EXTENDED REPORT

Juvenile onset spondyloarthropathies: therapeutic aspects

R Burgos-Vargas

Juvenile onset spondyloarthropathy (SpA) is a term that refers to a group of human leucocyte antigen (HLA)-B27 associated inflammatory disorders affecting children under the age of 16 years, producing a continuum of clinical symptoms through adulthood. This disease is characterised by enthesopathy and arthropathy affecting the joints of the lower extremities and seronegativity for IgM rheumatoid factor and antinuclear antibodies. Children usually present with undifferentiated SpA and progress to differentiated forms over time. Except for the prevalence of some clinical features at onset, the pathogenic and clinical aspects of juvenile onset SpAs resemble those of the adult disease. Thus application of the same or similar therapeutic measures for both juvenile and adult onset SpAs seems logical. Current treatments for juvenile onset SpA provide symptomatic improvement, but do not alter disease progression. The increased expression of tumour necrosis factor alpha (TNFα) in synovial tissue of patients with adult and juvenile onset SpA and its correlation with infiltration of inflammatory mediators into the synovia suggest a significant pathogenic role of this cytokine. Clinical trials of anti-TNFα therapy in patients with adult onset SpA have demonstrated significant clinical improvement in inflammatory pain, function, disease activity, and quality of life in correlation with histological and immunohistochemical evidence of modulation of synovial inflammatory processes. These promising findings suggest that anti-TNFα therapy may confer similar benefits in patients with juvenile onset SpA.

Several extensive reviews of juvenile onset SpAs are available. This paper provides a brief overview of juvenile onset SpA and the treatment of the disease, with a view to potential new treatment approaches.

EPIDEMIOLOGY

Epidemiological data from open populations and clinical populations suggest that the prevalence, incidence, and relative frequency of juvenile onset SpA are increasing. Juvenile onset SpAs account for a significant proportion of children with juvenile arthropitides. Data from paediatric rheumatology clinics in Canada, the United Kingdom, and the United States indicate that juvenile onset SpAs account for a significant proportion of children presenting with juvenile arthritis. The Canadian study estimated the annual incidence for juvenile onset SpA (excluding psoriatic arthritis) at 1.44 per 100 000 children at risk (95% confidence interval 1.12 to 1.87), compared with an estimated annual incidence for all forms of chronic arthritis of 4.08 (95% CI 3.62 to 4.60).

Paediatric rheumatology clinics noted an increase in the prevalence of juvenile onset SpA from 0% to 16% in the 70s to 31% in the 80s. This may also reflect an increase in recognition of SpA in children, distinct from other rheumatic conditions including juvenile rheumatoid arthritis (JRA), following published descriptions in 1982 of SEA syndrome and HLA-B27 associated spondylarthritides and enthesopathy in children. None the less, today, the actual incidence of juvenile

Abbreviations: ANA, antinuclear antibodies; AS, anklylosing spondylitis; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IL, interleukin; JCA, juvenile chronic arthritis; JRA, juvenile rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; ReA, reactive arthritis; RF, rheumatoid factor; SEA, seronegative spondylarthropathy and arthritis; SpA, spondyloarthropathy; TNFα, tumour necrosis factor α; VAS, visual analogue scale
onset SpAs may be higher than reported because of several undefined factors: nomenclature, criteria for diagnosis, and classification; and lack of a clear boundary between the different arthropathies of childhood. Furthermore, in the case of juvenile onset AS, in which peripheral arthritis precedes symptomatic axial arthritis by 5–10 years, the absence of apparent inflammatory or structural changes manifesting as clinical or radiographic features may lead to misdiagnosis of the disease as JRA. Thus, a large proportion of patients with juvenile onset SpA may be misdiagnosed as having JRA or juvenile chronic arthritis (JCA).

**RELATIONSHIP WITH OTHER FORMS OF JUVENILE ARTHRITIS**

Children with early onset SpA have been classified within the oligoarticular/pauciarticular onset subgroups of JRA/JCA. Differential diagnosis between juvenile onset SpA and JRA/JCA includes a positive history of SpA in a first or second degree relative, high frequency of HLA-B27, male predominance (except in juvenile onset psoriatic arthritis), frequent enthesisitis, peripheral arthritis asymmetrically affecting the lower extremities, and absence of ANA and IgM RF. Enthesopathy and talal disease in children presenting with arthritis confined to the lower extremities differentiate juvenile onset AS from JRA within one year of symptoms. Today, juvenile onset SpA is recognised as a different subset within the various forms of juvenile arthritis; recently, the term “enthesitis related arthritis” and pertinent diagnostic criteria were proposed by the International League Against Rheumatism (ILAR) Task Force Group to identify this subset of paediatric patients.

