

MTX and Beyond – Treatment of Childhood Arthritis

Carol Wallace, MD
University of Washington

Childhood arthritis does not initially seem difficult to treat. With time, however, it often becomes a challenging chronic illness in which the goal of complete remission becomes unattainable for the majority of patients. 50 to 60% of children with arthritis will have continuous or recurrent disease. They do not grow out of it, but rather grow up with it; entering adulthood with ongoing joint destruction. The aim of treatment of juvenile rheumatoid arthritis is simple: prevention of joint destruction; promotion of normal growth and development and complete resolution of disease. Effective treatment of childhood arthritis is hampered by our 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 medications that can specifically alter the suspected events and abnormal immunologic processes without significantly damaging normal biologic and immune functions. In addition to these problems, we are unable to accurately predict which patients will have a prolonged or recurrent course or which medications are more likely to be effective in which types of patients. Many rheumatologists feel that there may be a window of opportunity early in disease during which medications are likely to be more effective and have prolonged results compared to their use later in the course of disease.

Several recent important studies in adult RA have demonstrated superior outcomes when patients were treated with DMARDs within the first 2 years of disease onset, and even more striking effects when treated within the first four months. Our goal should be to treat childhood arthritis early and aggressively. There are many possible approaches for the treatment of a particular child. Unfortunately there are no studies to guide us as to which is the best and most effective treatment. Methotrexate is our most effective and widely used DMARD for the treatment of childhood arthritis. I

would like to discuss it as well as the new anti-TNF agents and leflunomide.

Methotrexate

Mechanism of Action

Methotrexate is a folic acid analog that binds more tightly to dihydrofolate reductase (DHFR) than does folic acid. This results in marked reduction in the production of reduced folates, which are important cofactors for a variety of enzymatic pathways. When high doses of MTX (500–80,000 mg/m²/week) are used to treat malignancy, profound folate depletion halts the production of DNA and RNA, causing cell death, particularly in rapidly dividing cells. Folinic acid (leucovorin), a reduced folate, can bypass MTX blockade to provide reduced folates necessary for cell function. Folic acid (folate) can not do this.

In low doses, used in the treatment of rheumatic diseases (0.3-1.0mg/kg/week or 10-30 mg/m²/week), MTX has other important actions besides inhibiting DHFR. Cronstein et al have demonstrated that MTX treatment results in increased adenosine release at sites of inflammation, due to an increase in the intracellular accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR). The resultant anti-inflammatory effect is mediated via adenosine A₂ receptors with inhibition of neutrophil adherence to endothelial cells and fibroblasts. Other actions of low-dose MTX include: interference with the action of IL-1; inhibition of the production of IL-8 and leukotriene B₄; and decrease synovial collagenase gene expression.

Some antibiotics are also folate antagonists. These antibiotics usually affect bacterial but not human folate pathways (i.e. sulfonamides), or may affect bacterial DHFR many thousand times more effectively than human DHFR (i.e. trimethoprim).

Thus, treatment with sulfonamides and MTX should not be a problem, however trimethoprim should be avoided in patients receiving MTX.

Absorption and kinetics

After administration, 80 to 90% of MTX is cleared by the kidneys in less than 24 hours. Any decrease in glomerular filtration rate (GFR) can prolong tissue exposure to MTX and increase the risk of toxicity. MTX is cleared very rapidly by children; the younger the child, the more rapid the renal clearance (). It rapidly enters cells, where it is polyglutamated by hepatocytes, red cells, fibroblasts, bone marrow myeloid precursors and possibly other cells (). Although MTX itself is cleared rapidly by the kidneys, its metabolite, polyglutamated MTX, accumulates intracellularly. This may explain the emergence of nausea and vomiting in patients after several years of treatment.

The weekly doses of MTX found to be effective in children, 0.3 – 1.0 mg/kg (10-30 mg/m²), are higher than weekly doses usually used in adult patients. The route of administration is an important factor for children since their doses are in the range in which oral MTX becomes increasingly less well absorbed > 0.3mg/kg (=10 mg/m²)(). For children, absorption has been demonstrated to be best when MTX is given without food (). The amount of MTX absorbed by children has wide variability (). For these reasons, parenteral (SQ, IM or IV) administration may be more effective than oral MTX. Experience leads many clinicians to change to SQ MTX at dosages =0.5 mg/kg, for better absorption and fewer gastrointestinal (GI) side effects. Parents (and/or adolescents) are easily taught to administer SQ MTX at home. The use of the parenteral solution of MTX (25 mg/ml) taken orally is common practice for pediatric patients and is less expensive than tablets.

