On beyond methotrexate treatment of severe juvenile rheumatoid arthritis

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Introduction

Juvenile rheumatoid arthritis (JRA) is not a difficult disease to treat initially. With time, however, it often becomes a challenging chronic illness in which the goal of prolonged remission seems to be a continuing quest for many patients and pediatric rheumatologists. The aim of treatment of juvenile rheumatoid arthritis is simple: prevention of joint destruction and promotion of growth and development. The attainment of these goals after the first few years of treatment becomes more and more difficult as medication after medication loses effectiveness and flares of disease occur.

The treatment of juvenile rheumatoid arthritis is hampered by our current lack of understanding of its etiology, what causes it to persist and why it recurs after periods of remission. Treatment is further complicated by the lack of available medications that can specifically alter the vaguely understood events and immunologic processes without significantly altering normal biological and immune functions. Other dilemmas that add to treatment difficulty are the lack of ability to predict which patients will have a more prolonged course with significant joint destruction and which medications are more likely to be effective in which types of patients.

The current nomenclature of JRA - be it JCA, idiopathic chronic arthritis of childhood or other, are currently based on clinical presentations at onset rather than on the immunology of the disease. From my personal experience, only two groups of childhood arthritis stand out - systemic onset patients and those with rheumatoid factor positive symmetrical poly-articular disease. All other patients, including many with spondyloarthropathy, have little distinction and change so much over time, that I feel at a loss to be confident about a specific subtype, much less prognosis.

With these considerable limitations in mind, this paper will explore treatment options for persistent, severe childhood chronic arthritis beyond the use of methotrexate but before the leap to transplant. These strategies fall into three main categories: combinations with methotrexate; familiar single agents; and novel new drugs (Table I).

Methotrexate in combination

Corticosteroids

Corticosteroids are most likely part of the treatment regimen in any patient with severe juvenile rheumatoid arthritis. There are three strategies that are important to discuss: weekly high dose pulses (IV or PO), low dose daily, and intra-articular injections.

Weekly pulse solumedrol (30 mg/kg, 1 gm max) can be useful in the treatment of patients with very active disease as they transition from one regimen to another or during a flare of disease. Miller has been a pioneer in this treatment for children with chronic rheumatic diseases (1). Eight children with juvenile rheumatoid arthritis (3 poly, 5 systemic), all

Table I. Treatment strategies for severe JRA.

Methotrexate with:
Corticosteroids
Weekly pulse
Low dose daily
Multiple intra-articular
Sulfasalazine
Sulfasalazine and Hydroxychloroquine
Azathioprine
Cyclosporine
Cyclophosphamide
Single Agents
Azathioprine
Cyclosporine
Novel New Drugs
Entanercept
Infliximab
Leflunomide

initially responded to IV methylprednisolone 30 mg/kg or IV hydrocortisone 500 mg every 6 hours for four doses. Several patients continued infusions every 7-14 days for up to 3 years with good clinical response and without significant side effects or cushingoid features.

The occurrence of side effects is not uncommon, as described by Kline-Gitelman and Pachman in 213 children, including 25 patients with juvenile rheumatoid arthritis (2). Of the total group 22% had one or more adverse reactions to pulse IV methylprednisolone and 10% of the total eventually discontinued treatment because of side effects.

The most commonly reported short term adverse reaction in this group of children was a change in behavior, seen in nearly half of those experiencing reactions (most of these patients were also on daily oral corticosteroid). Other common reactions, occurring in 10-15% of patients, included allergic reactions, headache, abdominal pain, and vital sign changes during infusions. Out of an estimated 10,000 doses of pulse IV corticosteroids, one child developed anaphylaxis, another had low blood pressure which resolved, and a third had low blood pressure associated with tachycardia and diaphoresis which resolved after the infusion was interrupted. The use of diphenhydramine pre-infusion helped decrease side effects for many patients. For those patients who dislike the intravenous route of administration but find this treatment helpful, drinking the reconstituted methylprednisolone is an option.