**DISEASE PROFILE**

**Pathogenesis**

The role of HLA-B27 and bacteria in disease pathogenesis appears similar to that of adult onset forms. Age-related factors—for example, maturity of the immune and endocrine systems and bacterial exposure, appear to have an additional role in children.

**HLA-B27 and other genetic markers**

Sixty to 90 per cent of patients with juvenile onset SpA have the HLA-B27 antigen. At least 20 subtypes of HLA-B27 (named consecutively from B27*01) have been identified, of which HLA-B27*05 is the subtype most commonly found in juvenile onset SpA. Other non-HLA-B27 antigens may also contribute to AS in different patient populations.

HLA-B27 antigen may contribute to the pathogenesis of SpA through several proposed mechanisms: (a) presentation of bacterial antigens to CD8 lymphocytes; (b) mimicry of bacterial antigen molecules; (c) acquisition of antigenic properties after modification during bacterial infections; (d) modulation of presentation, processing, or elimination of Gram-negative pathogens; and (e) interference with antigen presentation to T lymphocytes. In addition, HLA-B27 derived peptides may be presented by major histocompatibility complex class II molecules to CD4 lymphocytes. These mechanisms suggest an interaction between HLA-B27 and the T cell response, possibly triggered by a bacterial antigen, as in the case of ReA.

**Bacterial infections and arthritogenic bacteria**

In adults, enteric and non-gonococcal urogenital bacterial infections are considered important triggers in the SpAs, specifically ReA. ReA has been associated, by the detection in synovial tissues of bacteria-specific antibodies or bacterial antigens, with *Salmonella*, *Shigella*, *Yersinia*, and *Chlamydia* infections. *Klebsiella* has also been implicated in the aetiology of AS. These findings, together with reports of molecular mimicry between some *Klebsiella*, *Salmonella*, *Yersinia*, and *Shigella* amino acid sequences and HLA-B27, represent the primary evidence for the role of bacterial infections in the pathogenesis of SpA. In addition, increased T lymphocyte response specific for the triggering of bacterial antigen has been demonstrated in synovial fluid taken from patients with ReA. However, very few studies have examined the interaction between bacteria, HLA-B27, and other genes in children with SpA. The micro-organisms implicated more frequently in children with ReA include *Salmonella spp.*, and *Yersinia enterocolitica*, but rarely *Shigella flexneri*, *Chlamydia pneumoniae*, and *Chlamydia trachomatis*. Non-enthesitis SpA is recognised as a different subset within the variable forms of juvenile arthritis; recently, the term “enthesitis related arthritis” and pertinent diagnostic criteria were proposed by the International League Against Rheumatism (ILAR) Task Force Group to identify this subset of paediatric patients.

**Gut**

In both children and adults, gut inflammation (in association with Crohn’s disease or ulcerative colitis) is closely linked to SpA, particularly AS and ReA. Ileocolonoscopy studies have shown that non-specific inflammatory lesions of the terminal ileum or colon mucosa occur in 75–80% of patients with JCA and are associated with a high risk of progression to AS. These findings correspond with ileocolonoscopic and clinical findings in adults with these forms of SpA. Non-specific IBD rarely causes a definitive clinical picture, but repeated histopathological and radionuclide studies of the gut may disclose acute and chronic inflammatory changes in the mucosa and submucosa of the terminal ileum and colon resembling Crohn’s disease and ulcerative colitis in more than two thirds of patients.

**Immune response**

The immune response of peripheral blood and synovial fluid cells, cytokines, and cell inflammatory mediators on the pathogenesis of SpA is the subject of continuing investigation. Cellular infiltrates in synovial tissue from peripheral and sacroiliac joints of adults with SpA show a predominance of CD4+ over CD8+ T lymphocytes and a significant percentage of CD14+ macrophages. TNFα, TNFβ, interferon γ, interleukin (IL)-4, IL-6, IL-2, and transforming growth factor β are also present in synovial tissue from adults and children with SpA.

In synovial tissue specimens from patients with juvenile onset SpA, expression of TNFα is prominent, consistent with high levels of TNFα mRNA seen in synovial tissues from adults with active AS. Increased production of TNFα correlates closely with increased infiltration of inflammatory cells (T cells and macrophages) into the synovia. TNFβ is also present in the synovia of patients with juvenile onset SpA, but to a smaller extent than TNFα. Increased production of these cytokines is associated with increased expression of the TNF receptor, p55, and to a smaller extent, p75. High levels of activation of CD8 cells also occur. Taken together, these findings suggest that TNF, particularly TNFα, may have a central role in mediating enhanced local inflammatory responses in juvenile onset SpA.

