New advances in juvenile spondyloarthritis

Shirley M. L. Tse and Ronald M. Laxer

Abstract | Juvenile spondyloarthritis (SpA) is a distinct disease to adult SpA, and usually manifests as peripheral arthritis and enthesitis. Importantly, many patients with juvenile SpA continue to be at risk of developing ankylosing spondylitis during their disease course. In this Review, the classification and diagnostic criteria, clinical manifestations and treatment guidelines for juvenile SpA will be discussed. Advances in the diagnosis of and management strategies for juvenile SpA will lead to earlier recognition, appropriate treatment and improved rates of inactive disease, which should lead to improved patient outcomes and quality of life.

Tse, S. M. L. & Laxer, R. M. *Nat. Rev. Rheumatol.* **8**, 269–279 (2012); published online 10 April 2012; doi:10.1038/nrrheum.2012.37

Introduction

Spondyloarthritis (SpA) encompasses a group of inflammatory arthritides with overlapping features that can eventually affect the spine and/or sacroiliac joints (SIJ). SpA usually begins in the third or fourth decade of life, but 10–20% of patients actually experience symptoms in their childhood; SpA accounts for up to 15–20% of arthritis in children. Progression to ankylosing spondylitis (AS) in both adults and children with SpA remains unpredictable. In contrast to adult SpA, juvenile SpA rarely has axial involvement (spine or SIJ) at onset, but usually presents with lower-limb arthritis and enthesitis.[1] Consequently, juvenile SpA is often referred to as an undifferentiated form of SpA. As this disease is a common form of childhood arthritis and has the potential to evolve to AS, identifying patients at risk of axial disease is critical so that earlier therapeutic intervention can be instituted. This Review will highlight the unique features of juvenile SpA, summarizing the classification, clinical features, therapeutic strategies and outcomes.

Classification

As juvenile SpA encompasses undifferentiated and differentiated forms (Box 1) and has clinical features distinct from adult SpA, using the current pediatric classification systems or applying the adult SpA classification criteria (discussed elsewhere in this Focus issue[2]) to this population could be challenging. Spine and/or SIJ involvement at presentation is infrequent in juvenile SpA and radiographic changes are late to develop.[3–5] Consequently, many patients with juvenile SpA will not meet the modified New York (mNY) criteria for AS.[6] In 2009, the Assessment in SpondyloArthritis international Society (ASAS) proposed classification criteria for axial SpA (axSpA),[7] which requires the presence of symptomatic back pain together with either imaging evidence of SIJ inflammation (on plain radiographs or MRI images), or with HLA-B27 positivity (see Supplementary Figure 1 online). Higher diagnostic certainty is conferred by imaging evidence of sacroiliitis in comparison with HLA-B27 positivity, in which case more SpA-associated features must be present to fulfill the classification criteria. The strict requirement for 3 months of symptomatic back pain in these criteria[7] might be problematic in applying them to children, as this manifestation is infrequent in juvenile SpA at disease onset,[3–5] even in those who have early evidence of sacroiliitis detected by MRI. Additionally, involvement of the hip—which is the most common site of axial involvement in juvenile SpA early in the disease course[8]—is not included in either the mNY[6] or ASAS classification criteria.[7]

The Amor[9–11] and European Spondyloarthropathy Study Group (ESSG) criteria[12] can be applied to children with SpA and represent the differentiated and undifferentiated forms of the disease, respectively. In these criteria, axial signs and symptoms of SpA are not a strict requirement for classification and other SpA features are also included, making these criteria useful in the classification of a juvenile SpA population. The new ASAS classification criteria[13] for peripheral SpA in adults who have predominantly arthritis, enthesitis or dactylitis performed better than the ESSG and Amor criteria, especially with regard to sensitivity. As patients with juvenile SpA typically present with peripheral involvement, this new classification system is relevant to pediatric patients and further validation studies are needed in this population to evaluate its performance.

Diagnostic or classification criteria for juvenile SpA have evolved over time and are summarized in Box 2. These criteria sets include seronegative enthesopathy and arthropathy (SEA) syndrome,[14] the Garmisch–Partenkirchen (G–P) criteria for juvenile SpA,[15] criteria for atypical SpA in children,[16] and the International League of Associations for Rheumatology (ILAR) classification criteria for juvenile idiopathic arthritis (JIA),

Competing interests
S. M. L. Tse declares competing interests with the following companies: Abbott, Schering–Plough (Merck) and Wyeth–Pfizer. See the article online for full details of the relationships.
R. M. Laxer declares no competing interests.

Division of Rheumatology, The Hospital for Sick Children, 555 University Avenue, University of Toronto, Toronto, ON, M5G 1X8, Canada (**S. M. L. Tse, R. M. Laxer**).

Correspondence to:
S. M. L. Tse
shirley.tse@sickkids.ca

Key points

- Juvenile SpA commonly manifests as peripheral arthritis and enthesitis affecting the lower extremities
- Spinal or sacroiliac joint involvement is infrequent at disease onset, but can develop during the disease course
- A single diagnostic or classification system that is representative of the juvenile SpA population is still needed
- MRI, whole-body MRI and power Doppler ultrasonography are useful imaging tools for the early detection and monitoring of disease activity in the joints and entheses
- Establishment of treatment guidelines with early and appropriate use of anti-TNF agents will assist in improving the outcomes of patients with juvenile SpA

Box 1 | Forms of juvenile SpA

Undifferentiated forms
- Seronegative enthesopathy and arthropathy syndrome
- Enthesitis-related arthritis (juvenile idiopathic arthritis subtype)

Differentiated forms
- Juvenile ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Arthritis associated with inflammatory bowel disease

Abbreviation: SpA, spondyloarthritis.

which are now used by most pediatric rheumatologists.[17,18] Juvenile SpA is represented within several subtypes of JIA: enthesitis-related arthritis (ERA), psoriatic arthritis (PsA) and some types of undifferentiated arthritis. This classification system, however, also excludes reactive arthritis and might not be able to capture all patients with juvenile AS. For example, a patient with juvenile AS who is HLA-B27 positive with isolated radiographic evidence of sacroiliitis (fulfilling mNY criteria), but without peripheral arthritis or enthesitis, would be unclassifiable by ILAR criteria. This misclassification occurs primarily because the definition used for arthritis is clinical (arthritis defined as effusion or limited range of motion with joint pain and/or tenderness) and does not include imaging evidence, which makes it difficult to apply these criteria to the SIJ. Furthermore, the ILAR classification system[17,18] places patients with both axial (sacroiliitis) and peripheral involvement into the ERA subtype, which is considered a form of undifferentiated SpA and not representative of AS.

Evaluation of the ESSG and Amor criteria in children has shown equivalent specificity but less sensitivity compared with using these criteria in adults with SpA.[19,20] The Amor criteria had higher accuracy than the ESSG criteria (94.6% versus 90.3%, respectively).[19,20] Only two studies have compared the criteria sets developed specifically for juvenile SpA (see Supplementary Table 1 online). Kasapcopur *et al.*[21] studied Turkish children with juvenile SpA ($n = 62$, undifferentiated and differentiated forms determined by expert physician opinion) or JIA ($n = 64$, excluding ERA and juvenile PsA). Highest sensitivity (95.2%) and specificity (98.4%) were associated with the G–P criteria and the atypical SpA in children criteria, respectively. However, none of the pediatric criteria performed well enough to replace the use of the ESSG or Amor criteria. Joos *et al.*[22] performed a similar validation study in Belgian children with late-onset pauciarticular juvenile chronic arthritis (JCA) compared with patients with other forms of JCA. Highest sensitivity was achieved by the G–P criteria (97.7%) and the lowest using SEA syndrome criteria (44.2%). All juvenile SpA criteria demonstrated high specificity (90–98%). Overall, the G–P criteria performed best even when compared with the ESSG or Amor criteria. Both studies are limited by the patient numbers and different juvenile SpA populations studied (that is, predominantly undifferentiated or mixed undifferentiated and differentiated SpA).[21,22]

Whether a separate classification system is truly needed for juvenile SpA or whether the adult criteria can be applied directly, or with some modification, to the pediatric population remains uncertain. The challenge with classification of juvenile SpA is that heterogeneity exists in the disease phenotype, and in the different sets of criteria. Further work is needed, including a consensus towards a classification criteria set that is inclusive of both the undifferentiated and differentiated forms of juvenile SpA, but with specific criteria to further separate patients into homogeneous SpA subtypes. Alternatively, the undifferentiated and differentiated forms of juvenile SpA could be considered separate from JIA, and perhaps akin to the subtypes in adult SpA classification criteria, to move towards grouping patients into predominantly axial or peripheral SpA.