Low dose daily prednisone (7.5 mg) for two years has been shown to substantially reduce the rate of radiologically detected progression of early rheumatoid arthritis (3). There has been much investigation into the possibility of an underlying deficiency of endogenous cortisone production in patients with rheumatoid arthritis. To date, most evidence demonstrates that the hypothalamo-pituitary-adrenal axis activity in rheumatoid arthritis patients is not significantly different from normal subjects (4). With regards to children, the major concern for the use of daily steroid is the risk of osteoporosis and inhibition of linear growth. Osteoporosis is often present before medications are started due to inflammation and progresses with untreated disease. Rather than worsening with low dose steroid treatment, osteoporosis may be counterbalanced by increased physical activity and reduction of joint inflammation in effectively treated patients. In my own experience, most children treated with the doses of corticosteroid 0.1 - 0.15 mg/kg per day are able to grow in linear height (some will grow at 0.3 mg/kg/day).

Intra-articular injection of corticosteroid in children with JRA is a safe and effective mode of therapy (5). Full remission of the joint injected usually occurs and the response duration is best with long-acting microcrystalline steroids such as triamcinolone and hexacetonide (6). Multiple joint injections under anesthesia is an effective treatment for many patients. The newer short-acting anesthetics make this a brief, simple procedure in an anesthesia staging area. Injection of 4 to 26 joints can result in immediate resolution of synovitis in the setting where a medical regimen has not produced full control of synovitis, or when there has been a flare of disease. An occasional patient with 10 or more joints injected (including large joints) may receive enough steroid to briefly gain weight and have rounder cheeks; but this resolves quickly. This treatment strategy is based on the premise that if the synovitis of many joints can be successfully squelched, a medication regimen may be able to prolong this response.

Methotrexate with sulfasalazine

Sulfasalazine was demonstrated to be effective in the treatment in juvenile chronic arthritis by Ozdogen *et al.* when administered to 18 patients (7). Later, Joos *et al.* reported significant improvement in 80% of patients with JRA (nearly all pauci) with remission in 51%, when these patients were treated with 30 - 50 mg/kg per day of enteric coated sulfasalazine (2,000 mg/day max) (8). Ansell *et al.* in the same year reported less spectacular results in 51 patients with juvenile chronic arthritis treated with 40 mg/kg/day of sulfasalazine for 12 months; 44% did not respond and 16% discontinued secondary to side effects (9). Hwang and Chen retrospectively studied 35 patients with juvenile spondyloarthritis and juvenile rheumatoid arthritis treated with sulfasalazine for a mean of 2.5 years (3 weeks to 8.1 years) (10). A clinically significant response occurred in 64% of the children with remission in 39%. While there was no difference in response rate between JRA and JSA patients, the time to remission was shorter in JSA patients (mean 5 months) than in JRA (mean 25 months). Side effects occurred in 11% of patients and only one discontinued sulfasalazine (persistent diarrhea).

Although there are no reports in children of the use of methotrexate with sulfasalazine, this is standard practice for many pediatric rheumatologists. Since the liquid form of sulfasalazine is no longer available, the use of this combination is difficult in young children. The adverse effects of sulfasalazine are similar to those of non-steroidal anti-inflammatory agents as well as methotrexate, except for skin rash and Stevens-Johnson syndrome. Sorting out the adverse reactions can be challenging in this combination of drugs. As per reports, sulfasalazine is often best tolerated when the enteric coated form is used and when the dose is gradually increased to the total amount over a 3- to 6-week time period (7, 9).

Methotrexate, sulfasalazine and hydroxychloroquine

The combination of methotrexate, sulfasalazine and hydroxychloroquine is commonly referred to as triple therapy for rheumatoid arthritis and is effective for many patients based on a multicenter, two-year, double blind, randomized study in which patients received sulfasalazine 500 mg BID and hydroxychloroquine 200 mg BID with methotrexate at 7.5 to 17.5 mg per week (11). This combination resulted in 50% improvement in 77% of patients compared to improvement in 33% of patients treated with methotrexate alone or 40% of patients treated with sulfasalazine and hydroxychloroquine. This combination has not been evaluated in children but is used by many pediatric rheumatologists.

Methotrexate with azathioprine

Methotrexate and azathioprine is another combination used frequently for the

treatment of rheumatoid arthritis that has not been investigated in the treatment of juvenile rheumatoid arthritis. Wilkins *et al*. (12) reported only 38% improvement with the combination of methotrexate and azathioprine compared to 45% improvement with methotrexate alone in a double blind, perspective, multi-center control trial in which the median dose of azathioprine was 100 mg per day and the median dose of methotrexate was 7.5 mg per week. The combination did not have enhanced efficacy nor increased toxicity. Doses of both medications are lower than what would be used with single medication treatment, in an attempt to decrease possible adverse effects since the toxicity profile of these two drugs is so similar.

