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REVIEW

Juvenile idiopathic arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in childhood, which represents a nonhomogeneous group of disorders that share the clinical manifestation of arthritis lasting at least 6 wk under the age of 16. The exact diagnosis requires exclusion of other diseases that cause arthritis. The exact etiopathogenesis of JIA is still unknown. The interactions between genetic factors, environmental exposures and immune mechanisms are thought to contribute to pathogenesis of the disease. The "International League Against Rheumatism" classification divides JIA into 7 subtypes: oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, systemic-onset JIA, enthesitis-related arthritis, juvenile psoriatic arthritis and undifferentiated JIA. Each subgroup of JIA is characterized by a different mode of presentation, disease course and outcome. The improvements in treatment of JIA in the last 2 decades, such as the early introduction of intraarticular corticosteroids, methotrexate and biologic agents, have dramatically upgraded the prognosis of the disease. If untreated, JIA may cause devastating results, such as disability from joint destruction, growth retardation, blindness from chronic iridocyclitis, and even multiple organ failure and death in systemic-onset JIA. The aim of treatment is the induction of remission and control the disease activity to minimize the pain and loss of function, and to maximize quality of life. JIA is a disease having a chronic course, which involves active and inactive cycles over the course of years. Recent studies showed that nearly half of the patients with JIA enter adulthood with their ongoing active disease. This review elucidates how recent advances have impacted diagnosis, pathogenesis and current treatment.

Key words: Juvenile idiopathic arthritis; Classification; Etiopathogenesis; Treatment; Prognosis; Outcome

Core tip: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in children. Diagnosis of JIA is based on the history and physical examination findings. There is not a diagnostic laboratory test for JIA. Recent advances in the understanding of the immune system pathways involved in inflammation and self-tolerance have provided new targets for treatment of JIA. Biologic agents targeting key cytokines implicated in JIA, suh as tumor necrosis factor α, interleukin (IL)-1, and IL-6 as well as signaling molecules involved in the regulation of B-cell and T-cell lymphocyte responses, have promising results.

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JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in childhood, which represents a nonhomogeneous group of disorders that share the clinical manifestation of arthritis lasting at least 6 wk under the age of 16[1-7]. The exact diagnosis requires exclusion of other diseases that cause arthritis.

HISTORICAL BACKGROUND

The disease was used to be known as juvenile rheumatoid arthritis; however, this term was later changed as "juvenile idiopathic arthritis" to reflect the differences between childhood arthritis and adult forms of rheumatoid arthritis. In 1972, American College of Rheumatology (ACR) subgrouped the disease, which they called "juvenile rheumatoid arthritis", as systemic-onset, oligoarticular and polyarticular disease[8]. However, pediatric rheumatologists belonging to European League Against Rheumatism (EULAR) thought that ACR classification did not cover all the disease subtype. They named the disease as "juvenile chronic arthritis" and subgrouped the disease as oligoarticular, rheumatoid factor positive polyarticular, rheumatoid factor negative polyarticular, juvenile spondylarthropathy, juvenile ankylosing spondylitis, juvenile psoriatic arthritis and inflammatory bowel disease-related arthritis in 1977[9]. In order to set up an international classification system, the American and European rheumatologists came together in Santiago in 1995 and established "International League Against Rheumatism (ILAR)" criteria. They termed the disease as "juvenile idiopathic arthritis"[10]. ILAR criteria for classification of JIA was first revised in Durban in 1997[11] and finally revised in Edmonton in 2001[12]. There are several reasons for the admirable efforts of pediatric rheumatologists to establish an international classification for this disease. The primary aim is to define relatively homogeneous categories of idiopathic childhood arthritis based on predominant clinical and laboratory features that can be used for research purposes; as well as to give opportunity to pediatric rheumatologists all around the world to speak the same language.

JUVENILE IDIOPATHIC ARTHRITIS CLASSIFICATION

The ILAR classification divides JIA into 7 subtypes: oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, systemic-onset JIA (sJIA), enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA) and undifferentiated JIA (Table 1).

