk (European v non-European)
Systemic juvenile idiopathic arthritis	Arthritis and daily fever ≥3 days, accompanied by at least one of the following: evanescent (non-fixed) erythematous rash, generalised lymph node enlargement, hepatomegaly or splenomegaly (or both), serositis	4-17	Throughout childhood	1:1	2.5
Oligoarthritis:	Arthritis affecting 1-4 joints during the first 6 months of disease	27-60	Early childhood (peak 2-4 years)	5:1	
Persistent	Arthritis affecting ≤4 joints throughout the disease course	40			3.3
Extended	Arthritis affecting >4 joints after the first 6 months of disease	20			6.0
Polyarthritis:	Arthritis affecting ≥5 joints during the first 6 months of disease				
Rheumatoid factor positive	Two or more positive tests for rheumatoid factor at least 3 months apart	2-7	Late childhood or adolescence	3:1	0.8
Rheumatoid factor negative	Tests for rheumatoid factor negative	11-30	Early peak 2-4 years and late peak 6-12 years	3:1	3.9
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in first degree relative	2-11	Late childhood or adolescence	1:0.95	6.4
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain (or both), HLA-B27 antigen positive, onset in boy over 6 years old, acute anterior uveitis, HLA-B27 associated disease* in first degree relative	1-11	Early peak 2-4 years and late peak 6-12 years	1:7	1.7
Undifferentiated arthritis	Arthritis that fulfils criteria in no specific category or meets criteria for more than one category	11-21			

*Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis.

subtype.^{w5} A large number of non-HLA candidate genes have been tested for associations, but only a few such as protein tyrosine phosphatase (PTPN22) and macrophage inhibitory factor (MIF) have been confirmed. A multiethnic Canadian cohort study showed a moderately increased risk for European origin compared with African, Asian, or Indian origin, and that subtypes differ significantly between ethnic groups (table 1).⁶ The typical age of onset also depends on subtype.^{w6} Table 1 lists the subtypes according to the currently accepted classification. Increased knowledge about the disease will probably refine the classification further. This might provide homogeneous subgroups for research and lead to tailored disease management.

How is the diagnosis made?

No conclusive laboratory tests are available for the diagnosis of juvenile idiopathic arthritis, so a good history and physical examination are important.⁷ The diagnosis is made by excluding joint problems with a discernable cause. Box 1 lists causes of joint pain in children.

History

After queries about joint pain and swelling (including previous episodes), ask patients and parents about morning stiffness that lasts for more than 15 minutes but improves during the day.^{7 9} Parents, other family members, or teachers may have noticed problems with, for example, walking, running, climbing stairs, standing up, writing, or sleeping. The child might need help with daily activities that were previously performed independently. Also ask about autoimmune disease in relatives, and in suspected psoriatic arthritis and enthesitis related arthritis (table 1) ask about specific family history.^{3 w7} Lastly, ask about any systemic features such as rash or intermittent pyrexia (see table 1).

Physical examination

Examine all joints for pain or tenderness, swelling, limited movement, decreased strength or muscle atrophy, and bony deformity.^{7 9} Observe the child while walking, standing up, sitting down, or climbing on to the examination table. In a general examination look for features such as lymphadenopathy, organ enlargement, systemic rashes, nail abnormalities, psoriatic rash, or enthesitis. Always measure growth parameters. Eyes should be checked by an ophthalmologist for uveitis.

Clinical features

Clinical features strongly depend on the subtype and differ in age at onset of disease, number and location of joints involved, disease course, presence of antinuclear antibodies or rheumatoid factor, presence of chronic or acute uveitis, presence of systemic features, and HLA allelic associations (table 1).^{w8} Patients with oligoarthritis (one to four joints affected in first six months of disease) usually present with arthritis in the knees, ankles, or elbows rather than the hips. Chronic anterior uveitis develops in a fifth of these patients and most will be antinuclear antibody positive.^{10 w8} Most patients with polyarthritis (five or more joints affected in first six months) present with symmetrical arthritis in large and small joints and less commonly with uveitis.^{w8} Onset may be acute or insidious. Systemic disease is characterised by fever with one or more daily spikes for at least three days. As well as arthritis, which affects a variable number of joints, there are systemic features (table 1).³ Arthritis may start weeks or even years after the onset of systemic features and can present as a single episode or become persistent. Patients with enthesitis related arthritis can present with oligoarthritis or polyarthritis of the large or small joints as well as enthesitis (table 1).^{3 w8} Patients who also have psoriasis, a history of psoriasis in a first degree