Methotrexate with cyclosporine

The combination of methotrexate and cyclosporine has been demonstrated to be effective for the treatment of severe rheumatoid arthritis (13,14). A 6-month double blind, randomized, multi-center trial showed that 48% of patients receiving methotrexate and cyclosporine experienced at least 20% improvement in the number of tender and swollen joints as well as improvement in at least 3 out of 5 other variables, compared to 16% continuing on methotrexate alone.

A report by Reiff *et al*. (15) is the only investigation of cyclosporine and methotrexate for the treatment of juvenile rheumatoid arthritis. Twelve children with JRA (9 systemic, 3 poly, and 1 pauci to poly) were continued on methotrexate (10 - 30 mg per week) with the addition of cyclosporine (2.1 - 5 mg/kg per day) for 6 to 32 months (median 15 months). At the end of the treatment, ten patients had a decreased active joint count and half of these decreased their joint count by 50% or more. Nine patients had been on corticosteroids; seven were able to decrease their dose by more than one-half and 5 were able to discontinue corticosteroids all together. No patient achieved remission.

Nephrotoxicity is a major problem with cyclosporine use in both adults and children with rheumatologic diseases. Seven of 12 children treated with both methotrexate and cyclosporine suffered a rise in serum creatinine of at least 0.2 mg/dl (15). Hypertension and hirsutism were not observed by Reiff *et al.*, but significant infection occurred in several patients.

Methotrexate with pulse methylprednisolone and cyclophosphamide

Arnold *et al*. (16) published discouraging results of pulse cyclophosphamide in 5 patients with severe rheumatoid arthritis (Steinbrocker functional class III). Only one patient improved after 6 treatments (500 mg/m^2) repeated every 4 - 6 weeks. More encouraging results were reported in 22 patients with systemic onset juvenile rheumatoid arthritis treated not only with monthly pulse cyclophosphamide (500 - 1000 mg/m^2), but also with pulse methylprednisolone (30 mg/kg, 1 gm max) and weekly methotrexate (17, 18). The significant response in all of these patients with juvenile rheumatoid arthritis may have been the result of the addition of solumedrol and/or the concomitant use of methotrexate. Although these initial reports were encouraging, subsequent use in patients with severe juvenile rheumatoid arthritis has not lead to such excellent results.

Single agents

Azathioprine

Azathioprine has been used in patients with rheumatoid arthritis for many years (19). In 1986 Kvien *et al*. reported azathioprine to be effective in the treatment of juvenile chronic arthritis at a dose of 2.5 mg/kg/day in a double blind, placebo controlled sixteen-week study (20). Most of the changes in disease activity measurements were in favor of azathioprine (n = 13) compared to placebo (n = 11), but statistical significance was only demonstrated for improved functional capacity and the subjective total assessment.

A larger, longer study by Savolainen *et al*. prospectively evaluated 129 consecutive patients with JCA treated with azathioprine 2.5 - 5.0 mg/kg/day for a median of 13 months, (range 3 days to 8.5 years) (21). The majority of patients significantly improved; 29% achieved remission and many were able to markedly decrease their corticosteroid use. 14% of patients discontinued treatment due to side effects, two-thirds of which occurred within the first two months of treatment. The most common adverse effects were abdominal pain, elevated transaminases, cytopenias and rash. The concern regarding later malignancy has dampened enthusiasm for azathioprine as a treatment modality for children, although the magnitude of this problem in pediatric patients is unknown. Adults treated with high dose azathioprine (up to 5 mg/kg/day) may be at only a two-fold risk of later lymphoproliferative disease compared to other RA patients (22).

Cyclosporine

Cyclosporine as a single agent may have a unique role to play in the treatment of the macrophage activation syndrome (MAS) of systemic onset juvenile rheumatoid arthritis. Mouy *et al.* reported its rapid effectiveness in 5 children with MAS treated with 2 - 8 mg/kg/day of cyclosporine (23). Within 48 hours the MAS had improved and it later resolved in all patients. Cyclosporine could be tapered, but later persistent synovitis developed in 4 of these 5 patients. Ravelli *et al.* have reported 3 patients with MAS who responded promptly to cyclosporine 3 - 5 mg/kg/day (24, 25). Long-term follow up was not available in these patients.