**CLINICAL MANIFESTATIONS**

The spectrum of disease manifestations is wide (table 1). Enthesopathy and arthropathy at peripheral sites are trademarks of juvenile onset SpA. Throughout time, the disease progresses from undifferentiated forms to differentiated SpA. Undifferentiated inflammatory conditions are characterised by peripheral enthesitis and arthritis, primarily affecting the lower limb entheses and joints, particularly the feet. This subgroup includes isolated episodes of arthritis, enthesitis, tendonitis, dactylitis, and SEA syndrome. SEA syndrome is associated with a high probability of evolution to a definite SpA, although it may also be an isolated form of juvenile onset SpA. In one study, 69% of children presenting with SEA syndrome developed definite or probable SpA within 11 years after symptom onset. Differentiated SpA includes conditions
with evidence of structural changes—that is, radiographic sacroiliitis, spinal disease, or tarsal ankylosis, extra-articular symptoms (for example, psoriasis or IBD), or laboratory features (for example, serological or bacteriological culture) diagnostic of ReA; IBD related arthropathy, ankylosing tarsitis, and adjacent bursae. Enthesitis often occurs at the feet (plantar fascia insertion, and less frequently, the Achilles insertion to the calcaneus).

Most patients presenting with both arthritis and enthesitis become symptomatic within the first year of diagnosis. The spine and sacroiliac joint may be affected early in the course of the disease. Arthropathy consists of tenderness, swelling, and limited joint movement, most often in the knee, mid-tarsus, and ankle, following a monoarticular or asymmetrically pauciarticular pattern. Arthritis in patients with juvenile onset SpA follows a variable course, occurring as single episodes of mono- or oligoarthritis, intermittent episodes of arthritis in the joints alternating with partial or complete remission, or severe persistent disease affecting multiple joints, IBD, juvenile onset AS, or ankylosing tarsitis. Enthesitis presents with pain and tenderness upon application of pressure, soft tissue swelling secondary to inflammation of tendon sheaths, and adjacent bursae. Enthesitis often occurs at the feet and is often severe enough to be disabling. Enthesitis follows a variable course, occurring as short term episodes of active inflammation, intermittent episodes of enthesis alternating with partial or complete remission, or severe and persistent enthesitis at multiple sites. Persistent enthesitis is associated with cortical bone erosions and joint ankylosis.

Disease activity and damage may be assessed by different methods. Joints and entheses with active inflammation as well as peripheral joint and spinal mobility are useful measures in juvenile onset SpA. Possibly, the application of a number of disease activity indices developed for adult onset populations (for example, visual analogue scale (VAS) for pain and Bath AS Disease Activity Index (BASDAI)) and for other forms of childhood arthritis (Childhood Health Assessment Questionnaire or CHAQ), may be useful. Imaging and laboratory assessment methods may include radiography, ultrasonography, and magnetic resonance, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Structural damage may be evaluated by determining the functional status and monitoring radiographic changes of the feet, hips, sacroiliac joints, and spine. Functional ability also plays a significant part in the evaluation of juvenile onset SpA. As with disease activity indices, adult onset instruments such as the Bath AS Functional Index (BASFI), as well as instruments for children with other forms of arthritis, may be useful in juvenile onset SpA.

**Course of the disease**

Children with juvenile onset SpA may enter into full remission after one or two mild or moderate episodes of disease activity.

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**Table 1 Clinical spectrum of juvenile onset spondyloarthropathies**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>Isolated arthritis</td>
<td>Usually mono- or oligoarthritis affecting ≤5 joints of the lower extremities</td>
</tr>
<tr>
<td>Isolated enthesitis</td>
<td>Occurs in single or multiple sites of the lower extremities, often at the feet (plantar fascia insertion, and less frequently, the Achilles insertion to the calcaneus)</td>
</tr>
<tr>
<td>SEA syndrome</td>
<td>Enthesopathy and arthropathy</td>
</tr>
<tr>
<td>AS, juvenile onset</td>
<td>Predominantly affects the feet</td>
</tr>
<tr>
<td>AS, HLA-B27</td>
<td>HLA-B27 positive children frequently, HLA-B27 negative children rarely, evolves into AS</td>
</tr>
<tr>
<td>IBD associated SpA</td>
<td>Typically involves episodes of lower extremity peripheral arthritis coinciding with gastrointestinal symptoms of IBD (CD, UC, or non-specific IBD)</td>
</tr>
<tr>
<td>ReA</td>
<td>Onset approximately 4 weeks after gastrointestinal or genitourinary bacterial infection (also see text)</td>
</tr>
</tbody>
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*Constitutional symptoms include high grade fever, weight loss, muscle weakness and atrophy, fatigue, lymph node enlargement, leucocytosis, and anaemia.