Clinical features

Articular manifestations

Apart from hip involvement, arthritis in juvenile SpA is predominantly peripheral and, unlike adult SpA, spine and/or SIJ involvement is uncommon at presentation.[3–5] Typically, the joints of the lower limbs are affected. Unique to juvenile SpA is tarsitis (inflammation of the intertarsal bones, overlying tendons, entheses and soft tissue) causing a painful, swollen and restricted midfoot (Figure 1).[23] Up to one-third of patients with juvenile SpA (according to ESSG criteria) reported tarsitis at onset.[24] Infrequently, upper extremity involvement can occur and usually involves the shoulder, sparing the small joints of the hands. Asymmetric oligoarthritis of the lower limbs is the form of the disease most prevalent at presentation, but polyarthritis occurs in up to 25% of patients at onset.[25]

Spinal and/or SIJ involvement can develop within 5–10 years from disease onset.[26–30] Such involvement within 3–5 years of disease onset has been reported in a population of Mexican children, with some patients even reporting axial symptoms within the first year of onset.[27,31] This observation has not occurred in other cohorts of juvenile SpA worldwide and could reflect either the unique environmental or genetic influences in the Mexican cohort, referral bias to the various health-care centers, and/or different inclusion criteria for the patient cohorts in each of the long-term studies. Axial symptoms can exhibit as pain or stiffness in the lower back or buttock and are often exacerbated by inactivity (such as sitting

for prolonged periods). Limited spinal mobility can be screened for using the modified Schober's test.[4]

Enthesitis, especially involving the lower limbs, occurs in 60–80% of patients (Figure 1).[25] Enthesitis is more common and affects more sites in juvenile SpA than in adult SpA. SpA should be suspected in children complaining of knee, foot or heel pain. Inspection for swelling and palpation for tenderness at the entheseal insertional sites should be performed, especially at the patellar ligament insertion sites (10, 2 and 6 o'clock positions of the patella), tibial tuberosity, Achilles tendon insertion and plantar fascial insertion into the metatarsal heads or calcaneus. In our opinion, it is important to exclude Osgood Schlatter disease before making a diagnosis of enthesitis involving the tibial tuberosity. In 32 newly diagnosed patients with ERA, Weiss *et al.*[33] reported that 66% of patients had at least one tender enthesis at diagnosis, whilst 44% had more than two entheseal sites involved. The most frequent enthesitis locations were reported as inferior pole of the patella (50%), plantar fascial insertion into the calcaneus (38%) or metatarsal head (22%), and Achilles tendon insertion into the calcaneus (22%).[33] Enthesitis was often persistent and the odds of having active enthesitis at 6 month follow-up increased significantly with the number of tender entheses at initial evaluation (odds ratio = 2.18).

Extra-articular manifestations

In children, uveitis and gastrointestinal involvement are the most common extra-articular features. Uveitis in patients with ERA is symptomatic and contrasts with the typical asymptomatic anterior uveitis associated with oligoarthritis or polyarthritis in patients with JIA. Gastrointestinal involvement can manifest as classic symptoms of inflammatory bowel disease, with subclinical gastrointestinal inflammation detected only endoscopically.[34,35] Slow growth and poor weight gain can be the first clues to gastrointestinal involvement. Alongside the psoriasis rash, dactylitis and nail pits are also common in patients with juvenile PsA. Stoll *et al.*[36] reported two distinct phenotypes in juvenile PsA. The first comprises of young (<5 years of age) females who are antinuclear antibody (ANA)-positive, and more likely to have dactylitis and a polyarticular onset. The second phenotype involves patients who are older age (>5 years), of equal gender distribution, who are ANA-negative and have more enthesitis, axial joint involvement and a persistent oligoarticular involvement. Finally, extra-articular manifestations seen in adult SpA (such as genitourinary involvement, apical pulmonary fibrosis or cardiac conduction abnormalities) are uncommon in juvenile disease. By contrast, valvular abnormalities in juvenile SpA, in particular aortic insufficiency, has been reported at similar rates to those in adult SpA.[37]

Imaging features

As radiographic evidence of juvenile SpA—especially in the SIJ—is delayed and might under-represent clinically active disease, clinicians are moving towards using imaging modalities such as MRI (Figure 2) and ultrasonography for early detection and monitoring of disease activity in the joints and entheses. Importantly, these technologies represent more sensitive methods for earlier detection of disease activity without the use of ionizing radiation and are safer to use in children than radiography, CT or radionuclide bone scans.

Contrast-enhanced MRI has detected early axial disease in juvenile SpA (modified ESSG criteria) and identified acute and chronic sacroiliitis with higher sensitivity than conventional radiography.[38,39] A comparison of MRI (short T1 inversion recovery) to standard radiography of the pelvis (normal in all patients) was carried out for the diagnosis of 11 patients with juvenile AS (ASAS criteria) with low back pain (73% HLA-B27 positive, mean age 12 years, mean duration of back pain 12 months).[40] Sacroiliitis was confirmed in all patients by pelvic MRI and additional signs of enthesitis–osteitis were noted in the pubic symphysis (91%), greater/lesser trochanter (55%), coxafemoral (45%), iliac crest (27%), and ischium pubis (27%) regions.[40]

Box 2 | Diagnostic or classification criteria for juvenile SpA

SEA syndrome[14]
- Onset of musculoskeletal symptoms before age 17 years
- Absence of RF and antinuclear antibodies
- Enthesopathic signs
- Arthralgias or arthritis

Garmisch–Partenkirchen criteria[15]
- Major: asymmetrical oligoarthritis with involvement of hip, knee or ankle joint; enthesopathy; pain of the lumbar spine or the sacroiliac region; acute iridocyclitis
- Minor: peripheral arthritis of ≥5 joints; male sex; disease onset after age 6 years; HLA-B27$^+$; (suspicion of) SpA in the family history
- Definition fulfilled with two major criteria or 1st two major criteria in combination with two minor criteria

Atypical SpA in children[16]
- Major: SpA family history; enthesopathy; arthritis of digital joints; sacroiliitis; HLA-B27$^+$; frequent recurrence of arthritis and arthralgias
- Minor: disease onset after 10 years; male sex; involvement of lower extremities; acute irdocyclitis or conjunctivitis; arthritis of hip joint(s); manifestation after history of enteritis
- Definition fulfilled with four major criteria, or three major plus three minor criteria

ILAR JIA classification[17,18]
- Arthritis of unknown etiology, onset before age 16 years, symptoms persistent for ≥6 weeks
- Subtypes: systemic; oligoarthritis (persistent or extended); RF$^-$ polyarthritis; RF$^+$ arthritis; PsA; ERA; undifferentiated arthritis
- ERA classification: arthritis and enthesisitis; or arthritis or enthesisitis with ≥2 of SIJ tenderness and/or inflammatory spinal pain, HLA-B27$^+$, family history of HLA-B27-associated disease in a 1st degree relative, acute anterior uveitis or onset of arthritis in a boy ≥6 years
- ERA exclusions: psoriasis in patient or 1st degree relative; IgM RF; systemic arthritis; arthritis fulfilling two JIA categories
- PsA classification: arthritis and psoriasis; or arthritis with ≥2 of dactylitis, nail pits or onycholysis, or psoriasis in a 1st degree relative
- PsA exclusions: arthritis in HLA-B27$^+$ male after 6th birthday; presence or history of AS, ERA, sacroiliitis with IBD, reactive arthritis or acute anterior uveitis in 1st degree relative; IgM RF; systemic JIA; arthritis fulfilling two JIA categories

Abbreviations: +, positive; –, negative; AS, ankylosing spondylitis; ERA, enthesitis-related arthritis; IBD, inflammatory bowel disease; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; SEA, seronegative enthesopathy and arthropathy; SIJ, sacroiliac joints; SpA, spondyloarthritis.

