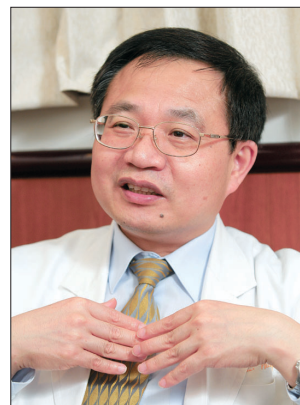# New Advances in Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) comprises a group of heterogeneous disorders of chronic arthritis in childhood with no apparent etiology. Juvenile idiopathic arthritis is the most common pediatric rheumatic disease and is associated with significant long-term morbidity and mortality. There have been major advances in recent years in our understanding of the pathogenesis of JIA, the definition of disease control, and biological treatments for JIA. Multiple environmental and genetic factors have been linked with the onset and / or the exacerbation of JIA, including perinatal factors, viral and bacterial infections, epigenetic factors, and malnutrition. However, no single causative factor has been identified to date. As our understanding of the complex network of immune cells and inflammatory cytokines has improved, biologics have been developed to modulate the inflammatory processes. Indeed, a number of such biologics have been demonstrated effective for the treatment of JIA. Although biologic agents may alleviate the inflammation associated with JIA and prevent disability caused by joint destruction, continued and comprehensive observation is required to determine the long-term outcomes associated with such treatment. *(Chang Gung Med J 2012;35:1-14)*

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Juvenile idiopathic arthritis (JIA) is a term that collectively refers to a group of chronic arthropathies, which together constitute the most common rheumatic condition in children. JIA is not a disease but an exclusion diagnosis that applies to any arthritis of unknown cause (such as infectious, oncologic, or other rheumatic etiologies) persisting for more than 6 weeks with an onset before the age of 16 years.[1,2] According to the International League of Associations for Rheumatology, JIA consists of 8 heterogeneous subsets with unique clinical patterns of disease (Table 1).[3] The aim of the new JIA classi-fication system was to define relatively homogeneous, mutually exclusive subsets of arthritis based on predominant clinical and laboratory features for both prognostic and research purposes.[4] The term JIA has replaced previous nomenclature, including the terms "juvenile rheumatoid arthritis" used in the U.S.A. and "juvenile chronic arthritis" used in European countries. The original classification of JIA has been revised several times, most recently in 2004, resulting in further clarification of the various subsets, correction of prior incongruence, and improvement in clinical utility to the rheumatolo-

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Table 1. International League of Associations for Rheumatology Classification of Juvenile Iidiopathic Arthritis Subtypes and Clinical Features[3]

Oligoarthritis	Arthritis of 4 or fewer joints during the first 6 months
Persistent	Affecting not more than 4 joints throughout the disease course
Extended	Extending to affect more than 4 joints after the first 6 months
Polyarthritis	Arthritis of 5 or more joints during the first 6 months
RF positive	Subdivided according to presence of RF
RF negative	
Systemic arthritis	Arthritis with or preceded by quotidian (daily) fever for at least 3 days, accompanied by one or more of the following:
	1. Evanescent erythematous rash
	2. Lymphadenopathy
	3. Hepatomegaly and/or splenomegaly
	4. Serositis
Psoriatric arthritis	Arthritis and psoriasis or arthritis and at least 2 of the following:
	1. Dactylitis
	2. Nail pitting or onycholysis
	3. Psoriasis in first-degree relative
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with 2 of the following:
	1. Sacroiliac joint tenderness or inflammatory lumbosacral pain
	2. HLA-B27 antigen
	3. Onset of arthritis after age 6 years in males
	4. Acute (symptomatic) anterior uveitis
	5. History of HLA-B27-associated disease in a first-degree relative
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or more than 2 of the above categories

Adapted from Petty et al.[5] and Brough and Cleary[104]

Abbreviations: RF: rheumatoid factor; HLA: human leukocyte antigen.

gist.[5]