Box 2 | Juvenile idiopathic arthritis core set of response variables¹⁹

- Global assessment of the disease activity by the doctor using a visual analogue scale (VAS) (range 0-100 mm, 0 best score)
- Childhood health assessment questionnaire (CHAQ) (range 0-3, 0 best score) used by the patient or parent (measures functional ability)
- Global assessment of wellbeing by the patient or parent using a visual analogue scale (range 0-100 mm, 0 best score)
- Number of joints with active arthritis
- Number of joints with limited movement
- A laboratory marker of inflammation—erythrocyte sedimentation rate or C reactive protein. Patients have responded if at least three variables have improved by 30% (50%, 70%, 100%) and no more than one variable has worsened by more than 30% (ACR pediatric 30%, 50%, 70%, or 100% response)¹⁹

relative, nail pitting, or dactylitis will probably have psoriatic arthritis unless rheumatoid factor is positive.^{3 w8}

Further investigations

Other investigations for all subtypes include laboratory tests—a full blood examination, inflammatory markers (erythrocyte sedimentation rate, C reactive protein), and autoimmune markers (rheumatoid factor, HLA B27, and antinuclear antibodies)—and imaging studies.^{7 9} Radiography can detect narrowing of the joint spaces or erosions and might show maturation differences or growth abnormalities in bones from an early stage.^{w9} Magnetic resonance imaging studies can also show inflamed synovium and increased joint fluid.^{w9}

Referral

Refer all children with suspected or confirmed juvenile idiopathic arthritis to a paediatric rheumatologist as soon as possible to prevent delay in treatment. A cohort study of 128 patients with juvenile idiopathic arthritis and a placebo controlled trial showed that time to treatment is an important factor in response to treatment.^{11 12}

How does juvenile idiopathic arthritis affect patients?

Patients with active arthritis have pain, fatigue, and limitation in performing daily activities, but the degree to which patients are affected differs. The course of the disease is related to the subtype—persistent oligoarthritis is generally the mildest form and systemic the most severe form. When disease is not completely controlled, long term local or systemic complications can occur, depending on the subtype, severity of the disease, and the treatment given. Case-control studies show that long term localised joint inflammation can lead to flexion deformities, damage of cartilage and bone, and bony overgrowth that results in limb length discrepancies.^{13 14} Observational studies show that overall growth can be affected by the disease itself and other factors, such as use of corticosteroids.^{w10-w12} Chronic inflammation can cause anaemia.^{w13} Uveitis, which occurs in 5-20% of patients, most commonly in the oligoarticular subtype, can be asymptomatic and can lead to cataracts and even blindness.¹⁰ Regular ophthalmology checks are indicated. The systemic subtype is associated with the most serious morbidity and even mortality.¹⁵ Conditions associated with this subtype include amyloidosis and macrophage activation syndrome.^{15 w14}

Despite improvements in treatment, a review published last year showed that a large proportion of children with juvenile idiopathic arthritis still have active disease throughout childhood and enter adulthood with active disease.¹⁶ Several clinical studies have shown that patients with active disease have low health related quality of life^{17 18}—the disease affects their physical, emotional, and social wellbeing. A review found that affected children have lower self esteem, are more likely to have behavioural problems than their peers, and are limited in their social lives because of mobility problems and pain.^{w15} The patient's family is also affected—the disease has an emotional impact on parents and limits family activities. Fortunately, several studies have shown that family cohesion is not affected.^{17 w15}

How is juvenile idiopathic arthritis treated?

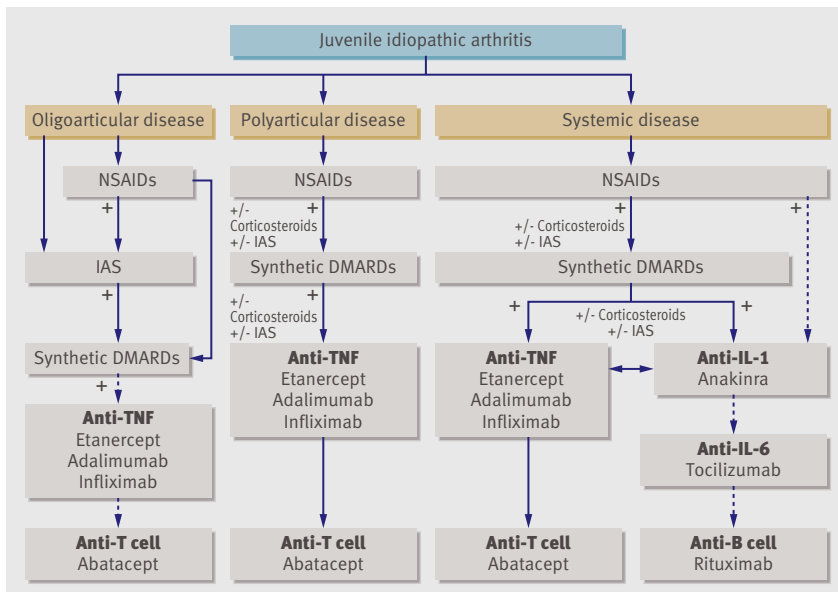
Because there is currently no cure for juvenile idiopathic arthritis, the goal of treatment is clinical remission (complete absence of disease).^{2 7 w16} Treatment aims to control the inflammatory process by decreasing the number of actively affected joints and to improve the quality of life. A validated set of response variables is used to measure the response to treatment in patients enrolled in clinical trials (box 2).¹⁹ Patients are considered to be in remission if they have had no active arthritis, fever, rash, serositis, or generalised lymphadenopathy attributable to juvenile idiopathic arthritis; no active uveitis; a normal erythrocyte sedimentation rate or C reactive protein; and no disease activity as assessed by a doctor for the past six months.²⁰