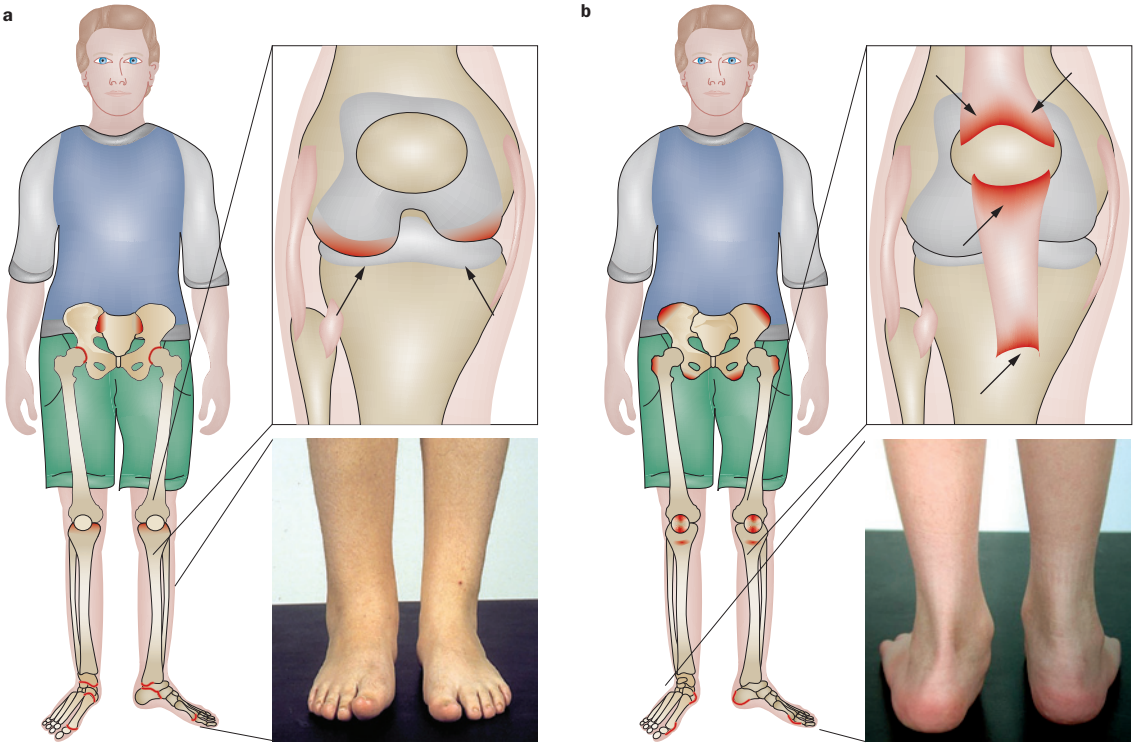

Figure 1 | Clinical manifestations of juvenile SpA. The regions in the lower extremities and pelvis that are frequently affected by **a** | arthritis and **b** | enthesitis are depicted by the black arrows and red areas. The photograph on the left (a) shows a patient with tarsiitis involving the right foot. The photograph on the right (b) shows a different patient with swelling of the right Achilles tendon insertion into the calcaneus. The areas of the knee affected by enthesitis are depicted by the black arrows illustrating the tendon attachment into the bone. Abbreviation: SpA, spondyloarthritis.

Rachlis *et al.*[41] evaluated whole-body MRI in monitoring disease activity, and correlated the findings to those from clinical examination in 23 patients with ERA. Whole-body MRI identified the characteristic lesions (arthritis and enthesitis) expected in patients with ERA, and was superior to clinical examination for the hips, SIJ and spine. In fact, for enthesitis, clinical examination overestimated disease activity in the periphery, making whole-body MRI an important tool to evaluate entheseal disease.[41] Importantly, these findings demonstrate that whole-body MRI potentially serves as an objective tool in the early detection and monitoring of disease activity in juvenile SpA.

Ultrasonography with power Doppler seems to be useful in the early detection of clinically silent enthesitis. Enthesitis on power Doppler ultrasonography images was examined in 26 patients with JIA (35% with ERA) and 41 healthy children.[42] No evidence of enthesitis was found in the healthy controls; overall, enthesitis confirmed by power Doppler ultrasonography was found in 9.4% of all patients with JIA, but was most prevalent in patients with ERA (70%).[42] In half of the sites with evidence of enthesitis by ultrasonography, the clinical examination was normal.

The use of MRI and/or ultrasonography seems to be promising in the early detection and monitoring of disease activity. However, some of the inconsistencies between imaging findings and clinical examination highlight that further work is needed to correctly interpret and correlate them with clinically relevant disease activity in juvenile SpA.

Genetic markers

The major genetic association with SpA, especially in AS, has been attributed to the MHC class I molecule HLA-B27. The influence of this molecule can be seen in HLA-B27-positive relatives of patients with AS, 20% of whom will eventually develop the disease.[43] However, there must be other genetic or environmental influences linked to SpA disease susceptibility as <5% of HLA-B27-positive individuals actually develop SpA. Genetic factors implicated in the development of SpA in adults are summarized in another Review in this Focus issue.[44]

Genetic studies in juvenile SpA populations have been sparse and limited by patient numbers. HLA-B27 is found in 60–80% of patients with juvenile SpA. A study conducted in 56 Latvian children with JIA (44% with ERA) who were *HLA-B27*-positive demonstrated eight *HLA-B27* subtypes with *HLA-B*2705* most commonly associated with ERA.[45] The authors also found that the *HLA-B27* subtypes might be useful in prediction of treatment response. A 2011 study by Hinks *et al.*[46] examined *ERAP1* (AS-associated gene) and *IL23R* (AS and PsA-associated gene) in patients with JIA ($n = 1{,}054$ including 65 with ERA, 76 with PsA and 24 with undifferentiated disease) and healthy individuals

as controls ($n = 5{,}200$). *ERAP1* was most strongly associated with the ERA subtype ($P = 0.005$). *IL23R* was significantly associated with PsA ($P = 0.04$), and there was a trend towards association in the ERA subtype. Neither *ERAP1* or *IL23R* were associated with the other JIA subtypes. It should be noted that both studies were underpowered; thus, future studies with a larger ERA cohort will be necessary to further explore and validate these findings. Further research should also study—and attempt to replicate—the genes implicated in adult SpA in the juvenile SpA population. This work could prove useful in understanding susceptibility to and pathogenesis of the various SpA phenotypes, as well as act as an adjunct to *HLA-B27* testing in making a diagnosis.

Treatment

NSAIDs provide symptomatic relief in juvenile SpA. Studies of adults with AS suggest that continuous NSAID use can result in disease remission.[47,48] Intra-articular steroid injections help control local and persistent arthritis and can even be administered into the SIJ with image guidance. In our experience, corticosteroids (oral or intravenous) can be administered for rapid control of severe disease, but are limited to short-term use owing to the adverse effects in children, especially with respect to bone health and linear growth.