Table 1 Classification of subtypes of juvenile idiopathic arthritis[12]

Systemic arthritis
Definition: Arthritis in one or more joints with or preceded by fever of at least 2 wk' duration that is documented to be daily ("quotidian") for at least 3 d, and accompanied by one or more of the following:
1 Evanescent (non-fixed) erythematous rash
2 Generalized lymph node enlargement
3 Hepatomegaly and/or splenomegaly
4 Serositis
Exclusions: 1 to 4
Oligoarthritis
Definition: Arthritis affecting one to 4 joints during the first 6 mo of disease. Two subcategories are recognized:
1 Persistent oligoarthritis: Affecting not more than 4 joints throughout disease course
2 Extended oligoarthritis: Affecting a total of more than 4 joints after the 6 mo of oligoarticular disease
Exclusions: 1 to 5
Polyarthritis (Rheumatoid factor negative)
Definition: Arthritis affecting 5 or more joints during the first 6 mo of disease; a test fot RF is negative.
Exclusions: 1 to 5
Polyarthritis (Rheumatoid factor positive)
Definition: Arthritis affecting 5 or more joints during the first 6 mo of disease; 2 or more tests for RF at least 3 mo apart during the first 6 mo of disease are positive.
Exclusions: 1, 2, 3, 5
Psoriatic arthritis
Definition: Arthritis and psoriasis, or arthritis and at least two of the following:
1 Dactylitis
2 Nail pitting or onycholysis
3 Psoriasis in a first-degree relative
Exclusions: 2, 3, 4, 5
Enthesitis related arthritis
Definition: Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
1 The presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2 HLA-B27 positivity
3 Onset of arthritis in a male over 6 yr of age
4 Acute (symptomatic) anterior uveitis
5 History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis in a first-degree relative
Exclusions 1, 4, 5
Undifferentiated arthritis
Definition: Arthritis that fulfills criteria in no category or in 2 or more of the above categories
Exclusion criteria for JIA
1 Psoriasis or a history of psoriasis in a first-degree relative
2 Arthritis in an HLA-B27 positive male following his 6th birthday
3 History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis (Reiter's syndrome), or acute anterior uveitis in a first-degree relative
4 The presence of IgM rheumatoid factor on 2 or more occasions at least 3 mo apart
5 The presence of systemic JIA in the patient

JIA: Juvenile idiopathic arthritis; HLA: Human leukocyte antigen.

EPIDEMIOLOGY

The true frequency of JIA is not known. The incidence of chronic childhood arthritis varies from 5.3 to 19.6 per 100000 children per year in different population-based studies[13-18].

Reports from variable countries represent differences in the disease manifestation of JIA among different populations. For example, compared to reports from Western countries, remarkably different features of JIA

were found in Turkish children, which included higher frequency of ERA and higher prevalence among boys[19]. Besides, in European and North American populations the majority of patients were females with the predominance of oligoarticular JIA subset[17,20-22]. Saurenmann *et al*[23] studied the influence of ethnicity on the risk of developing JIA in a multiethnic community in Canada. In this study, children of European origin had a higher relative risk for developing any of the JIA subtypes except polyarticular RF-positive JIA, and were particularly more likely to develop the extended oligoarticular and psoriatic subtypes. A higher frequency of enthesitis-related JIA was observed among patients of Asian origin, while those of black origin or native North American origin were more likely to develop polyarticular RF-positive JIA in the same study[23].

ETIOPATHOGENESIS

The exact etiopathogenesis of JIA is still unknown. The interactions between genetic factors, environmental exposures, and immune mechanisms are thought to contribute to pathogenesis of the disease.

Genetic factors

Prahalad *et al*[24] reported that family members of JIA patients were at increased risk for other autoimmune diseases[24]. The most important issue in genetic predisposition is the existence of certain human leukocyte antigen (HLA) types. It is well-known that HLA-B27 is associated with enthesitis-related arthritis[25,26]. Besides, HLA DR4 was shown to be associated with systemic onset JIA and polyarticular JIA[27,28].

Environmental exposures

Infections are believed to be the most important environmental factors that contribute to development of JIA. The disease may develop during or after an infectious period. Clinical findings of the disease may appear following especially; enteric infections, Parvovirus B19, rubella, mumps, hepatitis B, Epstein-Barr virus, mycoplasma and chlamydia infections[29-35]. Emotional stress and trauma were suggested as other contributors. Particularly, oligoarticular JIA may develop by the trigger of immune system after trauma.

Immune mechanisms

Humoral and cell-mediated immunity contribute to the pathogenesis of JIA. Activated T helper lymphocytes are differentiated into Th1 and Th2 subtypes. T lymphocytes have a central role, releasing proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1 and favoring a Th1 response. Humoral immunity abnormalities include the increased presence of autoantibodies, especially antinuclear antibodies, increased serum immunoglobulins, the presence of circulating immune complexes, and complement activation[1-6].