Old versus new approach to treatment

In the past, juvenile idiopathic arthritis was treated with non-steroidal anti-inflammatory drugs (NSAIDs), with delayed addition of synthetic disease modifying antirheumatic drugs (DMARDs) or systemic corticosteroids (or both), and lastly biological DMARDs. However, accumulating evidence from cohort studies and trials has shown that a more aggressive approach to disease control, with earlier introduction of DMARDs, prevents or minimises long term sequelae of the disease.^{11 12 16} Existing guidelines on care have not been revised to include such advice but do advocate “tight” clinical control.^{2 w16}

Drug treatment

Up to date international guidelines are currently lacking. The British Paediatric Rheumatology Group provided guidelines for the management of childhood arthritis in 2001,²¹ but because treatment is changing rapidly, this guideline needs revision. A recent guideline from the Royal Australian College of General Practitioners focuses on NSAID treatment only.⁹ New recommendations for the treatment of juvenile idiopathic arthritis were presented at the American College of Rheumatology 2010 November meeting but have not been published yet. They are based on studies also mentioned in this review and on expert opinions when evidence is lacking. The treatment modalities we describe are based on randomised controlled trials, case series, and cohort studies. The figure outlines a simplified approach to treatment.



Simplified approach to treatment of patients with juvenile idiopathic arthritis. Steps often rapidly succeed one another or are combined. DMARDs, disease modifying antirheumatic drugs; IAS, intra-articular steroids; IL, interleukin; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor

Non-steroidal anti-inflammatory drugs

During diagnosis, while other causes of arthritis are being excluded, most patients are given NSAIDs. These drugs relieve pain usually within a few days and do not, as more aggressive treatments can, interfere with the disease course in case of misdiagnosis. Several NSAIDs are used, and none has proved to be superior to another.²² Recent randomised trials found that the newer cyclooxygenase-2 inhibitors (rofecoxib, celecoxib, and meloxicam) were no more effective or safer than the most commonly prescribed NSAID, naproxen.^{w17-w19} More than half of patients achieved an ACR pediatric 30 response (box 2) after three months of NSAID monotherapy, an NSAID added to a stable dose of a synthetic DMARD, or biological DMARD treatment, although these responses were not compared with placebo.^{w17-w19}

Corticosteroids (intra-articular and systemic)

Children with oligoarticular disease are often given NSAID monotherapy, intra-articular corticosteroids alone, or a combination of both. Intra-articular cortico-

steroids are increasingly being used, and earlier in the disease course. In a retrospective study of 121 injected joints, all joints responded within one week, and after one year 52% were still in remission.^{w20} A randomised double blind trial confirmed this rapid and long lasting effect and showed that triamcinolone hexacetonide is superior to triamcinolone acetonide (85% of joints still in remission after one year) and should be the drug of first choice.²³ Skin atrophy at the injection site occurred in 2.3% of the treated joints.²³ The systemic absorption of triamcinolone, which peaks at eight hours after injection, is usually not clinically relevant, although cases of Cushing's syndrome and transient increases in blood glucose in patients with diabetes have been reported after intra-articular injection.^{w21 w22}

The long term use of systemic corticosteroids has declined because of side effects, particularly reduced growth and bone health.^{w12} These drugs are mainly used while waiting for DMARDs to take effect and in patients with severe systemic or polyarticular juvenile idiopathic arthritis unresponsive to treatment with synthetic and biological DMARDs.^{22 w7}

Synthetic disease modifying antirheumatic drugs

Patients with a definite diagnosis of polyarticular disease or oligoarticular disease refractory to intra-articular steroids are candidates for second line agents (DMARDs). Table 2 lists the typical doses, side effects, and contraindications of such drugs used in juvenile idiopathic arthritis.