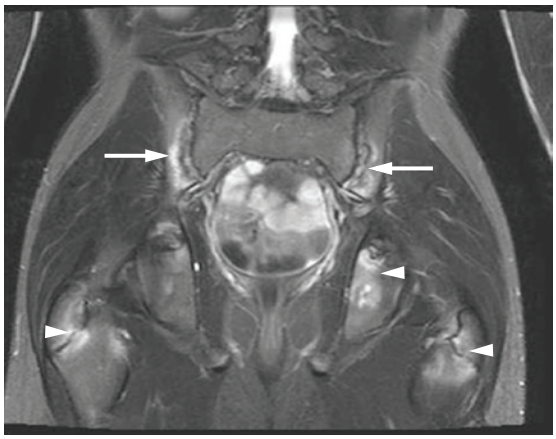

Figure 2 | MRI manifestations of juvenile SpA. The image is a STIR sequence obtained in the coronal plane in a 14-year-old boy with ERA (HLA-B27 positive). Fluid and pathology appear bright, as does spinal fluid. Increased signal abnormality is observed around bilateral triradiate cartilages and greater trochanteric apophyses (arrowhead), frequent areas of involvement for ERA. Also, signal abnormality appears on the iliac side of the sacroiliac joints bilaterally around more curvilinear dark sclerotic subchondral areas representing erosions and sacroiliitis (arrows). Abbreviations: ERA, enthesitis-related arthritis; SpA, spondyloarthritis; STIR, short T1 inversion recovery.

DMARDs

Two randomized placebo-controlled studies have shown sulfasalazine to be effective in patients with juvenile SpA. Burgos-Vargas *et al.*[49] reported that the only statistically significant difference between the sulfasalazine and the placebo group was confined to patient and physician assessment of improvement. A second trial reported that sulfasalazine was effective in controlling disease activity, safe and that the effects were sustained for many years.[50] Open-labeled studies of sulfasalazine treatment in juvenile SpA have also reported improvement in the majority of patients, with some even achieving remission.[51–54]

As arthritis in juvenile SpA is predominantly peripheral, methotrexate has also been used on the basis of efficacy and safety data from controlled studies in JIA.[55–57] However, the studies did not include patients with ERA and no controlled studies of methotrexate therapy in juvenile SpA have been performed.

For patients with juvenile SpA, in whom peripheral involvement of joints is more prevalent than in adults, the data we have discussed would support the use of DMARDs (sulfasalazine preferably over methotrexate) in these patients. Whether sulfasalazine has any benefit for those with juvenile SpA who have axial disease is still unclear, and biologic therapies would be recommended for such patients.

Biologic agents

Only one randomized placebo-controlled trial of biologic agents for juvenile SpA (ESSG criteria) has been performed.[58] Infliximab treatment resulted in a statistically significant improvement in arthritis, enthesitis, inflammatory markers, pain and physical function in 12 patients treated with infliximab compared with14 patients who received placebo.[58] Subsequently, all 26 patients entered into an extension phase.[59] At 52 weeks, all patients demonstrated sustained improvement. No adverse events were reported.

Three open-label observational studies have examined the efficacy of etanercept in juvenile SpA. Treatment of eight patients with refractory ERA with etanercept (0.2–0.8 mg/kg twice weekly injections) resulted in rapid and sustained improvement (>50%) in arthritis, enthesitis, inflammatory markers and morning stiffness over 104 weeks of treatment.[60] In a 12-month study of four patients with refractory juvenile SpA and ERA (patients fulfilled both ESSG and ILAR criteria) treated with etanercept (0.4 mg/kg twice weekly), all patients improved and achieved disease remission by 6 months.[61] In the follow-up study at 3–6 years, all patients remained in remission without any adverse events.[62] One patient from this trial had serial MRI and color power Doppler ultrasonography scans of the knees performed, which confirmed the rapid improvement and resolution of arthritis and enthesitis by 6 months and sustained remission to the follow-up imaging at 2 years.[63] Lastly, in a retrospective study of 20 patients with ERA receiving treatment with anti-TNF agents (19 on etanercept, one on infliximab), the remission rates at 3, 6 and 12 months were reported as 59%, 70% and 70%, respectively. Inflammatory markers decreased by ~90% by 3 months, and axial pain improved but required a mean of 6 months of treatment for optimal response.[64]

Two open-label observational studies with infliximab have been reported.[61,65] Two patients with juvenile AS (mNY criteria) treated with infliximab showed a rapid

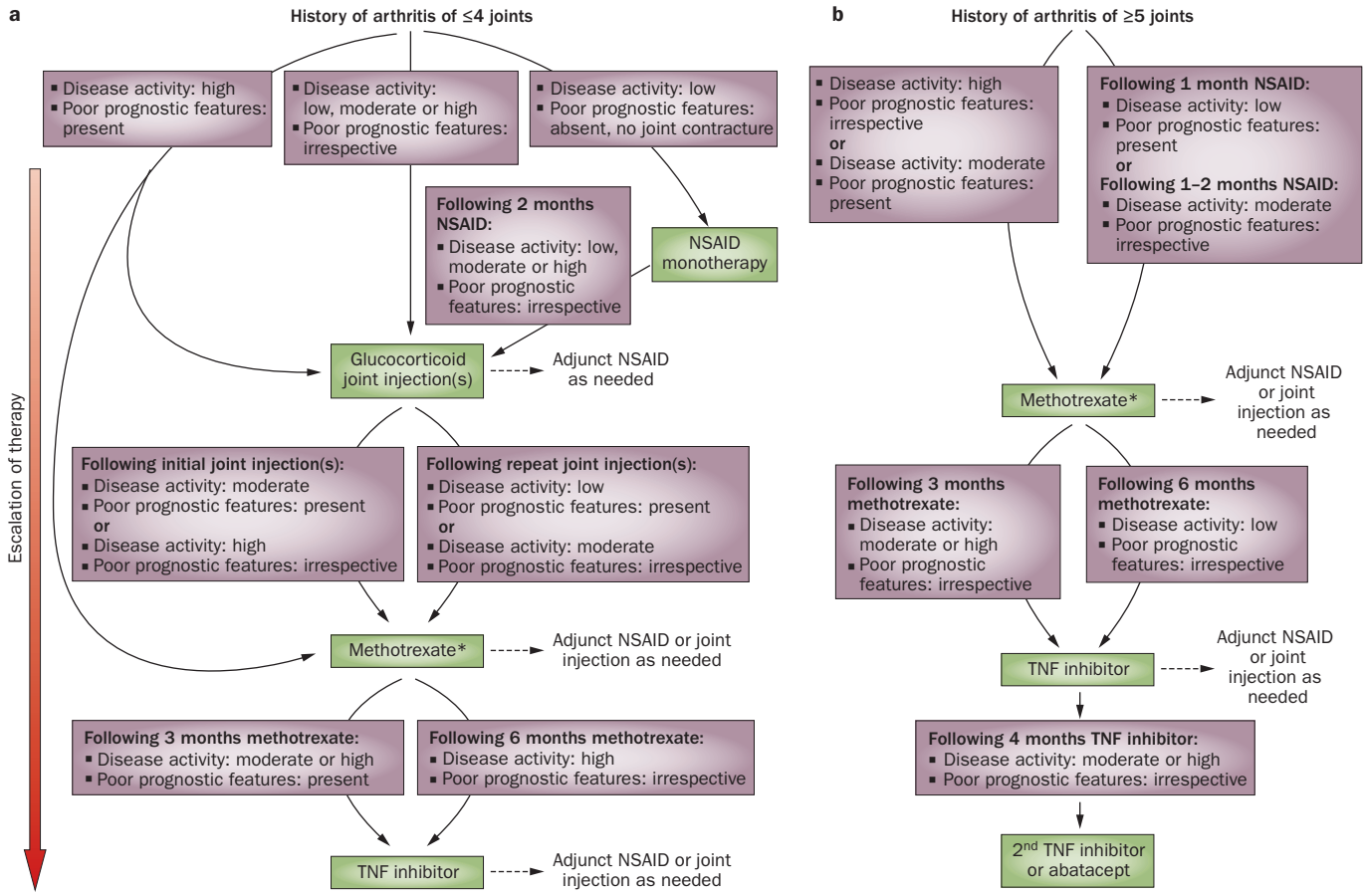

Figure 3 | 2011 ACR treatment recommendations for JIA. The treatment algorithms developed for JIA by the ACR can be applied to juvenile SpA.[67] *Sulfasalazine can be substituted for methotrexate in patients with ERA. Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis. Permissions obtained from Wiley © Beukelman, T. *et al. Arthritis Care Res.* **63**, 465–482 (2011).