Chronic inflammation of synovium is characterized by B lymphocyte infiltration and expansion. Macrophages and T-cell invasion are associated with the release of cytokines, which induce the proliferation of synovial cells. Scola *et al*[36] demonstrated that synovium contained mRNA for vascular endothelial growth factor and angiopoietin, as well as for their receptors, suggesting that induction of angiogenesis by products of lymphocytic infiltration may be involved in persistence of disease.

CLINICAL FINDINGS

Systemic-onset JIA

Systemic-onset JIA describes the form of the disease, which presents with intermittent fever, evanescent rash, and arthritis. It is known as the pediatric form of "adult-onset Still's disease". Systemic JIA is the most difficult subtype to diagnose for pediatric rheumatologists. Although arthritis lasting for at least 6 wk is necessary to establish the definite diagnosis, it may not exist in the early phase of the disease in some patients[3]. The exact diagnosis is suspected after exclusion of infections and malignancies as the initial differential diagnoses in majority of the patients.

Systemic-onset JIA equally affects males and females. The cases are distributed throughout the childhood. Articular manifestations are variable in this subtype. Arthralgias are common in the early course of disease and objective arthritis may not be prominent in this early stage. Any number of joints in any distribution such as wrists, knees, ankles, hands, hips, cervical spine and temporomandibular joints may be involved. Apart from oligoarticular and polyarticular JIA, the arthritis of systemic onset JIA may begin in the hips and may progress very rapidly. Micrognathia and cervical spine fusion are common manifestations of chronic systemic JIA. Patients with systemic-onset JIA require careful monitoring for the development of systemic complications, such as macrophage activation syndrome, pericarditis, and other forms of internal organ involvement, which are more common in this subtype of JIA than in any other form[3]. Macrophage activation syndrome is clinically characterized by persistent fever, hepatosplenomegaly, and lymphadenopathy, which is commonly accompanied by the laboratory evidence of cytopenia, decreased erythrocyte sedimentation rate, increased liver enzymes, high ferritin levels, and abnormalities of clotting profile[3].

Rheumatoid factor-negative polyarticular JIA

RF-negative polyarthritis describes the form of the disease, which presents arthritis that affects at least 5 joints during the first 6 mo of disease in the absence of IgM RF[11]. This form is probably the most heterogeneous subtype of JIA. A group of RF-negative polyarticular patients resemble early-onset oligoarticular juvenile idiopathic arthritis, by presenting asymmetric arthritis, early age at onset, female predominance, frequently positive ANA, increased risk of iridocyclitis, except for the number of joints affected in the first 6 mo of disease[3].

Another group resemble adult-onset RF-negative rheumatoid arthritis, by presenting symmetric synovitis of both large and small joints, onset in school age, increased erythrocyte sedimentation rate (ESR), and negative ANA[3]. Besides, a distinct small group of RF-negative polyarticular patients have dry synovitis, which shows negligible joint swelling but stiffness, flexion contractures, and normal or slightly raised ESR, which is often poorly responsive to treatment and cause destruction of joints[3].

Rheumatoid factor-positive polyarticular JIA

RF-positive polyarthritis describes the form of the disease, which presents arthritis that affects at least 5 joints during the first 6 mo of disease in the presence of IgM RF at least two occasions more than 3 mo apart[11]. This subgroup resembles the adult RF-positive rheumatoid arthritis and is particularly seen in adolescent girls[3]. The patients typically present with symmetric polyarthritis that affects the small joints of the hands and feet. The large joints, usually knees and ankles, may be affected at onset along with small joints. Rheumatoid nodules, which are rarely seen in other subsets of juvenile idiopathic arthritis, may be seen in the board of the forearm and elbow in some of the patients[3].

Oligoarticular JIA

Oligoarthritis describes the form of the disease, which presents arthritis that affects 4 or less joints during the first 6 mo of disease in the absence of psoriasis, a family history of psoriasis, HLA-B27-associated disease in a first-degree relative, and a positive rheumatoid factor[11]. The patients typically present with asymmetric arthritis, early onset (before 6 years of age), female predominance, high frequency of positive ANA, and high risk of iridocyclitis[3]. The ILAR classification subdivides oligoarticular JIA in 2 subsets: (1) persistent oligoarthritis, in which the disease is confined to four or fewer joints in the whole course of the disease; and (2) extended oligoarthritis, in which arthritis extends to more than four joints after the first 6 mo of disease. Oligoarthritis mainly affects the knees, followed by the ankles. In about half of the patients, only one joint is affected at disease onset. Acute-phase reactants are often normal or moderately increased; although in some cases ESR can be very high. Involvement of an upper limb joint and high sedimentation rate at onset have been identified as predictors for an evolution to the extended phenotype, which can take place in up to 50% of patients[37,38].