Methotrexate is the most widely used and first choice synthetic DMARD. A randomised placebo controlled trial (127 patients), a randomised placebo controlled crossover trial (43 patients with extended oligoarticular arthritis), and a dose finding trial (80 patients, mostly unresponsive to low dose methotrexate) found it to be effective—with significant reductions in active and limited joint counts, and high overall improvement—in patients with polyarticular and oligoarticular extended disease.^{24 w23 w24} However, it produced no overall improvement in systemic disease—the most difficult subtype to treat.²⁴ It is unclear how long after remission methotrexate should be withdrawn; a recent randomised clinical withdrawal trial found no differences in relapse rates in patients who continued the drug for six or 12 months (57% v 56%) after induction of remission.^{w25}

Table 2 | Synthetic disease modifying antirheumatic drugs

Agent	Dose*	Contraindication	Common side effects
Methotrexate (Emthexate, Metoject)	10-15 mg/m ² once weekly orally or subcutaneously(maximum 25 mg/m ²)	Liver dysfunction, kidney dysfunction, immunodeficiency, bone marrow dysfunction, active infection, pregnancy, breast feeding	Gastrointestinal symptoms (nausea, vomiting, anorexia); less commonly transient rises in liver transaminases and haematological disturbances
Sulfasalazine (Salazopyrin)	50 mg/kg orally divided into 2 or 3 doses a day(maximum 2000 mg/day)	Salicylate hypersensitivity, systemic disease	Gastrointestinal symptoms, allergic reactions; less commonly, myelosuppression
Leflunomide (Arava)	<20 kg: 100 mg orally for 1 day and then 10 mg every other day; 20-40 kg: 200 mg orally for 2 days and then 10 mg/day;>40 kg: 100 mg orally for 3 days and then 20 mg/day	Severe immunodeficiency, bone marrow dysfunction, serious infection, liver dysfunction, severe hypoproteinaemia, pregnancy, breast feeding	Gastrointestinal symptoms, rash, allergic reactions, headache, reversible alopecia; less commonly, transient rises in liver transaminases, haematological disturbances; can be teratogenic
Ciclosporin A (Neoral)	3-7 mg/kg daily orally or intravenously	Renal impairment, uncontrolled hypertension, uncontrolled infections, malignancy	Hypertension and nephrotoxicity; depletion of calcium and magnesium can be associated with muscle cramping; hirsutism and gum hyperplasia often reported at higher doses

*m² refers to body surface; kg refers to body weight.

A randomised placebo controlled trial (69 patients) also found sulfasalazine to be effective in the management of juvenile idiopathic arthritis, with a higher response rate than placebo (69% v 45%) after 24 weeks of treatment.²⁵ However, the drug was not well tolerated, and nearly a third of patients discontinued treatment.²⁵ With the development of newer biological DMARDs, the use of sulfasalazine has decreased. In a relatively small randomised controlled trial, leflunomide was found to be less effective than methotrexate but with similar adverse event rates.²⁶ There are no controlled studies of ciclosporin A in juvenile idiopathic arthritis, although small case series show a beneficial effect in severe systemic disease.^{w26 w27} A large observational study of 329 patients treated with ciclosporin A found a 9% complete response rate; most patients discontinued the drug because of inefficacy.^{w28} Case series have shown that ciclosporin A might be effective in macrophage activation syndrome.^{w29 w30} The use of leflunomide and ciclosporin A in juvenile idiopathic arthritis is limited. Other synthetic DMARDs (auranofin, penicillamine, and hydroxychloroquine) have not been shown to have a significant therapeutic advantage over placebo, in contrast to findings in adult patients with rheumatoid arthritis.^{w31 w32}

Biological disease modifying antirheumatic drugs

With the introduction of biological DMARDs (also know as biologicals or biologics) the goal has shifted from reducing inflammation to “switching off” the autoimmune system by targeting inflammatory cytokines. Table 3 lists the

biological DMARDs currently available or under investigation for juvenile idiopathic arthritis.

Tumour necrosis factor is a proinflammatory cytokine that plays a central role in the pathogenesis of juvenile idiopathic arthritis.^{w33} In systemic disease, interleukin 1 (a proinflammatory cytokine synthesised by fibroblasts in the synovium and macrophages) and interleukin 6 (concentrations of which correlate with fever, disease activity, and platelet counts) are also thought to be important.^{w33-w35} If inhibition of these cytokines is not sufficient, other drugs aimed at T cell blockade and B cell depletion are available.^{w36} Only etanercept, adalimumab, and abatacept have been approved by the European Medicines Agency and the Food and Drug Administration for the treatment of juvenile idiopathic arthritis after testing in placebo controlled withdrawal trials.²⁷⁻²⁹ These trials are designed so that all patients start the drug in an initial open label part of the trial. Those with an ACR pediatric 30 response to treatment (box 2) enter a double blind study and are randomly assigned to receive placebo or the biological DMARD until the disease flares. The response rates (ACR pediatric scores) reported from these trials come from the open label phase and represent the initial responders.^{w37} Results from the randomised blinded phase are presented as flare rates. This design is used in paediatric rheumatology trials to minimise the consequences of placebo treatment.