and sustained improvement in their arthritis, enthesitis, inflammatory markers and physical function.[65] Similarly, in a 12-month study, eight patients with refractory ERA treated with infliximab showed improvement in these parameters and all achieved disease remission by 6 months of therapy.[61] In the extension phase with 3–6 year follow-up, all eight patients remained in remission.[62] No adverse events were reported in either study.[61,62]

Finally, from a multicenter Dutch observational biologic registry, 22 patients with ERA (68% HLA-B27 positive, median follow-up duration 1.2 years, refractory to one or more DMARD) treated with anti-TNF agents (20 on etanercept, one on adalimumab, one on infliximab, two switched from etanercept to either adalimumab or infliximab) showed that inactive disease was achieved in 32%, 38% and 64% after 3, 15 and 27 months, respectively, of treatment.[66] In contrast to the previously described studies, the Dutch registry showed that sustained disease remission was more difficult to achieve. Although no patients were able to discontinue their anti-TNF agents, the patients tolerated these agents and no serious adverse events were reported.

The American College of Rheumatology (ACR) treatment recommendations for JIA were published in 2011 and define treatment based on clinical parameters including: current treatment, disease activity and features of poor prognosis.[67] Most patients with ERA or juvenile PsA will be represented by the first three JIA treatment groups: history of arthritis of ≤4 joints; history of arthritis ≥5 joints and active sacroiliac arthritis. The treatment guidelines for patients with active sacroiliitis are based on features of poor prognosis and disease activity levels and can be applied to the juvenile SpA population (Figure 3 and Box 3). Ideally, in patients with high disease activity and poor prognostic features, a TNF inhibitor is recommended following an adequate trial of NSAIDs for 1–2 months. Patients with isolated high disease activity or ongoing moderate disease activity can proceed to a TNF inhibitor after 3 months of methotrexate or sulfasalazine. Finally, patients with ongoing low disease activity and poor prognostic factors following 6 months of sulfasalazine treatment can also escalate treatment to a TNF inhibitor. By contrast, in patients without active sacroiliitis, TNF inhibitors are not considered until at least 3–6 months of methotrexate or sulfasalazine in addition to 1–2 months of previous treatment with NSAIDs and intra-articular glucocorticoid joint injections.

Some limitations exist with the current ACR recommendations.[67] The indicator of poor prognosis is based on radiographic evidence of damage (joint-space narrowing

or erosions). However, radiographic evidence of sacroiliitis is often delayed in patients with juvenile SpA and does not reflect clinically active disease. It would be useful to modify the indicator of poor prognosis to include evidence of disease on radiographs or MRI images and, specifically, detection of inflammatory lesions in the SIJ and/or spine using MRI. Additionally, no reference to the presence of HLA-B27 as a prognostic factor was made,[67] which is important given that the combination of MRI-evident sacroiliitis along with HLA-B27 positivity is highly predictive of developing AS.[68,69] Inflammatory markers for axial disease might not reflect clinically active disease and are often normal or only minimally elevated in patients with juvenile SpA. Consequently, monitoring disease activity is reliant on global assessments by the physician and patient and/or parent. Clinical parameters, such as back or buttock pain, are not included whilst normal back flexion is listed as a low disease activity parameter. Finally, enthesitis is not listed as a clinical parameter for either the peripheral or axial JIA treatment groups.

Recommendations have been made for the use of anti-TNF agents in adult SpA[70,71] (shown in Supplementary Figure 2 online and discussed elsewhere in this Focus issue[72]) and could be applicable to children. These recommendations support the presence of any SIJ or spinal inflammation or damage by any imaging modality as a poor prognostic feature necessitating the early use of TNF inhibitors, and are not reliant on radiographic evidence of damage as listed in the JIA treatment guidelines. High disease activity is defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and must be a score of four of higher. The BASDAI needs to be validated in juvenile SpA, although a preliminary study in the juvenile SpA–ERA population has confirmed it is reliable in this patient group.[73] Patients with axSpA who have high disease activity proceed to treatment with TNF inhibitors after failure of 4–6 weeks of NSAIDs. Despite the requirement for at least two different NSAIDs each for a minimum course of 2 weeks, NSAID inefficacy is declared earlier than in the JIA treatment guidelines, which require 1–2 months of NSAID monotherapy. For patients with concomitant or predominantly persistent peripheral manifestations, the use of a DMARD (preferably sulfasalazine) is either suggested, but not obligatory,[70] or limited to 3 months[75] before proceeding to the use of TNF inhibitors. Finally, the Canadian Rheumatology Association–SPARCC (Spondyloarthritis Research Consortium of Canada) recommendations define persistent peripheral inflammation as either synovitis or enthesitis, and do not limit disease activity only to the presence of arthritis.[75]

In summary, the development of treatment guidelines for juvenile SpA has started, and further work is warranted to ensure they are appropriate and applicable to the spectrum of features in juvenile SpA. Most importantly, indications for early and appropriate use of TNF inhibitors need to be defined for patients with axial involvement and those with refractory peripheral arthritis and enthesitis.

Box 3 | Application of JIA treatment recommendations to juvenile SpA

Factors indicative of poor prognosis

- Radiographic damage of any joint (erosions or joint-space narrowing on plain radiographs)

Disease activity levels

- Low (must satisfy all criteria): normal back flexion; normal ESR or CRP levels; physician assessment score of <4 of 10; patient or parent assessment score of <2 or 10
- Moderate (does not satisfy either the low or high activity criteria): one or more features greater than low disease activity levels and <2 high disease activity features
- High (must satisfy >2 features): ESR or CRP >2 times the upper limit of normal; physician assessment score ≥7 of 10; parent or patient assessment score of ≥4 of 10

Initiation of TNF recommended

- Scenario 1: adequate trial of NSAIDs (up to 2 months); high disease activity; feature of poor prognosis present
- Scenario 2: methotrexate for 3 months; high disease activity; irrespective of poor prognosis features
- Scenario 3: methotrexate for 3 months; moderate disease activity; feature of poor prognosis present
- Scenario 4: methotrexate for 6 months; moderate disease activity; feature of poor prognosis absent
- Scenario 5: sulfasalazine for 3 months; moderate or high disease activity; irrespective of feature of poor prognosis
- Scenario 6: sulfasalazine for 6 months; low disease activity; feature of poor prognosis present

Adapted from 2011 ACR criteria for JIA.[67] Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis. Permissions obtained from Wiley © Beukelman, T. *et al. Arthritis Care Res.* **63**, 465–482 (2011).

Outcome

The disease course of juvenile SpA is variable, with disease remission reported for 17–39% of patients with juvenile SpA and up to 44% for those with ERA.[29,30,75,76] The variability in prognosis and outcomes is related to the differences in case definition and clinical outcome measures reported. The outcomes of patients with undifferentiated forms of juvenile SpA or ERA are summarized in Table 1. In contrast to an initial study that suggested better physical function in patients with ERA, studies over the past decade have all demonstrated a worse prognosis with poorer physical function, higher pain scores and ongoing disease activity in these patients, in comparison.[29,30,77,78] Up to 40% of patients eventually developed AS (mNY criteria).[28–30] Moreover, ongoing enthesitis is common and a large proportion of patients with ERA had damaged joints (35%), with the hip (29%) being the most common joint affected.[78] None of the patients in this study received biologic therapy; earlier treatment with biologic agents might have improved their disease course.