Twenty years ago, it was commonly believed that JIA might subside in adulthood. Recent reports have shown that sustained resolution of articular disease occurs in only a small minority of JIA patients and that at least 50% of children with JIA enter adulthood with ongoing, active disease.[6,7] The findings from these studies indicate that many patients diagnosed with JIA will have a prolonged disease course, require long term treatment, and likely be exposed to multiple medications. Fortunately, there have been significant advances in treatment over the last 2 decades that have led to improvements in the management of JIA. The major aims in the treatment of children with JIA are the following: 1) Recognize the specific challenges and obligations of a multidis-ciplinary team of specialized healthcare workers; and 2) Initiate early and aggressive treatment to not only control inflammation, but also switch off the disease process.[3,8]

Epidemiology

Approximately 1 in every 1000 children worldwide has JIA; however, the reported incidence and prevalence of JIA varies widely, in part because JIA is a heterogeneous disorder that is clinically identified and does not have a specific diagnostic test. Indeed, the available data are likely to underestimate the true incidence and prevalence of JIA because of underdiagnosis and because most studies are clinic-based rather than community-based. Prevalence rates ranging between 0.87 and 220 / 100,000 have been

reported in different population-based studies.[9] According to a National Health Insurance database study, the prevalence of JIA in Taiwan is 3.7 / 100,000, which is higher than the prevalence in Japan, but lower than the prevalence in most Caucasian populations.[10]

Overall, more females than males are affected by JIA;[11] however, the sex distribution varies by disease subtype, with a striking female predominance in the oligoarticular and polyarticular onset subtypes, an even distribution of sexes in the systemic onset subtype, and a male predominance in the enthesitis-related arthritis subtype. The age of onset also varies. The onset of oligoarthritis occurs at a median 5-years of age, followed by enthesitis related arthritis, and seropositive polyarthritis at a mean age of at least 8 to 9 years. Similar to most countries, the most common JIA subtype in Taiwan is oligoarthritis.

The environment and JIA

The majority of autoimmune diseases in adults and children are considered complex in etiology, with risk conferred by both genes and the environment. The incidence of some autoimmune diseases, such as type 1 diabetes, have significantly increased during the past several decades to an extent that cannot be explained by genetics alone. This suggests that environmental changes over the past several decades have likely contributed to the increased incidence of some autoimmune diseases. Unfortunately, little research has been undertaken to identify specific environmental risk factors for JIA. Indeed, only a handful of studies have been reported over the last two decades, the outcomes of which have not been replicated in independent populations. There are several barriers to JIA environmental risk factor research including: (1) the changing subtype classification systems, which can make comparison of studies published at different times difficult; (2) the low disease incidence, which limits prospective collection of pre-disease environmental data; and (3) the need to separately consider the different JIA subtypes, which further reduces the number of cases for comparison in studies with already small numbers.[12]

Early life events and the intrauterine environment have been epidemiologically associated with various diseases.[13] In a 7-year cohort study, Jaakkola and Gissler reported that maternal smoking during pregnancy increased the risk of JIA in newborn

Finnish girls (N = 58,841).[14] Specifically, the authors reported that children born to mothers who smoked during pregnancy had a 2-fold higher rate of polyarthropathies than children born to mothers who did not smoke during pregnancy.

Breastfeeding has been reported to reduce the risk of developing JIA. Mason et al. performed a study to analyze the relationship between breastfeeding and the development of JIA and found that the odds ratio (OR) for JIA decreased with the duration of breastfeeding (0-3 months: OR = 0.56, 95% confidence interval [CI] = 0.23, 1.14; > 3 months: OR = 0.28; 95% CI = 0.10, 0.67).[15] However, Mason's study had a number of limitations, including low statistical power, selection bias, and the use of recall study methods. In a small scale study, Young et al. reported that children who were HLA-DR4 negative and breastfed for over 3 months were protected from developing JIA with rheumatoid factor positivity.[16] Taken together, the available evidence suggests that there may be a relationship between breastfeeding and the development of JIA; however, this relationship has not been investigated in a large scale to date.

