New Treatments for Juvenile Idiopathic Arthritis

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Key words: juvenile idiopathic arthritis, juvenile rheumatoid arthritis, non-steroidal anti-inflammatory drugs, infliximab, etanercept, methotrexate, anti-tumor necrosis factor therapy, autologous stem-cell transplantation

IMAJ 2002;4:39–43

Juvenile idiopathic arthritis (previously called juvenile rheumatoid arthritis, until recent reclassification) is the most common rheumatic disease of childhood and consists of seven disease subtypes with specific clinical, genetic and prognostic characteristics [1]. The treatment of JIA is dependent to a large extent on the disease subtype, and combines drug use with physical and occupational therapy, dietary manipulation, and psychosocial and educational partnership with patients and parents.

In general, the initial treatment of JIA (or juvenile rheumatoid arthritis) consists of non-steroidal anti-inflammatory drugs, but only a third of the children will satisfactorily respond to these drugs [2]. Intraarticular corticosteroid injections are often used, especially in pauci-articular JIA, and may induce disease remission in as many as 60% of patients [3].

These modalities are usually not adequate for treating patients with polyarticular or systemic-onset JIA. Prior to 1990, the treatment approach for these patients was dubbed the "therapeutic pyramid." This meant that the intensity of therapy was gradually increased in unresponsive patients, thus "climbing" the pyramid. Initially, NSAIDs and other low toxicity drugs were used in nearly all patients. Doses were gradually increased and NSAIDs were substituted with other drugs in unresponsive patients. Second-line drugs were added later, usually one at a time. These medications commonly included hydroxychloroquine, gold compounds, penicillamine and sulfasalazine. Immunosuppressive medications were used as a last resort. Often, mainly in systemic JIA, it was necessary to use systemic steroids, despite the devastating side effects, especially in growing children.

Two important developments changed this philosophy in the early 1990s. Studies showed that active JIA continued into adulthood in at least 50% of children, and that most patients developed radiologic erosions within 2 years of disease onset [4]. A landmark multinational study found that low dose methotrexate (10 mg/m^2/week) is effective in the treatment of JIA, is well tolerated, and may slow the radiologic progression of disease [5,6]. Therefore, most children with progressive polyarticular and systemic-onset JIA are started early with methotrexate. However, only two-thirds of the patients with polyarticular JIA and a smaller proportion of patients with systemic-onset JIA respond to this dose [5,7]. Several small studies have shown that some patients respond to higher doses of methotrexate [8,9].

Immunosuppressive medications or regimens that combine drugs are proposed for patients who do not respond to high doses of methotrexate. Only a few uncontrolled studies have reported on the efficacy and safety of these therapies in children with JIA [10,11].

This review will focus on two new advances in the treatment of juvenile idiopathic arthritis (also known as juvenile rheumatoid arthritis): anti-tumor necrosis factor therapy and autologous stem-cell transplantation.

Anti-tumor necrosis therapy: etanercept and infliximab

The developmental process of etanercept is novel in childhood rheumatic diseases. The efficacy of most "traditional" medications was first demonstrated in controlled clinical trials. Later studies explained the mechanism of action and the effect on disease pathogenesis. Many medications were borrowed from other subspecialties, including oncology and gastroenterology. Furthermore, most drugs were initially developed for adults with rheumatoid arthritis and later adopted in children. Methotrexate is an excellent example of this process. Most anti-rheumatic drugs do not act specifically on the disease process.

Etanercept was developed in the opposite direction – from "bench to bedside." The important role of TNF-α in the pathogenesis of JIA was first discovered in basic research studies [12,13]. Based on this knowledge, the drug was developed initially to treat arthritis, and was studied simulta-

JIA = juvenile idiopathic arthritis
NSAIDs = non-steroidal anti-inflammatory drugs

TNF = tumor necrosis factor

neously in adults with rheumatoid arthritis and children with JIA [14,15]. Etanercept represents the first "biologic modifying" drug in JIA and targets a molecule directly implicated in the pathogenesis of JIA.

TNF-α is a pro-inflammatory cytokine, secreted mainly by macrophages activated by the trimolecular complex of the antigen T cell receptor major human compatibility molecule. TNF-α induces many events in the inflammatory process that eventually cause cartilage damage and joint destruction. TNF-α and TNF-β (lymphotoxin) levels are elevated in both the serum and synovial fluid of patients with JIA, and these levels correlate with disease activity and levels of other pro-inflammatory cytokines [12,13]. TNF-α is bound to two membrane-bound receptors in T cells, p55 and p75 [16]. In addition to membrane-bound receptors, soluble TNF receptors are found in the synovial fluid. Soluble TNF receptor levels correlate with levels of TNF in the synovial fluid [13].

Two therapeutic approaches were adopted to reduce TNF activity in arthritis. The first is based on specific murine anti-TNF monoclonal antibodies [17]. These antibodies (infliximab, Remicade™, Centcor, USA) have been approved in Israel for use in Crohn's disease and for RA in the United States in combination with methotrexate. Several small, uncontrolled open studies in JIA have shown that infliximab has an efficacy similar to etanercept when given intravenously at a dose of 3 mg/kg every 2 to 8 weeks [18,19]. Controlled studies of infliximab in JIA are underway.