Poor prognostic predictors identified in the past decade included those for failure to achieve remission (presence of AS in a first degree relative, *HLA-DRB1*08* and ankle arthritis within the first 6 months), development of sacroiliitis (persistently elevated inflammatory markers or ESR, hip arthritis within first 6 months) and poor physical health (female sex, family history of AS and high numbers of affected joints within first 6 months).[29] Disability (high score on the Childhood

Table 1 | Outcomes in juvenile SpA

Study	Population	HLA-B27 positive (%)	Mean follow-up (years)	Summary of outcomes for those with juvenile SpA
Undifferentiated juvenile SpA				
Minden *et al.* (2002)[30]	ERA (*n*=33) versus JIA (*n*=182)	24.0	16.0	Better HAQ Disease remission rate in 18% (2nd lowest) 39% developed AS (mNY criteria), 36% with probable AS
Flato *et al.* (2006)[29]	ERA (*n*=55) versus JIA (*n*=205: oligoarthritis or polyarthritis)	85.0	15.3	Worse HAQ Poorer physical health and increased body pain (SF-36) Disease remission in 44% 35% developed AS (mNY criteria, 75% had decreased spinal mobility
Selvaag *et al.* (2005)[77]	Juvenile SpA (*n*=12: 3 juvenile AS [mNY criteria], 4 SEA, 5 juvenile PsA) versus juvenile RA (*n*=185)	50.0	3.0	Worse CHAQ (physical function) Highest pain scores and patient/physician global assessment of disease
Oen *et al.* (2010)[79]	ERA (*n*=36) versus JIA (*n*=318)	59.0	0.5	50% ongoing active arthritis (median AJC=1) 31% ongoing active enthesitis, inactive disease activity in 19% (2nd lowest)
Sarma *et al.* (2008)[78]	ERA (*n*=49)	53.0	6.0 (median)	Abnormal HAQ in 75% (49% moderate to severe disability) 62.6% ongoing active enthesitis Disease remission in 8% 35% had evidence of radiologic damage (especially hips) 65.3% experienced lost years of education 28.6% had decreased spinal mobility
Juvenile-onset AS				
Calin *et al.* (1988)[82]	Juvenile-onset AS (*n*=135) versus adult-onset AS (*n*=135)	NA	Juvenile=24.5 Adults=23.5	Better employment rate More hip replacement
Stone *et al.* (2005)[83]	Juvenile-onset AS (*n*=326) versus adult-onset AS (*n*=2,021)	NA	Juvenile=18.3 Adult=13.4	Greater delay in diagnosis Worse BASFI Outcomes worse in females than in males Age and income status correlated to worse functional outcome
O'Shea *et al.* (2009)[4]	Juvenile-onset AS (*n*=84) versus adult-onset AS (*n*=183)	Juvenile=75 Adult=81	Juvenile=14.7 Adult=16.7	More peripheral and less axial features (spinal mobility impairment, radiographic involvement) Better BASFI, HAQ and quality of life (SF-36), and less fatigue Disease remission in 11%

Abbreviations: AJC, active joint count; AS, ankylosing spondylitis; BASFI, Bath Ankylosing Spondylitis Functional Index; CHAQ, Childhood Health Assessment Questionnaire; ERA, enthesitis-related arthritis; HAQ, Health Assessment Questionnaire; JIA, juvenile idiopathic arthritis; mNY, modified New York; NA, not applicable; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SF-36, Short Form 36; SpA, spondyloarthritis.

Health Assessment Questionnaire [CHAQ]) and poor well-being within the first 6 months were found to be the best predictors of poor outcome at follow-up.[77]

From an inception cohort of Canadian children[79,80] with JIA (ILAR criteria), early outcomes at 6 months showed that treatment—NSAIDs (81%), DMARDs (47%), oral corticosteroids (8%) and intra-articular corticosteroid injections (3%)—resulted in normal to near-normal physical function (CHAQ) in the majority of juvenile patients with ERA. Disease control in those with juvenile PsA and those with oligoarthritis was similar.[79] The only independent predictor of inactive disease in all JIA subtypes was found to the Juvenile Arthritis Quality of Life Questionnaire, which is an instrument that scores disease activity, disability and influence on quality of life.[80]

Progression to AS can occur in about 40% of patients with undifferentiated juvenile SpA within 10 years of disease onset.[28–30] As previously discussed, early evolution to AS within 3–5 years has only been seen in a cohort of Mexican children.[27,31] Apart from the Mexican cohort, the rates of disease progression to AS in children (40%) remains lower than the reported rates in adults with undifferentiated SpA (60%) followed over a similar period of time.[81]

Comparison of the outcomes in adult and children with AS is summarized in Table 1. In general, patients with juvenile-onset AS are more likely to have peripheral involvement rather than spine and/or sacroiliac features. However, patients with juvenile-onset AS had more severe hip disease requiring total hip replacement (17% versus 4%, $P<0.01$) but had significantly better full-time employment rates (74% versus 56%, $P<0.01$) than those with adult-onset AS.[82] Uveitis was more common in juvenile-onset AS and was twice as likely to occur over the disease course compared with adult-onset AS.[3] Except for one study,[83] most studies on juvenile-onset AS reported better physical function and quality of life measures compared with adult-onset AS.

The comparison of clinical outcomes in juvenile SpA between studies remains a challenge as no disease activity measures specific to this condition exist. Disease activity measures for JIA are referred to as the pediatric core set.[84] Similarly, the Wallace criteria for inactive disease and clinical remission[85] have been published for JIA, but excluded the ERA subtype in the original

development. Both the pediatric core set and Wallace criteria for inactive disease (see Supplementary Table 2 online) are not optimal for juvenile SpA as most of these patients have oligoarthritis, their inflammatory marker levels are not necessarily elevated or a reliable indicator of disease and the current variables in these criteria do not capture SIJ or entheseal involvement.[84,85] Moreover, application of the adult SpA disease activity measures, core sets and definitions for improvement—BASDAI, DC-ART (Disease-Controlling AntiRheumatic Treatment), ASDAS (Ankylosing Spondylotis Disease Activity Score), ASAS 5/6 improvement criteria (all summarized here in an ASAS handbook[86])—to juvenile SpA is limited, mostly owing to the heavy emphasis and reliance on axial signs and symptoms in these definitions, which are not prevalent in the pediatric population. New disease activity measures need to be developed, or existing activity measures adapted, so that they can be applied to, and accurately represent, the juvenile SpA population.

The socioeconomic impact of treating JIA during the first year after diagnosis has been examined by Thornton *et al.*,[87] who reported that higher costs were associated with patients with ERA than other forms of JIA. In general, the highest health-care provider costs were attributed to consultant rheumatology appointments, referrals to other specialists, clinical imaging, drugs and laboratory tests. The higher costs incurred by patients with ERA are likely to be due to the increased need for clinical imaging (especially use of MRI).

Conclusions

Juvenile SpA is characterized by peripheral arthritis and enthesitis, and is distinct in its presentation compared with adult SpA. Despite the different phenotypes, preliminary work has suggested that there may be some shared genetic influences in both the adult and pediatric SpA populations. However, more studies in patients with juvenile SpA are needed to validate the known SpA genetic contributions and their role towards the disease pathogenesis, susceptibility and treatment response. Juvenile SpA is associated with morbidity, and high health-care costs, and up to 40% of patients continue to be at risk of developing AS during the disease course. This Review has highlighted some of the advances in the diagnosis and management of juvenile SpA, including the use of imaging techniques (MRI, whole-body MRI or power Doppler ultrasonography) in addition to the early and appropriate use of anti-TNF agents. Further work in refining the juvenile SpA classification, diagnostic criteria and treatment guidelines, as well as establishment of disease activity measures, will lead to earlier recognition, appropriate treatment, improved rates of inactive disease, possible alteration of the disease course and improvement in patient outcomes.