Other biological DMARDs are prescribed off label, although some (infliximab, anakinra, tocilizumab) have been tested in patients with juvenile idiopathic arthritis in placebo controlled withdrawal trials (table 3).^{w38-w40}

Table 3 | Biological disease modifying antirheumatic drugs currently available or under investigation for juvenile idiopathic arthritis

Agent	Action	Dose*	Used in subtypes	Other paediatric indications (approved or off label)
TNF-α blocking agents				
Etanercept (Enbrel)	TNF-α receptor fusion protein	0.4 mg/kg twice weekly SC or 0.8 mg/kg weekly SC (max 50 mg/week)	All patients with polyarticular course and seldom in oligoarticular persistent	Plaque psoriasis
Adalimumab (Humira)	Human monoclonal anti-TNF antibody	<30 kg: 20 mg every two weeks SC; >30 kg: 40 mg every two weeks SC	All patients with polyarticular course‡	Crohn’s disease, ulcerative colitis, uveitis
Infliximab (Remicade)	Chimeric murine-human monoclonal anti-TNF antibody	6-10 mg/kg IV at 0, 2, and 6 weeks, then every 4-8 weeks	All patients with polyarticular course†	Crohn’s disease, ulcerative colitis, plaque psoriasis, uveitis
T cell co-stimulation modulator				
Abatacept (Orencia)	T cell co-stimulation modulator	10 mg/kg IV at 0, 2, and 4 weeks (maximum 1000 mg), then every 4 weeks	All patients with polyarticular course¶	
Interleukin 1 blocking agents				
Anakinra (Kineret)	IL-1 receptor antagonist	1-2 mg/kg daily SC (maximum 100 mg)	Systemic disease†	Cryopyrin associated periodic syndrome
Riloncept (Arcalyst)	IL-1 receptor-IL1RacP-FC fusion protein	Loading dose of 4.4 mg/kg SC (maximum 160 mg), then weekly doses of 2.2 mg/kg	Systemic disease**	Cryopyrin associated periodic syndrome
Canakinumab (Ilaris)	Human IL-1β antibody	<40 kg: 2-4 mg/kg every 8 weeks SC; >40 kg: 150-300 mg every 8 weeks SC	Systemic disease**	Cryopyrin associated periodic syndrome
Interleukin 6 blocking agent				
Tocilizumab (RoActemra)	IL-6 receptor antibody	<30 kg: 12 mg/kg every 2 weeks SC; >30 kg: 8 mg/kg every 2 weeks SC	Systemic disease††	
B cell depletion agent				
Rituximab (Rituxan)	Chimeric anti-CD20 monoclonal causing B cell depletion	<40 kg: 2 doses of 500 mg IV 2 weeks apart; >40 kg: 2 doses of 1000 mg IV 2 weeks apart	Systemic disease**	Systemic lupus erythematosus, B cell non-Hodgkin’s lymphoma

Abbreviations: . IL=interleukin, IV=intravenous, TNF=tumour necrosis factor, SC=subcutaneous.

*kg refers to body weight.

Placebo controlled withdrawal trials published for:

†Subtypes: systemic, oligoarticular extended, and polyarticular (rheumatoid factor positive and negative).

‡Patients with a polyarticular course (any subtype).

¶Subtypes: systemic (without systemic manifestations), oligoarticular extended, and polyarticular (rheumatoid factor positive and negative).

**No randomised trials (yet) published in juvenile idiopathic arthritis.

††Systemic subtype only.

Choice of biological DMARD is based on effectiveness, safety, route of administration, and arthritis subtype.

Etanercept was the first and for a long time the only registered biological DMARD for the treatment of juvenile idiopathic arthritis; 74% of patients previously resistant to other drugs, including methotrexate, met the ACR pediatric 30 target after three months in the placebo controlled withdrawal trial.²⁷ Many observational studies have provided data on safety and response; the drug seems to be well tolerated and effective.^{w41-w46} It is the most commonly prescribed biological DMARD for patients with this disease, followed by adalimumab. A prospective registry study found that etanercept reduced disease activity and improved quality of life in all aspects affected by the disease.¹⁷ A health related quality of life study of abatacept showed similar results.^{w47} A placebo controlled withdrawal trial showed that abatacept was effective in patients for whom anti-tumour necrosis factor was not effective (ACR pediatric 30 response in 39%), thereby providing a valuable alternative treatment.²⁹