The relationship between various maternal, pregnancy, and birth characteristics, and early life infections and the risk of developing JIA was investigated in a register-based, case-control Swedish study that included 3,334 children with JIA and 13,336 control children. Birth after 42 weeks of gestation and birth by cesarean section were borderline associated with later onset JIA.[17] Exposure to infection and other environmental factors at an older age increases the risk of developing an autoimmune disease. Infectious agents are believed to be the most important environmental factors leading to the development of autoimmunity.[18,19]

The role that infection plays in the initiation and augmentation of the symptoms of JIA is well established. Patients with JIA have been reported to have higher rates of infection with mycoplasma pneumonia,[20] streptococcus,[21] parvovirus B19,[22] and Epstein-Barr virus than children who do not have JIA.[23] However, the mechanism through which infection increases the risk of JIA and other autoimmune diseases remains unclear. Molecular mimicry, whereby self-reactivity is triggered by cross-recognition of a self-peptide and an infectious peptide because of sequence similarity, has been reported.[12] Infection may trigger activation of polyclonal lym-

phocytes and increased immunogenicity of organs following infection-related inflammation.[24] The onset of autoimmune diseases following vaccination has also been reported and various vaccines have been suggested to act as disease triggers.[25,26] Vaccines may induce JIA through various mechanisms such as molecular mimicry (ie, where the vaccine acts as a self-antigen), antigen non-specific bystander activation, and polyclonal lymphocyte activation during the immune response to the vaccine.[18]

Case reports of JIA exacerbation following vaccination are rare. Only a single case of exacerbation of systemic JIA following rubella vaccination (a live-attenuated viral vaccine) has been described.[27] The findings from epidemiologic studies suggest that there is no increased incidence or exacerbation of JIA shortly after vaccinations and that the introduction of new vaccines did not change the incidence of JIA.[28,29] In a prospective study evaluating the effectiveness of hepatitis B vaccination in children with JIA, no children were found to experience disease flare-up or clinical deterioration after vaccination.[30] In another study, Borte et al. reported that there was no worsening of disease activity or any increase in medication use after children with JIA (being treated with anti-inflammatory medications including methotrexate and etanercept) received live-attenuated measles, mumps, and rubella vaccinations.[31]

Vitamin D plays an important role in modulating the human immune system.[32] Indeed, $1,25(OH)_2D_3$ is able to enhance the innate immune system. Further, $1,25(OH)_2D_3$ has been shown to activate an antibacterial response by stimulating the production of antimicrobial peptides.[33] Furthermore, $1,25(OH)_2D_3$ has also been demonstrated to influence the differentiation and maturation of dendritic cells in response to antigen presentation, and downregulate the expression of cytokines, such as interleukin (IL)-12, that are associated with T helper (Th)1 cells.[34] Th1 cells are known to mediate the autoimmune response in JIA. The newly described Th cell, Th17, which produces the proinflammatory cytokine IL-17, is thought to play a role in the pathogenesis of autoimmune diseases, including JIA.[35] There is evidence to suggest that $1,25(OH)_2D_3$ inhibits the secretion of Th17 cells via a number of pathways, including reduction of the expression of the Th17 stimulatory factor IL-6.[36-38] These study

findings support the theory that vitamin D plays a role in the pathophysiology of JIA.

Although the findings from many studies and various immune mechanisms highlight the association between JIA and the environment, the causal relationship between JIA and environmental factors is obscure and requires more comprehensive investigation. Multiple environmental factors have been reported to induce or exacerbate JIA, however, no single causative factor has been identified thus far.[18]

The genetics of JIA

Several genetic loci have been proposed to be associated with susceptibility to JIA and the severity of JIA. A number of well documented and replicated associations between human leukocyte antigens (HLA) and JIA have been reported. These associations vary between JIA subtypes. For HLA class I alleles, HLA-A2 has been shown to be associated with JIA, particularly in children with an early disease onset. HLA-B27 has long been associated with the development of enthesitis-related arthritis in both adults and children. For HLA class II alleles, increased frequencies of HLA-DRB1*08, 11 and 13 and DPB1*02 have been reported in Caucasian children with JIA, while an increased frequency of HLA-DRB1*0405 has been reported in Asian children with JIA.[39] Although many different non-HLA candidate loci have been investigated for associations with JIA and JIA subtypes, very few have been identified. Prahalad and Glass reported that although over 100 different candidate genes have been studied in over 150 association-based studies of JIA,[40] only a handful (MIF, NRAMP1, PTPN22, TNFA, and WISP3) have shown replication. Prahalad et al. reported strong associations between the TNFAIP3 variant and oligoarticular JIA and the STAT4 variant and polyarticular JIA.[41]