The second approach is based on the absorption of TNF-α by development of a genetically engineered p75 soluble TNF receptor fused to the Fc domain fragment of human immunoglobulin G1 in order to increase the biologic half-time of the receptor (etanercept, Enbrel®, Immunex, Seattle, USA).

To date, there is more than 3 years experience of use with etanercept in JIA [15,20]. Etanercept was first tested in a two-phase withdrawal study [15], when it was given to 69 children with polyarticular JIA unresponsive to methotrexate. All slow-acting anti-rheumatic drugs were discontinued prior to the start of the study. Etanercept was administered subcutaneously, 0.4 mg/kg/dose twice weekly. The mean age of the patients was 10.6 years (range 4–17) and disease duration 5.9 years. Outcome measures were a core set of six measures defined by the Pediatric Rheumatology Collaborative Study Group [21]. These include the number of joints with arthritis, number of joints with limitation of motion, erythrocyte sedimentation rate, global assessment by parents and physician, and functional ability assessed by the Childhood Health Assessment Questionnaire. In the first open phase of the trial, 51 children (74% of the patients) were defined as responders. These patients were entered into a 4 month randomized double-blind study. Twenty-five patients continued to receive etanercept and 26 received placebo injections. Disease flare occurred in 81% of the patients who received placebo, after a mean of 28 days. Among patients who continued to receive etanercept, only 28% flared, after a mean of 116 days.

The study was extended for another year as an open-label trial in 58 patients [20]; 50 patients completed this phase. Seventy percent of the patients continued to demonstrate a profound response (JIA core set improvement of 50%) and more than 30% entered remission. Side effects were mild, mainly injection site inflammation, upper respiratory infections, and headaches. In the double-blind phase there were no significant differences between the etanercept and placebo groups. In the extended open phase, two children developed mild varicella infection. Severe sepsis and malignancies have not been observed in children. However, one child developed diabetes mellitus after 2 months of etanercept therapy [22]. The child's serum was found to contain anti-GAD antibodies prior to starting etanercept. Since rare cases of sepsis have been reported in adults with RA (often in patients with diabetes mellitus), it is recommended to discontinue etanercept during a febrile illness and to treat varicella exposures as in steroid-treated patients.

Despite the encouraging results and initial enthusiasm, many unanswered questions remain regarding the use and long-term safety of etanercept. Etanercept is very expensive. The cost in Israel of one 25 mg vial is US$157. Therefore, the annual cost for an adult or child weighing more than 60 kg is more than $15,000. The drug has been approved in Israel for use in polyarticular JIA but is not yet included in the Ministry of Health's "drug basket." Should etanercept be given early in the disease process, or should it be limited to patients who do not respond to traditional therapy? In order to answer this question, it is necessary to compare etanercept to methotrexate in children with early polyarticular disease. It needs to be determined whether etanercept is a true disease-modifying drug that slows radiologic progression of joint damage.

Another unanswered question in children is whether etanercept is effective in other types of JIA. Small uncontrolled studies and a questionnaire survey of pediatric rheumatologists in the U.S. have suggested that etanercept is less effective in patients with systemic-onset JIA [23,24]. An excellent response to etanercept was found in five patients with enthesitis-related JIA (spondyloarthritis) [25]. There are still no markers to predict which patients will respond to etanercept and whether higher doses are effective and safe for the 25% of these children who do not respond. In one study, higher doses (1.1 mg/kg/dose) were generally not effective in patients with polyarticular JIA unresponsive to usual doses of etanercept [26]. No significant side effects were observed at the higher dose. The duration of etanercept use after remission induction is still unknown. Studies in the USA are underway to answer these questions.

Long-term safety questions related to immune manipulation have yet to be answered, mostly concerning the development of autoimmune diseases and subsequent malignancies. Patients should be cautioned about these issues prior to starting treatment.

RA = rheumatoid arthritis

In summary, etanercept shows great promise with excellent short-term safety in the treatment of children with polyarticular JIA unresponsive to traditional therapy. However, many questions have yet to be addressed, including indications in other forms of JIA, use in early JIA, cost, and long-term safety issues.

Autologous stem-cell transplantation

There is substantial evidence that abnormal autoreactive T cell clones have an important role in the pathogenesis of JIA [27,28]. Massive immunosuppression to delete these clones may induce disease remission. Bone marrow reconstitution with non-autoreactive T cell precursors will hopefully produce a normal T cell repertoire without memory T cells. Early observations of long-term remission of RA were seen following stem-cell transplantation for malignant diseases or aplastic anemia [29,30]. Remission following ASCT in many patients with RA and systemic lupus erythematosus has been demonstrated [31–33], however, early recurrences occurred in unmanipulated grafts [34].