Box 3 | Safety and monitoring of synthetic* and biological disease modifying antirheumatic drugs

Overall recommendations

Do not start treatment in patients with an active infection, current or previous tuberculosis, immunodeficiency, cancer, or precancerous state^{w54}

In each infectious episode during treatment, consider the need to discontinue the drug temporarily^{w54}

Perform regular check-ups with full blood counts and liver and kidney function tests^{w54}

Be aware of adverse events, including neurological and neuropsychological disorders, new onset autoimmune diseases, and cancers^{w54}

Avoid live (attenuated) vaccines until more data are available^{w55 w56}

Killed (or inactivated) vaccines are safe, although the immune response may be suboptimal and boosters may be needed^{w57-w59}

Yearly influenza vaccination is recommended^{w54}

Give any susceptible patient exposed to varicella specific immunoglobulin and aciclovir at first sign of infection; consider vaccination before starting disease modifying antirheumatic drugs^{w54}

Drug specific recommendations

Methotrexate

Give folate supplements 24-48 hours after starting methotrexate to reduce the gastrointestinal and hepatic side effects^{w60}

In higher doses parenteral application is recommended because of better bioavailability and tolerability^{w61}

Leflunomide and ciclosporin A

Measure blood pressure regularly^{w54}

Infliximab

Monitor for acute hypersensitivity reactions until two hours after infusion^{w54}

Give methotrexate concomitantly to prevent immunogenicity^{w62}

*Applies only to synthetic DMARDs that affect the immune system (methotrexate, leflunomide, ciclosporin A)

The treatment of systemic disease is challenging.¹⁵ In a controlled clinical withdrawal trial and case series anakinra seemed to be better than etanercept in reducing systemic symptoms.^{15 w38 w48-w50} Other biological DMARDs (table 3) have shown promising results in clinical trials or case series. No head to head trials on choice of biological DMARD exist for these patients. Today, most experts favour anakinra when systemic features are prominent, but the timing of this treatment is debatable.³⁰ More studies on management of systemic arthritis are needed.

The most commonly encountered adverse events of biological DMARDs are local reactions at injection sites and opportunistic infections.^{31 w51} Most injection site reactions resolve as a result of tolerance. Consult a paediatric rheumatologist if the drug has to be discontinued because of a serious infection. Less commonly encountered but important adverse events are neurological or neuropsychological disorders, new onset autoimmune diseases, and cancer. The most common cancers reported related to anti-tumour necrosis factor treatment are hepatosplenic T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukaemia, although there is no convincing evidence of an increased risk.^{31 w52 w53} Similarly, although safety studies with long term follow-up have shown new onset of the above complications in patients taking biological DMARDs, we have insufficient data to compare incidence rates in patients taking biological DMARDs with those in patients not taking biological DMARDs.^{w41-w46} If one of these conditions is suspected in a patient taking a biological DMARD or other immunosuppressive drug, consult the treating paediatric rheumatologist immediately to discuss discontinuing the drug. Box 3 provides recommendations for safety and monitoring of DMARDs.

Other treatments

Depending on the subtype and severity of disease, the British Society for Paediatric and Adolescent Rheumatology standards of care recommends regular checks by a paediatric rheumatologist, ophthalmologist, dermatologist, orthopaedic surgeon, orthodontist, general practitioner, psychologist, and physiotherapist or occupational therapist. The idea is that a well chosen multidisciplinary team will enable the best possible care.²

A Cochrane review has shown that physiotherapy is important to maintain normal muscle and joint function.^{w63} Rehabilitation—using heat or cold treatment, massage, therapeutic exercise, and splints—is crucial to returning to activities of daily living again once these have been limited by disease.⁹ The British Society for Paediatric and Adolescent Rheumatology standards of care guideline also recommends psychological therapy and education.²

Supplements may be needed to prevent certain side effects of treatment. During corticosteroid treatment patients are at increased risk of osteoporosis and osteopenia. Several studies, including a randomised clinical trial, found a small but significant beneficial effect of calcium and vitamin D supplements on bone mineral density.^{w64 w65} Children using methotrexate might benefit from folic acid supplements. Although evidence that weekly folic acid reduces methotrexate related adverse