Pathogenesis

Juvenile idiopathic arthritis encompasses a heterogeneous group of diseases characterized by chronic inflammatory processes involving the synovial membrane, cartilage, and bone.[1] The classification of JIA subgroups are based on clinical and laboratory characteristics including the number of affected joints and the presence of autoimmune markers. The histopathological hallmark of JIA is infiltration of the synovium by lymphocytes, plasma

cells, macrophages, and dendritic cells.[42] The proliferation of fibroblast- and macrophage-like synoviocytes is another prominent feature of the inflamed synovium in JIA. Histologically, systemic JIA (sJIA) is subsumed under the term JIA. However, from a pathophysiological point of view, sJIA may be better categorized as an autoinflammatory syndrome. Children with sJIA do not exhibit signs of lymphocyte-mediated, antigen-specific immune reactions. Rather, the typical clinical signs of sJIA are associated with granulocytosis, thrombocytosis, and upregulation of acute phase reactants, indicating uncontrolled activation of the innate immune system.[43] In our previous study, increased expression of leukocyte adhesion molecules such as E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 were shown in patients in both the active and remission stages of JIA.[44] Subsequent recruitment of perivascular neutrophil infiltrates and proinflammatory activation of monocytes have also been reported.[45]

Juvenile idiopathic arthritis has been suggested to be a Th1 cell-mediated disorder, driven by a population of T cells producing inflammatory cytokines and chemokines.[46] Cytokines are directly implicated in many of the immune processes that are associated with the pathogenesis of JIA. Numerous cytokines are secreted and are functionally active in synovial tissues. The most important proinflammatory cytokines produced by phagocytes are tumor necrosis factor-α (TNF-α), IL-1, and IL-6. These cytokines play roles in specific immunological processes that promote autoimmunity, chronic inflammation, and tissue destruction.[47] Expression levels of TNF-α, IL-1β, and IL-6 appear to be highest in patients with sJIA compared with patients with polyarticular or pauci-JIA,[48] and correlate with the severity of JIA disease and joint destruction.

Heat shock proteins (HSPs), proteins produced in response to stress, are also potential autoantigens in JIA. Circulating T cells from JIA patients, but not control individuals, react to human HSP60.[49,50] Human HSP is also expressed on the synovial membrane in patients with JIA, potentially acting as an autoantigen.[51] Wu et al. reported that serum concentrations of Hsp60 in patients with active and inactive oligoarticular and polyarticular JIA were significantly higher than in normal control individuals.[52] Serum concentrations of anti-Hsp60 were 49.25 ng/mL in

patients with active oligoarticular JIA and 35.76 ng/mL in control individuals ($p = 0.059$). Serum concentrations of anti-Hsp60 were 65.05 ng/mL in patients with polyarticular JIA ($p = 0.008$ vs control). Further, serum concentrations of Hsp60 correlated with the time from remission to flare-up in patients with JIA.[52]

Synovial fluid samples from patients with different JIA subtypes show markedly different CD4 / CD8 ratios,[53] proportions of activated CD4 and CD8 T cells,[53] degrees of clonal expansion,[54] associated HLA-DR B1 loci, and involvement of Vβ families among the highly oligoclonally expanded T cells.[55] These findings suggest that different autoantigens may be involved in different JIA subtypes. Yao et al. reported mutation of the RANTES gene promoter in patients with JIA and this mutation was associated with increased RANTES secretion and synovial membrane inflammation.[56] Persistently abnormal serum levels of RANTES in the remission stage of JIA may be an important predictor of disease flare-up within 6 months.[57] Antigen-driven T cells play a central role in the pathogenesis of JIA,[42] including the predominance of T lymphocytes in the synovial infiltrate, and the activated phenotypes of the infiltrating CD4 and CD8 T cells as indicated by expression of CD25 (IL-2R), CD45RO, CD69, very late activation antigen type 1, MHC class II and several activation-dependent chemokine receptors such as CCR5, RANTES and CXCR3.[53,58-60]