ANA is positive in about 70%-80% of oligoarticular JIA patients, and the presence of ANA increases the risk of iridocyclitis[39,40]. Iridocyclitis is a characteristic feature of oligoarthritis and affects about 30% of patients[39,40]. The onset of iridocyclitis is insidious and often entirely asymptomatic in contrast to painful acute iridocyclitis of enthesitis-related arthritis. One or both eyes may be affected and may be present before the onset of arthritis. Most patients develop iridocyclitis during the first 5 years of disease. The severity of ocular findings is not parallel to the clinical course of arthritis[39,40]. Since iridocyclitis is asymptomatic at onset, children with this disease should be screened periodically by slit-lamp examination according to the recommended frequencies by American Academy of Pediatrics[41].

Enthesitis-related JIA

Enthesitis-related arthritis (ERA) describes the form of the disease, which mainly affects male patients after the age of 6 years and is characterized by the association of enthesitis and arthritis. The asymmetric arthritis of the lower limbs is typical. Apart from other JIA subtypes, unilateral hip involvement is common at presentation. About half of patients have four or fewer joints affected throughout the entire course of the disease[3]. Small joints (dactylitis) as well as large joints may be involved. In some patients, arthritis could progress to affect the sacroiliac and spinal joints, thus producing the clinical picture of ankylosing spondylitis[3]. The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon and plantar fascia. The course of the disease is often remitting and can be mild. However, presence of sacroiliitis, polyarticular involvement, high ESR, and ankle arthritis are associated with poor prognosis[42,43]. Most patients with ERA are HLA-B27 positive. This group of patients, especially if untreated, progress into ankylosing spondylitis[3].

Juvenile psoriatic arthritis

The diagnosis of juvenile psoriatic arthritis requires the presence of arthritis and a typical psoriatic rash at the same time. Or in the absence of typical rash, the patient with arthritis must fulfill at least 2 of the following: family history of psoriasis in a first-degree relative, dactylitis, and nail pitting or onycholysis[11]. The definition of juvenile psoriatic arthritis is controversial[44]. Some authors believe that this subtype does not represent a clearly defined entity because it has a heterogeneous clinical presentation[45]. A group of patients resemble early-onset oligoarticular juvenile idiopathic arthritis by presenting early onset, asymmetric oligoarthritis, and increased risk of iridocyclitis[46]. The main difference in this group of psoriatic arthritis is the greater frequency of dactylitis and involvement of both small and large joints than do children with oligoarthritis. Another group of juvenile psoriatic arthritis patients resemble ERA by presenting enthesitis with arthritis and/or sacroiliitis[46]. Depending on the case, the prognosis and treatment options appear to be similar to that for patients with oligoarticular JIA or ERA, but as the disease is very rare, few studies have been performed.

TREATMENT

If untreated, JIA may cause devastating results, such as disability from joint destruction, growth retardation, blindness from chronic iridocyclitis, and even multiple organ failure and death in systemic-onset JIA[43,47-49].

Table 2 American College of Rheumatology pediatric core set criteria for improvement in juvenile idiopathic arthritis[52]

Criteria	
1	Physician's global assessment of overall disease activity by VAS
2	Parent of patient global assessment of overall well-being by VAS
3	Functional ability
4	Number of joints with active arthritis
5	Number of joints with limited range of motion
6	Erythrocyte sedimentation rate
ACR Pediatric 30 response	A minimum of 30% improvement from baseline in a minimum of 3 out of 6 components, with a worsening by > 30% in no more than one component
ACR Pediatric 50 response	Requires 50% improvement in 3 out of 6 components with worsening of 30% in no more than one component
ACR Pediatric 70 response	Requires 70% improvement in 3 out of 6 components with worsening of 30% in no more than one component

VAS: Visual analogue scale 0-10 cm. ACR: American College of Rheumatology.