TIPS FOR NON-SPECIALISTS

- Exclude all other causes of joint problems when considering a diagnosis juvenile idiopathic arthritis
- Immediately refer all patients with suspected or confirmed juvenile idiopathic arthritis to a paediatric rheumatologist and prescribe a non-steroidal anti-inflammatory drug to relieve symptoms
- Examine any patient who develops a fever while taking immunosuppressive drugs and consult a paediatric rheumatologist if drugs need to be (temporarily) discontinued
- Look out for adverse events—including neurological and neuropsychological disorders, new onset autoimmune diseases, and cancer—in patients taking disease modifying anti-rheumatic drugs
- Avoid live (attenuated) vaccines in patients taking immunosuppressive drugs; killed (or inactivated) vaccines are safe (although the immune response may be suboptimal)
- Yearly influenza vaccination is recommended
- Be aware that the disease also affects the patient's emotional and social wellbeing and the patient's family

ADDITIONAL EDUCATIONAL RESOURCES**Resources for healthcare professionals**

Takken T, Van der Net J, Helders PJ. Methotrexate for treating juvenile idiopathic arthritis. *Cochrane Database Syst Rev* 2001;4:CD003129

Woo P, Laxer RM, Sherry DD. Paediatric rheumatology in clinical practice. Springer, 2007

Cassidy JT, Petty RE, Laxer R, Lindsley C. *Textbook of pediatric rheumatology*, 6th ed. Elsevier, 2011

Szer IS, Kimura Y, Malleson PN, Southwood TR. *Arthritis in children and adolescents: juvenile idiopathic arthritis*. Oxford University Press, 2006

Resources for patients and parents

Lehman TJA. A parent's guide to rheumatic disease in children. Oxford University Press, 2008

Paediatric Rheumatology European Society (www.printo.it/pediatric-rheumatology/)—Information for patients on rheumatological diseases in many different languages

Children with chronic arthritis (www.ccaa.org.uk)—Website that aims to provide help and information for children with arthritis, their families, and professionals involved in their care

SOURCES AND SELECTION CRITERIA

As well as using our personal reference collections, we searched Medline, Embase, and Cochrane Central for clinical studies and reviews using the keywords “juvenile idiopathic arthritis”, “juvenile rheumatoid arthritis”, “juvenile chronic arthritis”, “diagnosis”, “treatment”, “therapy”, “non-steroidal anti-inflammatory drugs”, “corticosteroids”, “disease modifying antirheumatic drugs”, “biologicals”, and “biologics.” We also reviewed guidelines from the British Society for Paediatric and Adolescent Rheumatology and the Royal Australian College of General Practitioners.

effects in children is weak, studies in adults with rheumatoid arthritis have shown significant effects.^{w66 w67}

Autologous stem cell transplantation was used in autoimmune diseases before biological agents were available, and several patients with juvenile idiopathic arthritis have been successfully transplanted.^{w68 w69} However, because of the risks involved (9% transplant related mortality) and relatively high relapse rates (>30%), this treatment is reserved for patients who are resistant to combinations of synthetic DMARDs, corticosteroids, and biological DMARDs and who have severe, debilitating, and potentially fatal disease.

What will the future hold?

Despite the lack of a cure, biological DMARDs have provided a better quality of life for many patients with juvenile idiopathic arthritis who were previously refractory to treatment. In addition, the current trend of early aggressive treatment has improved long term outcomes. However, a proportion of patients still have ongoing active disease and associated long term sequelae that limit daily life.^{w70} Individual children must be managed according to subtype, severity of disease, and prognostic factors. Research into biomarkers and genetic markers of disease subtype, as well as advances in radiographic imaging, may one day provide earlier diagnosis, better monitoring of disease activity, and more tailored treatments. Outcomes improve with earlier disease control, and trials to investigate the efficacy of various treatments (combining different drugs according to different time schedules) are under way.^{w71-w73} The new biological DMARDs—targeted at interleukins 1 and 6, T cells, and B cells—have shown promising results and might improve treatment for specific patients groups.

Disease registries are important sources of data from large patient groups. They can be used to compare different outcomes of treatments, while accounting for patient and disease characteristics, disease course, and occurrence of adverse events during (multiple) treatments over long periods. Registry data provide a real life picture of patients as treated by their doctor. Initiatives to combine registries have begun in Europe and the United States and should help us answer questions on the long term safety of biological DMARDs. A worldwide consolidated juvenile idiopathic arthritis registry would be ideal.