Patients with active adult Still's disease also appear to respond rapidly to cyclosporine. Marchesoni *et al*. reported 6 patients with active adult Still's who responded well to treatment with cyclosporine 3.7 - 4.4 mg/kg/day (26). Three of these 6 patients experienced increased blood pressure and elevated serum creatinine, however. A decreased dose of cyclosporine improved these side effects. One patient discontinued cyclosporine because of severe muscle cramps.

Cyclosporine as a single agent for the treatment of rheumatoid arthritis has been demonstrated to be effective in the 5 - 10 mg/kg/day dosage range, but with considerable toxicity (27). 35% of patients discontinued the medication, over half of them because of renal dysfunction. Cyclosporine at a dose of 3 mg/kg/day is better tolerated and has been shown to slow the progression of joint damage in patients with rheumatoid arthritis (28).

Its efficacy as a single agent for the treat-

ment for juvenile rheumatoid arthritis, however, has not been as encouraging. Ostensen *et al*. reported temporary symptomatic effects on disease activity in 14 patients with JRA after 6-20 months of treatment with cyclosporine 4 - 15 mg/kg/d (29). Eleven of these 14 patients discontinued cyclosporine due to lack of efficacy (n = 4) or side effects (n = 7). The most common adverse effects included hypertrichosis, increases in serum creatinine or potassium, and decreased hemoglobin.

Pistoia *et al.* investigated the efficacy and safety of cyclosporine at a mean dose of 5 mg/kg/day in 9 patients with JRA treated for 9 - 23 months. Patients had a significant improvement in joint inflammation and reduction of steroid dose (30). This dose was well tolerated by these 9 patients with no elevation of serum creatinine, but mild hypertension, hypertrichosis, hypoproteinemia, tremors and alopecia did occur. Reiff *et al*. reported five patients with systemic onset JRA treated with cyclosporine 2.7 - 3.5 mg/kg/day for six months (15). In 3 patients the steroid dose could be lowered, but in only one was the synovitis improved. All patients, however, experienced an abatement of fever with cyclosporine treatment.

Novel new drugs

There are three new medications available for the treatment of rheumatoid arthritis - leflunomide, and the anti-TNF drugs entanercept and infliximab. Only entanercept has FDA approval for use in juvenile rheumatoid arthritis. Entanercept and leflunomide have FDA approval for use in RA, and infliximab approval is pending. However, there is no long-term data regarding the safety or efficacy of these drugs in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, or other diseases.

Entanercept

Entanercept (Enbrel) is a fusion protein consisting of the extra-cellular ligand-binding portion of the human tumor necrosis factor receptor (TNFR-p75) linked to the Fc portion of human IgG1. It binds to tumor necrosis factor (both alpha and beta) and blocks its interaction with cell surface TNF receptors. Blocking TNF modulates responses that are induced or regulated by TNF, including the expression of adhesion molecules responsible for leukocyte migration (i.e., E selectin and ICAM-1), serum levels of IL-6 and other cytokines, and serum levels of matrix metalloproteinase-3 (MMP-3).

The half-life of entanercept in patients with rheumatoid arthritis is about 115 hours (range 98 - 300 hours) with an average serum concentration of 1.7 - 5.6 mcg/ml. Children with JRA achieve similar serum concentrations after repeated doses of 0.4 mg/kg administered subcutaneously twice weekly (max 25 mg/injection). Developmental toxicity studies have been performed in rats and rabbits at doses of entanercept ranging from 60 to 100-fold higher than the human dose and revealed no evidence of harm to the fetus. However, since there have been no studies yet in pregnant woman, entanercept is not recommended for women who are pregnant.

Studies in patients with rheumatoid arthritis treated with 25 mg SQ twice weekly have revealed 59% improvement with ACR 20 criteria by 6 months, while 40% show ACR 50 improvement by 6 months (31). The clinical response generally appeared within 1 to 2 weeks after the initiation of therapy and nearly always occurred by three months. In patients with rheumatoid arthritis, entanercept has been used in conjunction with methotrexate in a study of 59 patients with excellent results - 71% with ACR 20 criteria at month 6 and 39% with ACR 50 criteria (32). The authors conclude that the addition of entanercept provided significant clinical benefit beyond that seen with MTX alone.