Review criteria

A search for original English-language published articles on PubMed was undertaken using the terms "juvenile, pediatric and/or childhood spondyloarthritis", "enthesitis related arthritis", "juvenile psoriatic arthritis", "classification", "treatment", "outcome", "imaging", "TNF α inhibitors", "axial and/or peripheral spondyloarthritis", alone and in combination. We also searched the reference lists of identified articles for further relevant papers. Additional references related to spondyloarthritis and other related topics were retrieved from the author's personal collection.

1. Burgos-Vargas, R. The juvenile-onset spondyloarthritides. *Rheum. Dis. Clin. North Am.* **28**, 531–560 (2002).
2. van Tubergen, A. & Weber, U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat. Rev. Rheumatol.* **8**, 253–261 (2012).
3. Lin, Y. C., Liang, T. H., Chen, W. S. & Lin, H. Y. Differences between juvenile-onset ankylosing spondylitis and adult-onset ankylosing spondylitis. *J. Chin. Med. Assoc.* **72**, 573–580 (2009).
4. O'Shea, F. D. *et al.* Comparison of clinical and radiographic severity of juvenile-onset versus adult-onset ankylosing spondylitis. *Ann. Rheum. Dis.* **68**, 1407–1412 (2009).
5. Baek, H. J. *et al.* Juvenile onset ankylosing spondylitis (JAS) has less severe spinal disease course than adult onset ankylosing spondylitis (AAS): clinical comparison between JAS and AAS in Korea. *J. Rheumatol.* **29**, 1780–1785 (2002).
6. van der Linden, S., Valkenburg, H. A. & Cats, A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* **27**, 361–368 (1984).
7. Rudwaleit, M. *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann. Rheum. Dis.* **68**, 777–783 (2009).
8. Kleinman, P., Rivelis, M., Schneider, R. & Kaye, J. J. Juvenile ankylosing spondylitis. *Radiology* **125**, 775–780 (1977).
9. Amor, B., Dougados, M. & Mijiyawa, M. Criteria of the classification of spondylarthropathies [French]. *Rev. Rhum. Mal. Osteoartic.* **57**, 85–89 (1990).
10. Amor, B. *et al.* Evaluation of the Amor criteria for spondylarthropathies and European Spondylarthropathy Study Group (ESSG). A cross-sectional analysis of 2,228 patients [French]. *Ann. Med. Interne (Paris)* **142**, 85–89 (1991).
11. Amor, B. In *50 ans de Rhumatologie…et l'avenir* 29–31 (Expanscience, Courbevoie, 2005).
12. Dougados, M. *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum.* **34**, 1218–1227 (1991).
13. Rudwaleit, M. *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann. Rheum. Dis.* **70**, 25–31 (2011).
14. Rosenberg, A, M. & Petty, R. E. A syndrome of seronegatvie enthesopathy and arthropathy in children. *Arthritis Rheum.* **25**, 1041–1047 (1982).
15. Hafner, R. Juvenile spondarthritis. Retrospective study of 71 patients [German]. *Monatsschr. Kinderheilkd.* **135**, 41–46 (1987).
16. Hussein, A., Abdul-Khaliq, H. & von der Hardt, H. Atypical spondyloarthritis in children: proposed diagnostic criteria. **148**, 513–517 (1989).
17. Petty, R. E. *et al.* Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J. Rheumatol.* **25**, 1991–1994 (1998).
18. Petty, R. E. *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J. Rheumatol.* **31**, 390–392 (2004).
19. Prieur, A. M. Spondyloarthropathies in childhood. *Baillieres Clin. Rheumatol.* **12**, 287–307 (1998).
20. Prieur, A. M. Spondylarthropathies in children. *Ann. Med. Interne (Paris)* **149**, 156–158 (1998).
21. Kasapcopur, O. *et al.* Evaluation of classification criteria for juvenile-onset spondyloarthropathies. *Rheumatol. Int.* **25**, 414–418 (2005).
22. Joos, R. *et al.* Sensitivity and specificity of criteria for spondyloarthritis in children with late onset pauciarticular juvenile chronic arthritis as well as their characteristics. *Clin. Exp. Rheumatol.* **27**, 870–876 (2009).
23. Burgos-Vargas, R., Pacheco-Tena, C. & Vazquez-Mellado, J. Juvenile-onset spondyloarthropathies. *Rheum. Dis. Clin. North Am.* **23**, 569–598 (1997).