Recently, studies in animals using a model of collagen-induced arthritis (CIA) have implicated IL-17 producing T cells in the pathogenesis of autoimmune disease.[61] The inflamed joints in patients with JIA are enriched with IL-17-producing T cells and high levels of IL-17, in excess of serum levels, have been detected in synovial fluid from patients with polyarticular JIA.[35,62] Interleukin-17 may induce synoviocyte production of IL-6, matrix metalloproteinases 1 and 3, and IL-8 (which is chemotactic for neutrophils), all of which have been implicated in the joint destruction process.[62] Further, it has been reported that mice lacking expression of Th1-cell associated genes, including interferon (IFN)-γ, IFN-γR, and IL-12 *p35*, can develop CIA.[63-65] In contrast, and consistent with Th17 cells playing a role in mediating arthritic disease, IL-6^{-/-} mice and IL-23 p19^{-/-} mice do not develop CIA, and inhibition or overexpression of IL-17 in the joint suppresses or

worsens joint inflammation and damage, respectively.[61] The findings from these studies suggest that Th17 cells can be induced by IL-6 and IL-23 and thus act as the key effector-cell subset in inflammatory arthritis. An excess of Th17 cells has been detected in the joints of adults with rheumatoid arthritis[66,67] and in children with JIA, particularly in those individuals with more advanced disease.[68] Weaver et al. reported that IL-17 drives neutrophil differentiation, maturation, activation, cytokine release, monocyte activation, and synovial fibroblast activation, chemokine release, prostaglandin production and matrix metalloproteinase synthesis.[69] A synergistic interaction between IL-17, IL-1β, and TNF-α, leading to synovial fibroblast activation and cytokine secretion, suggests that IL-17 plays a role in the pathogenesis of joint destruction.[61,70]

Recent investigations have focused on mediators of the innate immune system in JIA. Serum concentrations of the calcium-binding proteins S100A8, S100A9, and S100A12, which are produced from activated neutrophils and monocytes, are increased in oligoarticular and polyarticular JIA and correlate with the severity of joint inflammation.[71] S100A12 has proinflammatory properties in vitro at concentrations found in sJIA serum in vivo[72,73] and is highly expressed in patients with sJIA.[74] These molecules are damage-associated molecular pattern proteins, which act as endogenous danger signals and activate immune cells and the vascular endothelium.[75] Protein S100A12 seems to be a member of a novel inflammatory signaling pathway involving the receptor for advanced glycation end products which transduce proinflammatory signals in endothelial cells and phagocytes.[75,76] Protein S100A12 may induce the expression of adhesion molecules as well as proinflammatory cytokines on endothelial cells in a nuclear factor-κB-dependent manner. Proteins S100A8 / S100A9 and S100A12 act early in the inflammatory cascade associated with periods of disease activity.[72,77] The early phases of a clinical trial examining the importance of S100A8 / S100A9 and S100A12 in chronic arthritis has been completed with positive results. The specific overexpression of IL-1, IL-18, S100A8, S100A9, and S100A12 may play a novel role in the pathogenesis of sJIA. All of these molecules are secreted by a so- called alternative pathway, which is different from the classic intracellular transport mechanism involving the endothelium and Golgi complex. The initial activation of IL-1 and IL-18 involves a proteolytic cleavage of inactiveprocytokines by a multiprotein complex called an inflammasome. The uncontrolled activation of inflammasomes and cleavage of pro-IL-1 by caspase-1 have been suggested to be important molecular mechanisms in systemic JIA.[45,78,79]

Advances in the treatment of JIA
Standardized measures of clinical outcomes

The goals in treating JIA are to eliminate active disease, normalize joint function, preserve normal growth, prevent long-term joint damage, and prevent patient disability.