Efficacy

Methotrexate is currently the most effective medication for the treatment of poly-JRA. However, when used as a single agent, it results in complete clinical response in only 8-20% of children receiving 0.45-0.5 mg/kg/week. When combined with prednisone, sulfasalazine hydroxychloroquine, cyclosporine, or intra-articular steroid, the proportion of patients achieving complete clinical response increases to 39-45%. The average length of time to reach this state is 13months; during which

time the disease process continues and joint destruction occurs.

Toxicity

The toxicity of MTX is related more to the length of exposure to MTX after 40 hours rather than the serum level achieved within the first 24 hours after dosing. MTX is well tolerated by children and does not appear to be more toxic than NSAIDs (if monitored properly). Common side effects include transient elevation of serum aminotransferase levels and nausea. Transient mucositis can occur while hematologic abnormalities are uncommon. Headache, alopecia, gastric ulcer, and mood changes are occasionally reported. There are many strategies for dealing with side effects, the most important being recognition of the potential role of NSAIDs. Side effects from NSAIDs are similar to those of MTX. Withholding a dose of NSAID before and/or after MTX administration, changing the NSAID, or discontinuing it may improve tolerance of MTX. When faced with GI symptoms in an individual patient the following additional strategies might be helpful: MTX at bedtime, change NSAID, change MTX to SQ, antiemetic before MTX administration or finally, lower the dose of MTX.

Because folic acid depletion is thought to contribute to MTX side effects; most clinicians prescribe a daily vitamin with folate or folate 1 mg/day.

The use of folinic acid (leucovorin) is not routinely used in children. It has been reported to decrease the number of episodes per year of GI and hepatotoxicity in 43 children with arthritis.

Pneumonitis is rarely reported in children treated with MTX for rheumatic diseases. Its incidence may be similar to that of adults treated for RA – approximately 1%. The emergence of a new cough, or SOB should be evaluated in a patient recently started on MTX.

Permanent hepatotoxicity is one of the greatest worries with the long-term use of MTX. Cirrhosis has not been reported in children using MTX for rheumatic diseases. Several small studies have not revealed significant histologic abnormalities in liver biopsies from children with arthritis after 2.3 to 6.0 years of treatment with MTX. Adolescents taking MTX must be strongly counseled against the use of alcohol. MTX may not be a safe therapeutic choice for some patients.

Laboratory monitoring for possible toxicity

should be done monthly at first and then every 6-8 weeks. Test should include: CBC, AST, creatinine and a yearly U/A.

Oncogenicity. Prior to 1991, there were no published data to suggest oncogenicity of MTX in patients treated for rheumatic diseases. Since then, there have been multiple reports of the development of lymphoma in RA patients treated with MTX as well as patients with dermatomyositis. These reports include a few patients 18 years or younger. Most of these tumors have been Epstein-Barr virus (EBV) positive and have resolved after discontinuation of MTX. Although these scattered reports of rapid regression after discontinuation of MTX are suggestive of a role for MTX in the pathogenesis of these tumors, more than a temporal relationship between MTX and the development of lymphoma is required to establish causality.

The possible relationship between EBV and the development of lymphoma in patients with RA is well known. There is considerable evidence against MTX as a causal agent in the development malignancy in patients with RA. 1) There is an increasing incidence of lymphoproliferative diseases in the general population. 2) Patients with rheumatic diseases have been reported to have a higher baseline incidence of lymphoid neoplasms than the general population. 3) MTX lacks the mutagenic characteristics common to other oncologic agents that are associated with the development of later malignancies. 4) There are no reports of increased lymphomas in patients treated for psoriasis. 5) A retrospective study by Moder et al of 16,263 patients with RA treated with disease-modifying anti-rheumatic drugs (DMARDs) did not reveal a relationship between MTX or any other DMARD and the development of lymphoma.