An investigation of the efficacy of entanercept in children with JRA has been very encouraging. By 3 months of treatment with 0.4 mg/kg administered subcutaneously twice weekly, 76% of children demonstrated a clinical response as defined by: ≥ 30% improvement in at least 3 of 6, and ≥ 30% worsening in no more than 1 of 6, JRA course set criteria (which include physician and patient global assessments, active joint count, limitation of motion, functional assessment, and ESR) (33). Patients had at least 5 active joints (with at least 3 joint showing loss of motion plus pain or tenderness) and ranged in age from 4 - 17 years. 96% were on stable NSAIDs and 37% were on stable steroid. This JRA study was unique because all the patients were given an active drug initially. After 3 months, those who responded were then randomized to receive either placebo or the active drug. 81% of those patients who were randomized to receive placebo flared within a median of 28 days. Those that remained on enbrel continued their response at 7 months (end of study).

Entanercept has been studied in 1,039 patients with rheumatoid arthritis and in 69 patients with polyarticular course juvenile rheumatoid arthritis. In patients with rheumatoid arthritis, the most common side effects were injection site reactions (37%) and upper respiratory tract infections. Serious infections and death from sepsis have been reported in patients with rheumatoid arthritis. There are no long-term studies available using entanercept in patients with rheumatoid arthritis to assess carcinogenesis, mutagenesis, or impairment of fertility.

The side effects in patients with JRA have consisted primarily of mild injection site reactions and upper respiratory tract infections. More children reported abdominal pain (17%) and vomiting (14.5%) than in studies in adult patients. While receiving entanercept, 2 children developed varicella infections associated with signs and symptoms of aseptic meningitis, but both resolved their infection without sequelae. It is recommended that children receiving entanercept be tested for vericella immune status and if not immune, entanercept should be temporarily discontinued when there is significant exposure to varicella. Responses to immunizations have not been studied in children receiving entanercept.

Entanercept appears to be an effective drug for those JRA patients who are intolerant of, or have failed methotrexate and other treatment regimens. However, the possibility of serious infection must be monitored closely.

Infliximab (Remicade)

Infliximab is a chimeric human/mouse anti-TNF monoclonal antibody which binds to TNF alpha and blocks its binding to cell surface receptors. It is given intravenously and has a half-life of about

10 days.
Hypersensitivity reactions including fever, chills, urticaria, dyspnea and hypertension have been reported. Some patients have developed human anti-chimeric antibodies or autoantibodies. One patient with RA and one with Crohn's disease developed antinuclear antibodies and a lupus-like syndrome. Infections (mild to severe) are noted in 8 - 40% of patients with rheumatoid arthritis treated with infliximab (34 - 36) .
A randomized, double-blind trial comparing a single infusion of infliximab to placebo demonstrated a statistically significant improvement, with a Paulus 20% response in 30 of 39 patients at 4 weeks after the infusion (34). Patients received either 1 mg/kg (n=25) or 10 mg/kg (n=24) of infliximab. Over half responded by the more stringent 50% Paulus criteria. The same investigators later treated seven of the responders with 2 to 4 repeated infusions of infliximab (35). The timing of the subsequent infusions was dictated by the loss of response to the previous infusion. Seven patients received two infusions, five 3 infusions and four 4 infusions. Patients discontinued infliximab prior to 4 infusions because of urticaria, autoantibodies or persistent synovitis. The mean time between cycles was 5 weeks. All patients responded to the repeated infusions with a similar magnitude of response, but the duration of the response repeatedly decreased after each infusion.
More recently Maini *et al.* reported a 26-week, double blind, placebo controlled multi-center trial of infliximab with and without methotrexate in 101 patients with active RA (36). There were 7 treatment groups (14 - 15 patients per group) which included intravenous infliximab at 1, 3 and 10 mg/kg with and without methotrexate 7.5 mg/wk and placebo. Infusions were at weeks 0, 2, 6, 10 and 14 with follow up through week 26. A 70 - 90% reduction in the swollen joint count, tender joint count and c-reactive protein level was maintained for the entire 26 weeks in patients receiving 10 mg/kg of infliximab with methotrexate. The patient dropout rate was highest in the placebo + methotrexate and in the 1 mg/kg infliximab without methotrexate groups, due to lack of efficacy. Adverse events in 6 patients receiving infliximab necessitated the discontinuation of treatment. The most common adverse events were mild infection, headache, diarrhea and rash. 50% of the patients receiving 1 mg/kg of infliximab alone developed antibodies to infliximab.
Other monoclonal antibodies that have been used in therapeutic trials for the treatment of rheumatoid arthritis include murine, humanized or chimeric antibodies to IL-6, ICAM-1, and T-cells (both depleting and not depleting against CD-7, CD-5, CDw52, CD-4 cells) (37). Although these agents have been shown to be clinically effective in suppressing inflammation in rheumatoid arthritis, they are expensive and their action is short-lived. Some of these agents may find a role in the treatment of rheumatoid arthritis, most likely at the initiation of treatment, during the control of disease flares, or in combination with established DMARDs.