The American College of Rheumatology Pediatric 30 criteria (ACR Pedi 30) defines improvement as involving at least 3 of 6 core set variables, with no more than 1 of the remaining variables worsening by > 30%. The 6 core set includes physician global assessment, active joint count, number of joints with limited range of motion, inflammatory markers, and patient or parent assessments. These measures of global and specific health-related outcomes have been developed and refined to evaluate JIA while keeping pace with the development of new therapies.[3] Important steps have occurred in the optimization of treatment for JIA.

Intra-articular injection of corticosteroids

Intra-articular corticosteroid injections are used early in the disease course,[80,81] and can be a rapid and long-lasting effective therapy used solely or in combination with other systemic treatments. Patients with JIA who were treated with intra-articular triamcinolone hexacetonide (TH) had significantly higher response rates at 6 months compared with patients who were treated with triamcinolone acetonide (TA) (81.4% vs 53.3%, $p = 0.001$).[82] Similarly, patients treated with TH had a longer time to relapse than patients treated with TA (10.14 vs 7.75 months, $p < 0.001$).[81] These findings suggest that TH offers a significant advantage over TA in the treatment of large inflamed joints in JIA, particularly for patients with oligoarticular JIA.

Biologic agents

Advances in our understanding of the immune system have revealed details of the pathways involved in inflammation and self-tolerance and have

led to the development of new medications for treatment of JIA. A major advance in the management of JIA has been the advent of biological therapies developed to target specific mediators of the inflammatory response. Biologic agents are genetically engineered drugs designed to selectively block the effects of 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 (Table 2).[6]

TNF-α Antagonists

TNF-α is a potent proinflammatory cytokine. Elevated serum and synovial fluid TNF-α concentrations have been detected in patients with JIA. Three biologic agents targeting TNF-α (etanercept, infliximab, and adalimumab) are currently being used to treat JIA.

Etanercept

The first multicenter, double-blind randomized controlled trial of biologic therapy (etanercept) for JIA was undertaken in 51 patients (aged 4 to 17 years) with refractory polyarticular JIA.[83] Patients treated with etanercept were found to have signifi-

cantly lower rates of disease flare-up in the subsequent 4-month period than patients treated with a placebo (28% vs 81%, $p = 0.003$). Radiographic progression of joint damage was also reduced following treatment with etanercept in children with JIA.[84] Billiau et al. further reported that etanercept improved linear growth and bone mass after 18 months of treatment in 16 children with methotrexate (MTX)-resistant polyarticular JIA.[85]

Etanercept treatment is associated with satisfactory short- and long-term safety and tolerability. The Dutch National Register reported that 77% of patients with JIA (N = 146) met ACR Pedi30 criteria in the initial 3 months of treatment with etanercept (median follow-up = 2.5 years / patient; range = 0.3 to 7.3 years).[86] For the majority of patients, this improvement was sustained, with 36% of patients meeting remission criteria. Lovell et al. performed an 8-year clinical trial of etanercept demonstrating the long-term safety and efficacy of this treatment.[87] Mild adverse events including injection site reactions, upper respiratory tract infection, and headache were reported at a rate of 0.15 to 0.21 events per patient-year of exposure, while serious adverse events such as bacterial infection and hospitalization

Table 2. Biologic Therapeutics in Use or in Development for Treatment of Juvenile Idiopathic Arthritis