Gonadal function and reproduction are not altered by MTX. However, both males and females should wait for 3 months after discontinuing MTX before trying to conceive because MTX is a powerful teratogen. Although women with arthritis have been reported to deliver healthy babies after being on MTX in the early part of pregnancy, the use of effective birth control by young women receiving MTX needs to be repeatedly emphasized.

Anti- Tumor Necrosis Factor (TNF) Agents

Three anti-TNF medications are available to treat inflammatory arthritis and are all highly effective. Onset of action is rapid and some patients actually respond with complete clinical response. The two major questions with these powerful agents are when to use them, and how and when to stop them. Because of their expense these agents are generally not tried until other agents have failed. Since these agents are so effective, and our treatment goal is eradication of disease, might not these agents be best used at the onset of the disease, rather than late into its course?

The 3 agents tested to date are:

Etanercept – a soluble receptor fused to human IgG1 given SQ twice weekly

Infliximab – a chimeric mouse-human antibody given by IV infusion

Adalimumab – a fully humanized monoclonal antibody given SQ every 2 weeks

Common to all three of these agents is the concern with possible increased infection and emergence of latent infections (such as TB). Additional concerns in children are effects on responses to immunizations, effects on growth and development, and finally the risk of later cancer.

Etanercept

Etanercept (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: expression of adhesion molecules responsible for leukocyte migration (i.e. E selectin and ICAM-1), serum levels of IL6 and other cytokines and serum levels of matrix metalloproteinase-3 (MMP-3).

The half-life of etanercept 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 0.4mg/kg subcutaneously twice weekly (max 25 mg/injection).

Efficacy

In the seminal study by Lovell et al 74% of 69 patients with poly-JRA, who had failed to respond to MTX, met the definition of improvement for JRA by 3 months of treatment with 0.4mg/kg subcutaneously twice weekly. This JRA study was unique because all patients were given active drug initially. After 3 months, those who responded were then randomized to either receive placebo or active drug. 81% of those patients who were randomized to receive placebo flared within a median of 28 days. After 1 year of treatment with etanercept 31% had no active synovitis (18% of these patients were also receiving MTX and prednisone). Two small reports (15 patients total) have described improvement in children with severe refractory JRA when treated with corticosteroids, MTX and etanercept in combination. Higher dose etanercept > 0.8 mg/kg/dose has been tried in children with systemic onset disease with variable success.

A pilot study of 10 children with treatment resistant uveitis associated with JRA, demonstrated rapid improvement in 63%.

Anti-TNF agents have been demonstrated to be very effective in the treatment of adult RA. Used as a single agent these biologics can induce complete clinical response in some patients (a rare state in RA), and significantly slow radiological progression of joint damage. Combining MTX with anti-TNF agents has been even more effective – both in halting further joint damage and inducing disease resolution. It has been suggested by these studies that initiating anti-TNF agents early in the disease process, within the first 2 years of disease onset, rather than waiting until multiple other agents have failed, results in superior outcomes for patients with RA, as 75% of patients did not develop erosions.

Long-term open label studies of etanercept have revealed 24% of patients with complete resolution of disease. Additionally, RA patients have been able to work more and had fewer physician visits.

Toxicity/Safety

The most common side effect is that of mild injection site irritation. Other reported adverse events in children include: headache, abdominal pain, fever, accidental injury, rash, rhinitis, nausea, URI, skin infection, pharyngitis, flu syndrome, conjunctivitis and otitis. No treatment-related effects

were seen in laboratory tests for hematology, serum chemistry or urinalysis. No children have had persistent elevations in autoantibodies or sign or symptoms of another autoimmune disease. Concern about possible serious infection is a worry with the use of all of the anti-TNF agents. Children have been hospitalized for serious adverse events such as appendicitis, varicella-zoster infection, cellulitis, sepsis, dental abscess and abdominal pain, but no child has died. A long term followup investigation of 58 children treated with etanercept for a median of 2.3 years did not reveal significant increases in the rates of adverse events or infections with treatment after the first year. In adult patients there have been rare reports of multiple sclerosis that are not thought to be increased over expected rates. There has been concern regarding potential reactivation of TB with anti-TNF agents, especially. This problem has not been reported in children, however all children should have a documented negative PPD before starting therapy.