Table 3 Preliminary clinical criteria to define the inactive disease status and clinical remission in oligoarticular, polyarticular and systemic onset juvenile idiopathic arthritis[53,54] arthritis[52]

Criteria
1 No active synovitis
2 No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to juvenile idiopathic arthritis
3 No active uveitis
4 Normal erythrocyte sedimentation rate and/or C-reactive protein
5 Physician's global assessment of disease activity indicates no active disease
6 Morning stiffness no more than 15 min
Inactive disease:
All criteria must be met
Clinical remission on medication:
Six continuous months of inactive disease on medication
Clinical remission off medication:
Twelve continuous months of inactive disease off all anti-arthritis and anti-uveitis medications

The aim of treatment is the induction of remission and control the disease activity to minimize the pain and loss of function, and to maximize quality of life. There is currently no exact cure for JIA. The treatment team of JIA should be multidisciplinary including pediatric rheumatologist, ophthalmologist, physiotherapist, psychiatrist and orthopedist.

JIA is a disease having a chronic course, which involves active and inactive cycles over the course of years[50]. Unfortunately, only a minority of patients may have sustained remission. Recent studies showed that nearly half of the patients with JIA enter adulthood with their ongoing active disease[43,51]. This means that many patients with JIA will be exposed to several periods of medications throughout their lifetimes.

In order to monitor the response to pharmacologic agents, the pediatric rheumatologists use the "pediatric core set", which identifies the level of ACR response (Table 2)[52].

The clinical criteria to define the inactive disease status and clinical remission were derived from studies including oligoarticular, polyarticular and systemic onset JIA (Table 3)[53,54]. However, there are still no studies defining the activity of ERA or juvenile psoriatic arthritis in the literature.

Since JIA is a heterogeneous disease, treatment algorithms differ between subtypes. The initial management of JIA has been relied on nonsteroidal anti-inflammatory drugs (NSAIDs) along with traditional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulphasalazine. Systemic corticosteroids or intraarticular corticosteroid injections may conjunct to therapy. Patients with polyarticular and systemic onset JIA are often unresponsive to traditional DMARDS and require chronic corticosteroid use to keep the disease under control or initiation of newer biologic therapies[50].

In order to provide guidance for treatment strategies in JIA, ACR published a guideline for treatment of JIA in 2011[55]. The ACR states that adherence to these guidelines and recommendations are voluntary, with the ultimate determination regarding their application are made by the physician in light of each patient's individual circumstances.

NSAIDs

NSAIDs have been the mainstay of therapy either alone or in conjunction with other drugs. The most widely used NSAIDs in children are non-selective ones, such as ibuprofen, indomethacin, tolmetine and naproxen. The patients with oligoarthritis may achieve clinical remission only with NSAIDs, while other subtypes require more potent and long acting anti-inflammatory therapies. Besides their several side effects, NSAIDs are generally well-tolerated by children. The most common side effects are abdominal pain and headache[56,57]. After the voluntarily withdrawal of rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term use, selective COX-2 inhibitors could not find a strong place in the treatment of JIA by pediatric rheumatologists.

Corticosteroids

Corticosteroids are the most potent ones among anti-inflammatory drugs. However, they are limitedly used in JIA treatment because of their wide spectrum of side effects and their insufficiency in preventing the destructive joint damage. Corticosteroids are particularly used as bridge therapy for concise intervals while newly started DMARDs show their effects. There are no randomized-controlled trials about the initiation and tapering dosage of corticosteroids in the literature. Corticosteroids, either orally or parenteral, may lower the systemic clinical findings in systemic onset JIA, however; the destructive course in joints persists[58].

Intraarticular corticosteroid injection is an effective treatment choice in oligoarticular JIA, particularly in patients unresponsive to NSAIDs[58]. In the existence of leg length discrepancy, muscle atrophy and joint contracture;