Drug	Action	Dose
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNFα	0.4 mg/kg twice weekly; 0.8 mg/kg/week; maximum 50 mg/dose; SC
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNFα and its membrane- bound precursor, neutralizing its action	6 to 10 mg/kg/dose weeks 0, 2 and 6; then every 4 to 8 weeks; IV
Adalimumab	A human immunoglobulin G1 monoclonal antibody which binds to TNFα	24 mg/m^2 every 2 weeks; maximum 40 mg/dose; SC
Abatacept	Soluble human fusion protein of the extracellular domain of cytotoxic T-lymphocyte-associated antigen-4, linked to a modified Fc portion of human immunoglobulin G1. A co-stimulatory signal inhibitor that binds competitively to CD80 or CD86, where it selectively inhibits T-cell activation	10 mg/kg weeks 0, 2 and 4; then every 4 weeks, maximum 1,000 mg/dose; IV
Anakinra	An interleukin-1 receptor antagonist	1 to 2 mg/kg/day, maximum 100 mg/dose; SC
Rituximab	Chimeric monoclonal antibody that binds to cell surface CD20 receptor of mature B cells	750 mg/m^2; two doses 2 weeks apart or 375 mg/m^2; 4 doses, weekly x 4, maximum 1,000 mg/dose; IV
Tocilizumab	A humanised anti-human interleukin-6 receptor monoclonal antibody	8 to 12 mg/kg every 2 weeks; IV

Adapted from Strand et al.[105]

Abbreviations: IV: intravenous; SC: subcutaneous; TNF: tumor necrosis factor; Fc: fragment,crystallizable; CD: cluster of differentiation.

occurred at rates ranging from 0.029 to 0.10 events per patient-year of exposure.[5]

Infliximab

Unlike etanercept, infliximab binds both soluble and membrane-bound TNF-α. A 14 week international, multicenter, randomized controlled trial of infliximab in patients with polyarticular JIA refractory to MTX (N = 122) revealed that a higher proportion of patients treated with infliximab met ACR Pedi 30 criteria than those treated with a placebo; however, the between group difference was not significant.[88] Patients treated with infliximab may experience mild infusion-related symptoms such as rash, headache, and severe anaphylactic reaction. These adverse events are possibly related to immune responses against the mostly humanized mouse monoclonal antibody.[89]

Adalimumab

Adalimumab is a fully humanized monoclonal antibody that binds soluble and membrane-bound TNF-α. Lovell et al. reported the results of a phase III randomized, double-blinded, placebo-controlled trial in which 171 patients with polyarticular JIA were treated with adalimumab for 16 weeks. All patients were either MTX naïve or had exhibited an inadequate response to MTX.[90] After 16 weeks of treatment, 74% of patients not receiving MTX and 94% of those receiving MTX met ACR Pedi 30 criteria. Of the patients receiving MTX, there was a significant increase in the number of disease flareups in those patients who subsequently received a placebo vs adalimumab (71% vs 43%, $p = 0.03$).

It is thought that the 3 TNF-α antagonists will have similar long-term side effects. Postmarketing surveillance studies have demonstrated increased risks of sepsis, opportunistic infections, tuberculosis, demyelinating diseases, and lupus-like reactions. Severe infections have been reported at a rate of 0.01 to 0.02 events per patient-year of exposure. The development of novel autoantibodies including antinuclear antibodies was also noted in 16% of patients after anti-TNF-α therapy.[84]

IL-1 antagonists

Anakinra is a recombinant form of the human IL-1 receptor antagonist that competitively binds the IL-1 receptor and thus blocks endogenous IL-1 sig-

naling. In uncontrolled studies in patients with refractory sJIA who were resistant to MTX and TNF-α antagonists, treatment with anakinra led to rapid (within days) and sustained remission.[50,91-93] However, recent reports suggest that not all patients with sJIA respond to treatment with anti-IL-1 and that the response is not always sustained.[94,95] These findings suggest there may be two distinct phenotypes of sJIA; one which is responsive, and the other which is non- or less responsive to IL-1 blockade.[96] Local injection site reactions and injection pain are frequent side effects of anakinra treatment. Infection and anaphylaxis have also been reported.[94]

Rilonacept (IL-1 Trap) is another IL-1 blocking agent currently undergoing trials in children with sJIA. Rilonacept is a recombinant fusion protein that combines IL-1 receptor protein components with the Fc portion of human IgG1. Rilonacept comprises extracellular domains of both receptor components required for IL-1 signaling ie, the IL-1 type 1 receptor and IL-1 receptor accessory protein. Rilonacept might be a more efficient inhibitor of in vivo IL-1 signaling than anakinra. Recently, rilonacept was proven effective in a phase II trial of familial cold autoinflammatory syndrome, which is similar to sJIA.[97] A double-blinded, placebo-controlled study of rilonacept in children with sJIA, followed by an open-label extension trial is in progress.