AS, ankylosing spondylitis; CD, Crohn’s disease; IBD, inflammatory bowel disease; MTP, metatarsophalangeal; ReA, reactive arthritis; SEA, seronegative enthesopathy and arthropathy; SpA, spondyloarthritis; UC, ulcerative colitis.
or they may have recurrent episodes of enthesitis and arthritis extending to the spine and sacroiliac joints (figs 1 and 2). Others may have persistent inflammation, with severe consequences early on in the course of the disease. Chronic course is characterised by an increasing number of entheses and joints affected. The functional ability of children, adolescents, and adults with juvenile onset SpA may be severely affected by disease activity and disease damage. Patients with active disease present with diverse levels of joint-limited range of movement and interference of daily life activities. Patients with severe signs and symptoms may have significantly impaired function, which may subside during recovery.

Long term follow up of HLA-B27 children with JCA/JRA has shown that 66–75% develop sufficient clinical and radiographic signs of spondylitis and sacroilitis to fulfil the diagnostic criteria for AS. Similarly, 70–90% of children with SEA syndrome fulfil the same criteria 5–10 years after onset. Children with Reiter’s syndrome or ReA may follow a similar course, but most of them are likely to go into full remission after one episode of disease activity.

Flato et al found that disease activity for more than five years predicted disability in juvenile onset SpA. According to Minden et al, the probability of remission is only 17% after five years of disease. Nearly 60% of children with SpA have moderate to severe limitations after 10 years of disease. In comparison with adults, patients with juvenile onset AS require more hip replacements throughout the course of disease, and more patients are in functional classes III and IV. Shortly after onset, foot enthesitis and arthritis and, less commonly, ankle and knee arthritis, produce pain and severe limitations from walking or standing up. As a result, children with SpA may abandon school and stop participating in sports and social activities. Sometime later, joint stiffness, muscle atrophy, and flexure contractures contribute to functional limitations.

Structural changes of the feet and hips lead to permanent functional limitations to which spinal disease may contribute. Some patients develop severe problems of the spine, specifically discitis and various deformities, which dramatically reduce their physical activity. Functional status of patients with juvenile onset SpA may reach class IV.

CURRENT TREATMENT

Treatment of juvenile onset SpA can be frustrating. Although therapeutic measures are aimed at alleviating symptoms of inflammation (that is, pain), maintaining or improving range of motion and muscle strength, preventing deformity, preserving function, and preventing or managing disease complications, short and long term results may be very unsatisfactory. Early and continuous physical and occupational therapy are critical to the patient’s maintenance of independent functioning. Physical measures include resting splints for inflamed joints and orthoses to protect entheses, local application of heat or cold packs for pain relief, and exercises to improve range of motion of the spine and chest.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the initial preferred pharmacological treatment for juvenile onset SpA. Sulfasalazine may be useful in juvenile onset SpA, but differences from placebo may be only slightly significant. Short term oral corticosteroid treatment at low to moderate doses may be required to control severe episodes of arthritis; higher doses may be needed for severe enthesitis. Intrarticular corticosteroid injection (triamcinolone hexacetonide, 1 mg/kg per joint) may resolve persistent arthritis.

Figure 1  Progression of children with juvenile onset undifferentiated spondyloarthropathy to fulfilment of the modified New York diagnostic criteria for AS over a 10 year period. The percentages of patients fulfilling each criterion are shown for each time. Most patients fulfill diagnostic criteria for definite AS after a mean of 7.5 years (range 5–10) after the onset of symptoms of juvenile onset SpA. Reproduced with permission of the authors and Rheumatic Disease Clinics of North America from Burgos-Vargas R et al. Rheum Dis Clin North Am 1997;23:569–98. Copyright © 1997 W B Saunders Company.

able therapeutic intervention prevents the progression of disease. Recently, attention has been given to the inflammatory processes underlying rheumatic conditions as potential sites for therapeutic intervention. For SpA, high levels of the proinflammatory cytokine TNFα have been documented in synovial tissue from patients with juvenile onset SpA, and adults with active AS. TNFα is a cytokine produced mainly by macrophages and mediates several inflammatory and immunoregulatory activities along the inflammatory cascade. Its activities include up regulation of several endothelial adhesion receptors, activation of lymphocytes and neutrophils, induction of synthesis of proinflammatory cytokines and chemokines, stimulation of other inflammatory mediators, induction of synthesis of metalloproteinases that mediate bone and cartilage destruction, and mediation of pain. In addition, TNFα has a key role in the pathogenesis of IBD, and its neutralisation by anti-TNFα has proved effective in Crohn's disease and IBD strongly associated with AS.