Table 4 Biologic agents used in the treatment of juvenile idiopathic arthritis

Drug	Target	FDA approval for JIA	Administration	Dosage
Etanercept	TNF-α	Polyarticular JIA ages 2 yr and older	Subcutaneous injection	0.8 mg/kg per dose once a week, maximum 50 mg/dose
Adalimumab	TNF-α	Polyarticular JIA ages 4 yr and older	Subcutaneous injection	24 mg/m^2 every 2 wk, maximum 40 mg/dose
Infliximab	TNF-α	No	Intravenous infusion	6-10 mg/kg per dose week 0, 2 and 6; then every 4 to 8 wk
Anakinra	IL-1	No	Subcutaneous injection	1-2 mg/kg per day, maximum 100 mg/dose
Canakinumab	IL-1	Systemic-onset JIA ages 2 yr and older	Subcutaneous injection	2-4 mg/kg every 4 wk
Rilonacept	IL-1	No	Subcutaneous injection	2.2-4.4 mg/kg once a week
Abatacept	Cytotoxic T-lymphocyte-associated antigen 4	Polyarticular JIA ages 6 yr and older	Intravenous infusion	10 mg/kg week 0, 2 and 4; then every 4 wk, maximum 1000 mg/dose
Rituximab	CD20	No	Intravenous infusion	750 mg/m^2; two doses 2 wk apart or 375 mg/m^2; four doses, weekly × 4, maximum 1000 mg/dose
Tocilizumab	IL-6	Polyarticular JIA ages 2 yr and older	Intravenous infusion	8 -12 mg/kg every 2 wk

TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; JIA: Juvenile idiopathic arthritis.

intraarticular corticosteroid injection may be performed without waiting the effect of NSAIDs in order not to lose time[59]. Besides, Sherry and colleagues demonstrated that early administration of intraarticular corticosteroid injection resulted in less leg length discrepancy in oligoarticular JIA when compared to NSAID use alone[60]. Triamcinolone hexacetonide is the first choice in the injection of large joints, while methylprednisolone acetate is preferred in small joints.

Disease-modifying anti-rheumatic drugs

DMARDs represent the main step of treatment of JIA. The analgesic and anti-inflammatory effects of these agents do not start immediately; they act their useful effects weeks-months later. Among these groups, only methotrexate and sulphasalazine were approved by Food and Drug Administration (FDA). After the studies showing the failure of D-penicillamine, hydroxychloroquine and azathioprine against placebo in the treatment of JIA, pediatric rheumatologists no longer use these drugs in the treatment schedules[61-63]. Leflunomide, thalidomide and cyclosporine A were the other DMARDs used in treatment of JIA. Cyclosporine A was only recommended in the treatment of macrophage activation syndrome, which is a complication of systemic-onset JIA. It is not an effective treatment option to prevent joint damage in any subgroup of JIA.

Biologic agents

Advances in the understanding of the immune system pathways involved in inflammation and self-tolerance have provided new targets for treatment of rheumatologic conditions. Biologic agents have been designed to target key cytokines implicated in JIA, including TNF-α, IL-1, and IL-6 as well as signaling molecules involved in the regulation of B-cell and T-cell lymphocyte responses[64-71]. Along with their promising results, these biologic agents may bring some severe risks such as susceptibility to infection and malignity, which require the careful monitoring of these agents. The biologic agents used in the treatment of JIA are listed in Table 4.

PROGNOSIS AND OUTCOME

The improvements in treatment of JIA in the last 2 decades, such as the early introduction of intraarticular corticosteroids, methotrexate, and biologic agents, have dramatically upgraded the prognosis of the disease. Most patients may continue active daily life. The comparison of earlier studies with those published in the last decade shows a decline in the frequency of patients with severe physical disability over years. However, many patients, particularly those with polyarticular disease, may have problems with active disease throughout adulthood, with sustained remission attained in a minority of patients[43,51]. Besides, patients with systemic-onset JIA tend to either respond completely to medical therapy or develop a severe polyarticular course that tends to be refractory to medical treatment, with disease persisting into adulthood[43,51]. Early hip or wrist involvement, symmetrical disease, the presence of RF, and prolonged active systemic disease have been associated with poor long-term outcomes[43,51]. Most children with oligoarticular disease may experience eventual permanent remission, although a small number progress to persisting polyarticular disease. It may be concluded that among the different JIA subtypes, the long-term outcome is best in persistent oligoarthritis and worst in RF-positive polyarthritis; the outcome of systemic arthritis is widely variable, perhaps reflecting the heterogeneity of this JIA subtype[72].

Several studies showed some psychosocial impairment among patients with JIA[73]. Patients with JIA were reported to have higher levels of depression, frustration, anxiety, fatigue and sleep disturbances when compared to healthy peers[74-76]. Therefore, careful psychosocial monitoring of children with JIA is essential to improve the quality of life.

There are concerns that the biologic agents may increase the risk of cancer among patients with JIA. However, lack of knowledge on the baseline risk of cancer in

this population has made this concern difficult to confirm. Based on a report of 48 children who developed malignancy while being treated with TNF-alpha antagonists, the FDA placed a boxed warning about malignancies on all TNF-alpha antagonists in 2009[77].

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