Abatacept

Abatacept is a recombinant fusion protein with a unique mechanism of action. Abatacept comprises the Fc portion of the human immunoglobulin molecule combined with the extracellular portion of cytotoxic T-lymphocyte-associated antigen 4.[98] Abatacept acts by preventing the generation of a costimulatory signal required for T-cell activation. Abatacept thus downregulates T-cell stimulation, leading to decreased B-cell and macrophage activation, and also modulates multiple downstream inflammatory cytokine pathways that have been implicated in the pathogenesis of JIA.[6] The results of a double-blind, randomized controlled withdrawal trial of abatacept in 190 patients with JIA and poor responses to disease-modifying antirheumatic drugs (DMARD), including anti-TNF therapy, have been reported.[99] After 4 months of treatment with abatacept, 65% of patients met ACR Pedi 30 criteria. More specifically, ACR Pedi 50, Pedi 70, and Pedi

90 response rates were 50%, 28%, and 13%, respectively. No serious or opportunistic infections were reported.

Rituximab

Rituximab is a chimeric monoclonal antibody to CD20, a cell surface marker found on mature B cells. Binding of the monoclonal antibody to CD20 results in selective depletion of CD20-positive B cells.[100] Although, rituximab has been shown effective in the treatment of adult rheumatoid arthritis, there are only rare reports of rituximab treatment in children with severe refractory JIA.[101,102]

Tocilizumab

Tocilizumab is a recombinant, humanized monoclonal antibody that binds to the IL-6 receptor and blocks downstream signaling of IL-6. Yokota and colleagues have reported the results of a phase III trial in which 56 children with sJIA who did not respond to DMARDs were treated with tocilizumab (8 mg/kg) for 12 weeks.[103] The authors reported that ACR Pedi 30, 50, and 70 criteria were met in 91%, 86%, and 68% of patients, respectively. A total of 80% of patients treated with tocilizumab maintained an ACR Pedi 30 response or better, compared with only 17% of patients who received a placebo.

It remains to be determined whether tocilizumab can outperform etanercept in a head to head comparison.

Summary

New definitions of inactive disease and clinical remission and increased understanding of the pathogenesis of JIA have facilitated the development of biologics and improved JIA treatment options. New insights into the complex network of immune cells and inflammatory cytokines have led to the development of drugs that target these mechanisms with proven effectiveness in the treatment of JIA. New biological agents are continually being developed to treat JIA. Performing clinical trials to prove the quality, safety, and efficacy of these biologics remains an ongoing challenge. Accumulating evidence suggests that early disease control may be important in determining long-term outcomes in patients with JIA. Although newer biologic agents may alleviate inflammatory arthritis and prevent the disability associated with joint destruction, continued and comprehensive observation is required to determine the long-term outcomes associated with these treatments.

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兒童特異性關節炎的新進展

黃璟隆

　　兒童特異性關節炎包含各式原因未明的慢性關節炎的疾病，屬兒科最常見的風濕性疾患且常合併各種併發症。最近幾年，有關兒童特異性關節炎的病因、疾病控制與否的定義及用來治療關節炎的生物製劑，其發展有很大的進展。兒童特異性關節炎發病原因與基因遺傳及環境都有關；其中包括周產期發生的因素、病毒或細菌感染、表觀遺傳學及營養不正常皆有關係。在本文中亦探討此病與發炎細胞素免疫反應的網路路徑，另外，亦描述新近發展生物製劑用於此病的現況。雖然生物製劑的使用對改善罹患特異性關節炎的兒童有很大的改善，但長期的副作用及預後，仍需更多時間的觀察。(長庚醫誌 2012;35:1-14)

關鍵詞：兒童特異性關節炎，病因，生物製劑