24. Alvarez-Madrid, C., Merino, R., De Inocencio, J. & Garcia-Consuegra, J. Tarsitis as an initial manifestation of juvenile spondyloarthropathy. *Clin. Exp. Rheumatol.* **27**, 691–694 (2009).
25. Petty, R., Cassidy, J. T. in *Textbook of Pediatric Rheumatology* (eds Cassidy, J. T., Petty, R, Laxer, R. & Lindsley, C.) 272–286 (Elsevier, Amsterdam, 2011).
26. Burgos-Vargas, R. & Vazquez-Mellado, J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum.* **38**, 835–844 (1995).
27. Burgos-Vargas, R. & Clark, P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. *J. Rheumatol.* **16**, 192–197 (1989).
28. Cabral, D. A., Oen, K. G. & Petty, R. E. SEA syndrome revisited: a longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. *J. Rheumatol.* **19**, 1282–1285 (1992).
29. Flato, B. *et al.* Long-term outcome and prognostic factors in enthesitis-related arthritis: a case-control study. *Arthritis Rheum.* **54**, 3573–3582 (2006).
30. Minden, K. *et al.* Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum.* **46**, 2392–2401 (2002).
31. Burgos-Vargas, R. *et al.* Genuine ankylosing spondylitis in children: a case–control study of patients with early definite disease according to adult onset criteria. *J. Rheumatol.* **23**, 2140–2147 (1996).
32. Burgos-Vargas, R., Lardizabal-Sanabria, J. & Katona, G. Anterior spinal flexion in healthy Mexican children. *J. Rheumatol.* **12**, 123–125 (1985).
33. Weiss, P. F. *et al.* Enthesitis in an inception cohort of enthesitis-related arthritis. *Arthritis Care Res. (Hoboken)* **63**, 1307–1312 (2011).
34. Mielants, H. *et al.* The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. *J. Rheumatol.* **22**, 2273–2278 (1995).
35. Mielants, H. *et al.* Gut inflammation in children with late onset pauciarticular juvenile chronic arthritis and evolution to adult spondyloarthropathy—a prospective study. *J. Rheumatol.* **20**, 1567–1572 (1993).
36. Stoll, M. L. *et al.* Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum.* **54**, 3564–3572 (2006).
37. Stamato, T. *et al.* Prevalence of cardiac manifestations of juvenile ankylosing spondylitis. *Am. J. Cardiol.* **75**, 744–746 (1995).
38. Bollow, M. *et al.* Use of dynamic magnetic resonance imaging to detect sacroiliitis in HLA-B27 positive and negative children with juvenile arthritides. *J. Rheumatol.* **25**, 556–564 (1998).
39. Bollow, M. *et al.* Use of contrast-enhanced MR imaging to detect sacroiliitis in children. *Skeletal Radiol.* **27**, 606–616 (1998).
40. Yilmaz, M. H., Ozbayrak, M., Kasapcopur, O., Kurugoglu, S. & Kanberoglu, K. Pelvic MRI findings of juvenile-onset ankylosing spondylitis. *Clin. Rheumatol.* **29**, 1007–1013 (2010).
41. Rachlis, A. C. *et al.* Whole body MR imaging in juvenile spondyloarthritis: will it provide vital information compared to clinical exam alone? [abstract]. *Arthritis Rheum.* **63**, S292 (2011).
42. Jousse-Joulin, S. *et al.* Ultrasonography for detecting enthesitis in juvenile idiopathic arthritis. *Arthritis Care Res. (Hoboken)* **63**, 849–855 (2011).
43. van der Linden, S. M., Valkenburg, H. A., de Jongh, B. M. & Cats, A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum.* **27**, 241–249 (1984).
44. Reveille, J. D. Genetic basis of spondyloarthritis—beyond the MHC. *Nat. Rev. Rheumatol.* **8**, 296–304 (2012).
45. Stanevicha, V. *et al.* HLA B27 allele types in homogeneous groups of juvenile idiopathic arthritis patients in Latvia. *Pediatr. Rheumatol. Online J.* **8**, 26 (2010).
46. Hinks, A. *et al.* Subtype specific genetic associations for juvenile idiopathic arthritis: *ERAP1* with the enthesitis related arthritis subtype and *IL23R* with juvenile psoriatic arthritis. *Arthritis. Res. Ther.* **13**, R12 (2011).
47. Wanders, A. *et al.* Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum.* **52**, 1756–1765 (2005).
48. Jarrett, S. J. *et al.* MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. *Ann. Rheum. Dis.* **68**, 1466–1469 (2009).
49. Burgos-Vargas, R., Vazquez-Mellado, J., Pacheco-Tena, C., Hernandez-Garduno, A. & Goycochea-Robles, M. V. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. *Ann. Rheum. Dis.* **61**, 941–942 (2002).
50. van Rossum, M. A. *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.* **41**, 808–816 (1998).
51. Imundo, L. F. & Jacobs, J. C. Sulfasalazine therapy for juvenile rheumatoid arthritis. *J. Rheumatol.* **23**, 360–366 (1996).
52. Suschke, H. J. Treatment of juvenile spondylarthritis and reactive arthritis with sulfasalazine [German]. *Monatsschr. Kinderheilkd.* **140**, 658–660 (1992).
53. Job-Deslandre, C. & Menkes, C. J. Treatment of juvenile spondyloarthropathies with sulfasalazine [French]. *Rev. Rhum. Ed. Fr.* **60**, 489–491 (1993).
54. Huang, J. L. & Chen, L. C. Sulphasalazine in the treatment of children with chronic arthritis. *Clin. Rheumatol.* **17**, 359–363 (1998).
55. Woo, P. *et al.* Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum.* **43**, 1849–1857 (2000).
56. 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.* **50**, 2191–2201 (2004).
57. Giannini, E. H. *et al.* Methotrexate in resistant juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N. Engl. J. Med.* **326**, 1043–1049 (1992).
58. Burgos-Vargas, R. Efficacy, safety, and tolerability of Infliximab in Juvenile-onset Spondyloarthropathies (JO-SpA): results of the three-month, randomized, double-blind, placebo-controlled trial phase [abstract]. *Arthritis Rheum.* **56**, S319 (2007).
59. Burgos-Vargas, R., Casasola-Vargas, J. & Gutierrez-Suarez, R. A 3-month, double-blind, placebo-controlled, randomized trial of infliximab in juvenile-onset spondyloarthritis (SpA) and a 52-week open extension. *Clin. Exp. Rheumatol.* **26**, 745 (2008).
60. Henrickson, M. & Reiff, A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. *J. Rheumatol.* **31**, 2055–2061 (2004).
61. Tse, S. M., Burgos-Vargas, R. & Laxer, R. M. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. *Arthritis Rheum.* **52**, 2103–2108 (2005).
62. Tse, S. M. L, Burgos-Vargas, R., O'Shea F, Inman, R. & Laxer, R. Long term outcome of anti-TNF therapy in juvenile spondyloarthropathy. *Arthritis Rheum.* **56**, 898 (2007).
63. Tse, S. M., Laxer, R. M., Babyn, P. S. & Doria, A. S. Radiologic Improvement of juvenile idiopathic arthritis-enthesitis-related arthritis following anti-tumor necrosis factor-alpha blockade with etanercept. *J. Rheumatol.* **33**, 1186–1188 (2006).
64. Sulpice, M., Deslandre, C. J. & Quartier, P. Efficacy and safety of TNFalpha antagonist therapy in patients with juvenile spondyloarthropathies. *Joint Bone Spine* **76**, 24–27 (2009).
65. Schmeling, H. & Horneff, G. Infliximab in two patients with juvenile ankylosing spondylitis. *Rheumatol. Int.* **24**, 173–176 (2004).
66. Otten, M. H. *et al.* Tumor necrosis factor-blocking agents for children with enthesitis-related arthritis–data from the Dutch Arthritis and Biologicals in Children Register, 1999–2010. *J. Rheumatol.* **38**, 2258–2263 (2011).
67. 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. (Hoboken)* **63**, 465–482 (2011).
68. Flato, B. *et al.* The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. *Arthritis Rheum.* **46**, 986–994 (2002).
69. Bennett, A. N. *et al.* Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum.* **58**, 3413–3418 (2008).
70. Braun, J. *et al.* 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann. Rheum. Dis.* **70**, 896–904 (2011).
71. van der Heijde, D. *et al.* 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann. Rheum. Dis.* **70**, 905–908 (2011).
72. Sieper, J. Developments in therapies for spondyloarthritis. *Nat. Rev. Rheumatol.* **8**, 280–287 (2012).
73. Batthish, M. R. A. *et al.* Intra-rater Reliability of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in Children with Spondyloarthritis [abstract]. *Arthritis Rheum.* **62**, S95 (2010).
74. Maksymowych, W. P. *et al.* The Canadian Rheumatology Association/ Spondyloarthritis Research Consortium of Canada treatment recommendations for the management of spondyloarthritis: a national multidisciplinary

stakeholder project. *J. Rheumatol.* **34**, 2273–2284 (2007).
75. Minden, K. *et al.* Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. *J. Rheumatol.* **27**, 2256–2263 (2000).
76. Flato, B., Aasland, A., Vinje, O. & Forre, O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. *J. Rheumatol.* **25**, 366–375 (1998).
77. Selvaag, A. M. *et al.* Early disease course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3 year prospective study. *J. Rheumatol.* **32**, 1122–1130 (2005).
78. Sarma, P. K., Misra, R. & Aggarwal, A. Outcome in patients with enthesitis related arthritis (ERA): juvenile arthritis damage index (JADI) and functional status. *Pediatr. Rheumatol. Online J.* **6**, 18 (2008).
79. Oen, K. *et al.* Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. *Arthritis Care Res (Hoboken)* **62**, 527–536 (2010).
80. Oen, K. *et al.* Predictors of early inactive disease in a juvenile idiopathic arthritis cohort: results of a Canadian multicenter, prospective inception cohort study. *Arthritis Rheum.* **61**, 1077–1086 (2009).
81. Sieper, J., Braun, J., Rudwaleit, M., Boonen, A. & Zink, A. Ankylosing spondylitis: an overview. *Ann. Rheum. Dis.* **61** (Suppl. 3), iii8–iii18 (2002).
82. Calin, A. & Elswood, J. The natural history of juvenile-onset ankylosing spondylitis: a 24-year retrospective case-control study. *Br. J. Rheumatol.* **27**, 91–93 (1988).
83. Stone, M. *et al.* Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. *Arthritis Rheum.* **53**, 445–451 (2005).
84. Giannini, E. H. *et al.* Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum.* **40**, 1202–1209 (1997).
85. Wallace, C. A., Ruperto, N. & Giannini, E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J. Rheumatol.* **31**, 2290–2294 (2004).
86. Sieper, J. *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann. Rheum. Dis.* **68** (Suppl. 2), ii1–ii44 (2009).
87. Thornton, J. *et al.* Costing juvenile idiopathic arthritis: examining patient-based costs during the first year after diagnosis. *Rheumatology (Oxford)* **47**, 985–990 (2008).

Author contributions

Both authors contributed equally to researching data for the article. S. M. L. Tse wrote the article and R. M. Laxer reviewed and edited the manuscript before submission.

Supplementary information

Supplementary information is linked to the online version of the paper at www.nature.com/nrrheum