Hopefully, these efforts will result in more choice of effective and safe drugs and an optimal treatment strategy for each patient. The ultimate goal is clinical remission off drugs that could be considered as a “cure.”³²

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- 1 Ostlie IL, Aasland A, Johansson I, Flato B, Moller A. A longitudinal follow-up study of physical and psychosocial health in young adults with chronic childhood arthritis. *Clin Exp Rheumatol* 2009;27:1039-46.
- 2 Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR standards of care for children and young people with juvenile idiopathic arthritis. *Rheumatol (Oxford)* 2010;49:1406-8.
- 3 Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.
- 4 Prakken BJ, Albani S. Using biology of disease to understand and guide therapy of JIA. *Best Pract Res Clin Rheumatol* 2009;23:599-608.
- 5 Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. *Autoimmun Rev* 2010;9:A319-24.
- 6 Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum* 2007;56:1974-84.
- 7 Wallace CA. Current management of juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2006;20:279-300.
- 8 Davidson J. Juvenile idiopathic arthritis: a clinical overview. *Eur J Radiol* 2000;33:128-35.
- 9 Australian Government. Clinical guideline for the diagnosis and management of juvenile idiopathic arthritis. www.racgp.org.au/Content/NavigationMenu/ClinicalResources/RACGPGuidelines/JuvenileIdiopathicArthritis/RACGP_JIA_guideline.pdf.
- 10 Foster CS. Diagnosis and treatment of juvenile idiopathic arthritis-associated uveitis. *Curr Opin Ophthalmol* 2003;14:395-8.
- 11 Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:46-51.
- 12 Van Rossum MA, van Soesbergen RM, Boers M, Zwiderman AH, Fiselier TJ, Franssen MJ, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. *Ann Rheum Dis* 2007;66:1518-24.
- 13 Flato B, Lien G, Smerdel A, Vinje O, Dale K, Johnston V, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. *J Rheumatol* 2003;30:386-93.
- 14 Sherry DD, Stein LD, Reed AM, Schanberg LE, Kredich DW. Prevention of leg length discrepancy in young children with pauciarticular juvenile rheumatoid arthritis by treatment with intraarticular steroids. *Arthritis Rheum* 1999;42:2330-4.
- 15 Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. *Nat Clin Pract Rheumatol* 2006;2:28-34.
- 16 Minden K. Adult outcomes of patients with juvenile idiopathic arthritis. *Horm Res* 2009;72(suppl 1):20-5.
- 17 Prince FH, Geerdink LM, Borsboom GJ, Twilt M, Van Rossum MA, Hoppenreijs EP, et al. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2010;69:138-42.
- 18 Ringold S, Wallace CA, Rivara FP. Health-related quality of life, physical function, fatigue, and disease activity in children with established polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2009;36:1330-6.
- 19 Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202-9.
- 20 Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research A, Pediatric Rheumatology International Trials O, Pediatric Rheumatology Collaborative Study G. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290-4.
- 21 Hull RG. Management guidelines for arthritis in children. *Rheumatol (Oxford)* 2001;40:1308.
- 22 Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005;294:1671-84.
- 23 Zulian F, Martini G, Gobber D, Plebani M, Zaccello F, Manners P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. *Rheumatol (Oxford)* 2004;43:1288-91.
- 24 Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum* 2000;43:1849-57.
- 25 Van Rossum MA, Fiselier TJ, Franssen MJ, Zwiderman AH, ten Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. *Arthritis Rheum* 1998;41:808-16.
- 26 Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005;352:1655-66.
- 27 Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763-9.
- 28 Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810-20.
- 29 Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;372:383-91.
- 30 Nigrovic PA, Mannion M, Prince FH, Zeff A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease modifying therapy in systemic juvenile idiopathic arthritis. *Arthritis Rheum* 2010 online 4 November.
- 31 Hashkes PJ, Uziel Y, Laxer RM. The safety profile of biologic therapies for juvenile idiopathic arthritis. *Nat Rev Rheumatol* 2010;6:561-71.
- 32 Sheno S, Wallace CA. Remission in juvenile idiopathic arthritis: current facts. *Curr Rheumatol Rep* 2010;12:80-6.

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ANSWERS TO ENDGAMES, p 113. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

T scores and z scores

Answers a, b, and d are true, whereas c is false.

ON EXAMINATION QUIZ

Chlamydia screening

Answer E is correct.

ANATOMY QUIZ

Axial computed tomography image through the base of the skull (bone windows)

- A Carotid canal
- B Jugular foramen

CASE REPORT

Repeated falls and broken bones

- 1 The patient has sustained two consecutive low energy fractures from a fall at low height. Both injuries suggest fragility fractures of the bone, and underlying osteoporosis is the most likely cause.
- 2 Dual energy x ray absorptiometry (DXA) should be performed to measure bone mineral density.
- 3 Risk of further fractures can be assessed by the WHO fracture risk assessment tool (FRAX), but a patient who has already had two fragility fractures has a high risk of further fracture and formal risk assessment may not be necessary.
- 4 All patients need appropriate lifestyle advice on regular physical activity, alcohol consumption, and smoking cessation. Multifactorial falls risk assessment and appropriate interventions should also be considered. Treatment with calcium and vitamin D; antiresorptive agents such as bisphosphonates, oestrogens, and related agents; strontium; or parathyroid hormone can reduce the risk of further fractures.