Leflunomide (ARAVA)
Leflunomide is a novel isoxazol drug. *In vitro* studies have shown that it is a prodrug and is quickly metabolized to its main active metabolite (A771726, referred to as M1). This metabolite reversibly inhibits the enzyme dihydro-orotate dehydrogenase, which is required for pyrimidine nucleotide synthesis. This drug has an antiproliferative effect on T cells *in vitro*, but little is known about its mechanism of action in patients with rheumatoid arthritis. After absorption, leflunomide is metabolized into its active metabolite M1 and reaches peak levels after 6 - 12 hours. The site of metabolism is unknown although studies suggest a role for the gastrointestinal wall, as well as the liver. 80% of the commercially available tablets are bio-available and high fat meals do not impact absorption. Due to the very long half-life of M1 (about 2 weeks) a loading dose of 100 mg per day for 3 days is used to facilitate the rapid attainment of steady state levels.
The active drug M1 is eliminated by further metabolism and excretion by both the kidneys and the bile system (half-and-half via each route). It is important to note that M1 is not dialyzable. Its elimination might be hastened by the use of activated charcoal (reported in one patient) or cholestyramine (3 patients). M1 is extensively bound to albumin and can cause a 13 - 50% increase in free non-steroidal anti-inflammatory drugs. It has been used with methotrexate with no apparent pharmaco-kinetic interactions.
The onset of leflunomide's effects have been evident at as early as four weeks and improvement continues until about 5 months. Thereafter the benefit appears to plateau and can be maintained. Rozman *et al*. reported that 52/100 patients treated with 10 and 58/101 patients treated with 25 mg leflunomide per day improved by 20% ACR criteria (38). In a 12-month multi-center trial, the improvement in disease activity in patients treated with 20 mg of leflunomide was 52% compared to a 46% improvement in patients treated with methotrexate (7.5 - 15 mg/week) (37). A 24-week trial revealed that patients treated with sulfasalazine at 2 g/d improved 56% compared to the 55% improvement seen in patients treated with leflunomidem (38). Patients with rheumatoid arthritis treated with leflunomide for 12 months have been demonstrated to have a slowing in the progression of X-ray damage (39).
Leflunomide has been studied in 1,339 patients with rheumatoid arthritis. The most common adverse reaction has been gastrointestinal symptoms, occurring in 10 - 27% of patients (diarrhea, anorexia, abdominal pain, dyspepsia, gastritis and elevation of transaminases). Other problems occurring in approximately 5 - 10% of patients include rash/allergic reactions, headache and reversible alopecia. Less common are weight loss and hypophosphatemia. Leflunomide is teratogenic, but there are no long-term studies to assess its carcinogenicity or its effect on fertility in humans.
Leflunomide has not been studied in children. Due to its lack of historical use in other diseases, its long half-life and its non-dialyzable formulation, it is difficult to recommend the use of leflunomide in children at this time.

Conclusion
In summary, with the strategy of using established medications in combination with intra-articular corticosteroid injections and the availability of new medi-

cations, there is an expansion of pathways along which to continue the quest for control of juvenile rheumatoid arthritis before resorting to autologous transplant.

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