Most children with JIA respond to conventional medical therapy that includes immunosuppressive medications, such as cyclophosphamide, azathioprine and cyclosporin [35]. However, a subset of patients, mainly those with systemic-onset JIA, and a few patients with severe polyarticular disease do not respond to any combination of medications. These patients develop rapidly progressive destructive joint disease, severe growth disturbances and, possibly, adverse reactions to their aggressive therapy. Spiegel et al. [36] found that thrombocytosis and steroid-dependent fever after 6 months of systemic-onset JIA are predictors of a poor prognosis and unresponsiveness to conventional medical therapy.

ASCT experience in JIA

Wulffraat and co-workers [37] in 1999 first reported on ASCT in four Dutch children with longstanding and unresponsive JIA: three with systemic disease and one with polyarticular JIA. All four responded well and were disease free (without anti-rheumatic drugs) after a follow-up of 6–18 months. Bone marrow reconstruction was rapid and mild varicella zoster infections developed in two of the children.

To date, approximately 30 patients have undergone stem-cell transplantation for JIA. Dramatic improvement was reported in 60–65% of the patients following ASCT. Wulffraat [38] reported to the American College of Rheumatology 2000 Conference on 13 patients from Holland with longstanding JIA – 11 with systemic and 2 with polyarticular disease. The median follow-up time after ASCT was 18 months (range 3–39). Seven patients entered long-term drug-free remission and two were in partial remission. The mean pain and disability severity decreased by 80%. The mean number of swollen joints decreased from 20 to 5 after 2 years. There were also significant decreases in the erythrocyte sedimentation rate and C-reactive protein levels, and a marked increase in the growth velocity.

However, two patients died from the macrophage activation syndrome 12 days and 5 months after transplantation. Another death after ASCT was reported from France in a 9 year old girl with systemic-onset JIA [39]. All three had highly active systemic disease during ASCT conditioning, and MAS was triggered by infection (Epstein-Barr virus, cytomegalovirus and *Toxoplasma*). Briefly, MAS entails massive activation of macrophages, resulting in liver failure, disseminated intravascular coagulation and encephalopathy. Bone marrow biopsies are characterized by macrophage hemophagocytosis. This syndrome is commonly seen in systemic-onset JIA, often after infections or gold injections. If untreated (steroids, cyclosporin), MAS is usually fatal. Other complications occurred in seven patients with varicella zoster infection, and in one patient with infection from atypical *Mycobacterium* and *Staphylococcus epidermidis*.

Principles of ASCT in JIA

There is still much debate on the technical details of ASCT in juvenile idiopathic arthritis. In general, stem cells are obtained from either bone marrow or peripheral blood. Under debate is whether granulocyte colony-stimulating factor should be used for priming, and the amount of CD3 depletion or CD34 (pluripotent stem cell)-positive selection. The conditioning regimen generally includes high dose cyclophosphamide and anti-thymocyte globulin. The use of total body irradiation is controversial. Besides steroids, which are weaned over 2–3 months, anti-rheumatic medications are discontinued prior to ASCT.

Following graft infusion, neutrophil and platelet recovery occur within 1 month. T cell recovery is slower. Normal T cell counts and mitogenic response are seen within 3–5 months after ASCT. Patients are treated for infection according to existing protocols. However, if fever persists, cyclosporin is added to treat for possible MAS.

Unresolved issues in ASCT for JIA

Many important issues remain unresolved regarding ASCT for juvenile idiopathic arthritis. First, is it ethical to propose a potentially fatal treatment for a disease that is usually non-fatal, although occasionally severely disabling? The length of follow-up is still too short to determine whether ASCT is effective and to fully assess the cost-benefit ratio. It is still unknown whether ASCT is sufficient to eliminate memory T cells of autoreactive clones.

Patient selection and timing of ASCT is crucial. While an adequate trial of conventional therapy must be given on the one hand, the patient must still have rehabilitation potential on the other. Furthermore, long-term immunosuppressive therapy may increase the hazards of ASCT. Future development of prognosis predictors may help to resolve this question.

As stated previously, mainly details regarding the conditioning protocol, graft preparation and post-transplantation prac-

ASCT = autologous stem-cell transplantation

tice remain undecided. Methods of early detection and treatment of MAS are essential. As a result of the three deaths from MAS, the protocols for ASCT were changed. Conditioning is now begun only after systemic features of JIA are controlled with high dose steroids.

There is debate on alternatives to ASCT. Some argue that allogeneic stem-cell transplantation may be more effective than ASCT in eliminating autoreactive T cell clones despite the greater risks. Other investigators claim that administration of high dose immunosuppressive medications without stem-cell transplantation may be sufficient, thus reducing complications of ASCT.

Recently, a workshop of European and American pediatric rheumatologists and transplantation experts representing centers that perform ASCT for JIA met in order to establish a unified protocol for ASCT [40]. The protocol, when completed, will define eligibility criteria, ASCT procedures and other issues that need to be addressed in future research projects. Currently, ASCT should still be considered an experimental therapy.

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