ANTI-TNFα THERAPY IN JUVENILE ONSET SpA

The anti-TNFα agents etanercept and infliximab have both been used in juvenile onset SpA. The effect of such agents in juvenile onset SpA can be rather striking from the clinical point of view. Using etanercept, a TNFα 75 kDa receptor IgG1 fusion protein, Reiff and Henrickson found a prolonged reduction in the number of active joints, morning stiffness, and ESR in eight patients with juvenile onset AS treated with 0.2–0.8 mg/kg subcutaneously twice weekly. The mean age of the group was 15.9 years (range 12–25), and the mean follow up of these patients was 15.4 months. All patients tolerated etanercept without side effects.

It should be noted, however, that this author (Burgos-Vargas, unpublished observations) has treated six patients with juvenile onset SpA with 5 mg/kg of infliximab (a chimeric human-murine monoclonal anti-TNFα antibody) at weeks 0, 2, 6, and then every two months for nearly a year. A remarkable reduction was found in peripheral and axial signs of disease after the first and second infusion of the drug. Improvement includes a significant decrease in the number of peripheral joints with active arthritis and tender entheses, in CRP values, in pain as evaluated by a VAS, as well as in BASDAI and BASFI scores. Interestingly, however, concurrent uveitis in one patient with juvenile onset AS seemed unresponsive to infliximab.

Although the use of anti-TNFα agents is still limited in children and adolescents with juvenile onset SpA, it seems that the effect of infliximab and etanercept in these disorders is at least as good as that seen in adult onset patients. The response appears so significant that most patients may stop NSAIDs and other drugs. Indeed, long term follow up is required to determine whether anti-TNFα agents can stop the devastating events that characterise juvenile onset SpA.

CONCLUSIONS

Juvenile onset SpA is a disorder distinct from JRA. The pathogenesis, radiological and clinical manifestations, and histopathology of the pathogenic lesions of juvenile onset SpA resemble those of the adult onset disease. Thus, treatment responses similar to those elicited in patients with adult onset SpA are expected in patients with the juvenile onset disease, and similar treatment strategies are employed in juvenile and adult onset SpA. Current treatments provide symptomatic relief but do not alter the natural course of the disease. New treatments are under investigation that target immune responses and cellular inflammatory processes which play a part in the pathogenesis of SpA. TNFα has been identified as a predominant proinflammatory cytokine in synovial tissue of patients with SpA. Clinical, histological, and immunohistochemical findings of studies of anti-TNFα antibody therapy in adult onset SpA suggest the possibility of altering the

Figure 3 Long term structural changes of the feet in a 20 year old patient with juvenile onset AS. (A) Dorsoplantar aspect showing metatarsophalangeal joint surface erosions and misalignment. (B) Left foot oblique view showing ankylosis of the first metatarsal and cuneal bones, metatarsophalangeal joint subluxations and enthesophytes at the margin of the 5th metatarsal-cuneal joint. (C, D) Right and left lateral views showing a spectrum of changes, including enthesophytosis at the plantar fascia attachment to the calcaneus and complete fusion of the tarsal bones (ankylosing tarsitis in C and enthesophytes at the margin of the 5th metatarsal-cuneal joint in D). These previously unpublished figures are provided courtesy of Dr R Burgos-Vargas.
progression of disease coincident with clinical improvement. These findings in adult onset SpA suggest that anti-TNFα therapy may confer similar benefits in juvenile onset SpA.

REFERENCES

R Burgos-Vargas, R. Pillay, H. Nieuwaer, C. J. M. van der Helm-van Mil, P. H. Peumuller, E. C. A. F. van der Linden, M. P. M. M. van den Berg, P. N. Malleson

These findings in adult onset SpA suggest that anti-TNFα therapy may confer similar benefits in juvenile onset SpA. The results of this study indicate that the efficacy and safety of anti-TNFα therapy in adult onset SpA is comparable to that seen in juvenile onset SpA. Furthermore, the results suggest that anti-TNFα therapy may be effective in the treatment of juvenile onset SpA. These findings support the use of anti-TNFα therapy in the treatment of juvenile onset SpA.

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