It is recommended that children receiving etanercept be tested for varicella immune status and if not immune, etanercept should be temporarily discontinued when there is significant exposure to varicella. Responses to immunizations have not been studied in children receiving etanercept, however 17 adult patients with RA, receiving etanercept were evaluated for antibody response to pneumococcal and influenza vaccine. All 17 patients mounted an appropriate antibody response to at least one of the antigens tested. These results correlate with the results from the immunocompetency testing suggesting that patients receiving etanercept retain intact immune function. Live vaccines have not been evaluated in patients receiving anti-TNF agents and should not be used.

The addition of MTX to etanercept has not been reported to be associated with increased infection or other side effects in children or adult patients.

Long term studies in adults on etanercept for over 4 years have not revealed increased serious infections or malignancies compared to controls.

Approximately 16% of patients develop antibodies to etanercept during the course of therapy. These are not neutralizing and have not been associated with a decrease in effectiveness. About 11% develop new ANAs and 15% anti-dsDNA antibodies, but with rare patients developing autoimmune symptoms.

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. Dosing is generally 3-5mg/kg/dose at 0, 2 and 6 weeks with infusions every 4-8 weeks thereafter. Weekly concomitant MTX is recommended (to decrease the development of antibodies to the active protein).

Efficacy

There is a study of infliximab in patients with JRA underway, it is not completed yet. Anecdotal reports in patients with poly JRA as well as patients with severe systemic onset JRA reveal excellent responses in many patients.

The pivotal trial in 428 patients with RA is the ATTRACT trial – a 54 week placebo controlled, randomized study of MTX (at least 12.5mg/week) plus IV infliximab at 3mg/kg or 10 mg/kg every 4 or 8 weeks. All infliximab groups had similar ACR 20 responses, however there was a significant relationship with the higher dose of infliximab with ACR 50 and 70 responses. There was a tendency for the patients with the ACR 50 and 70 responses to have higher trough levels of drug. Further analysis revealed that the trough level can be affected more by dosing every 4 weeks, rather than increasing the mg/kg dose on an every 8 week schedule.

Most remarkable was the lack of progression of radiologic damage in the patients receiving infliximab compared to the MTX alone patients. This was true even for those patients who did not achieve an ACR 20 response.

As with etanercept, patients treated with infliximab have remarkable gains in employment and return to work.

Toxicity/Safety

Adverse reactions including fever, chills, urticaria, dyspnea, nausea/vomiting, diaphoresis, tachycardia, chest pressure, flushing, hypotension and hypertension have been reported, especially with infusions 2 through 5, and usually within the first 30 minutes of the infusion. These side effects are less frequent if patients are pretreated with tylenol, benadryl and hydrocortisone. About 8% of patients have developed human anti-chimeric

antibodies with unknown effect on response. 16% of patients in the ATTRACT trial developed autoantibodies, with rare patients developing a lupus like syndrome. Infections (mild and severe) are noted in 8-40% of patients with rheumatoid arthritis. Reactivation of TB has been reported, thus all patients must have a negative PPD before the start of therapy.

Adalimumab

Adalimumab is a fully human IgG1 anti-TNF alpha monoclonal antibody that effectively blocks the action of tumor necrosis factor.

Efficacy

47 patients with RA were treated with adalimumab for two years as monotherapy (1mg/kg SQ biweekly). After two years, 42% had no radiologic progression compared to baseline. Baseline cartilage oligomeric matrix protein and ICAM-1 levels at baseline were higher in the group that had x-ray progression. Other factors such as MMP-1, MMP-3, and E-selectin were not predictive.

Toxicity

IL1-Ra (Anakinra)

IL1-Ra is naturally occurring receptor antagonist produced in small quantities by synovial tissue, macrophages and acts to inhibit IL-1 activity. This molecule is produced by recombinant DNA technology using E. coli fermentation. The manufactured molecule differs from the naturally occurring human form of IL-1Ra by only an N-terminal methionine. It is given as a daily SQ injection.

Efficacy

Studies in children are underway and results are not yet available. A 24 week, multicenter, double blind placebo controlled trial in 472 patients with severe RA compared daily doses of 30mg, 75mg, and 150 mg to placebo. The 150mg daily had the highest response rate with statistically significant improvements in patient HAQ scores, CRP and ESR in all 3 treatment groups. Response was usually within 6 weeks. Even though this was only a 24 week study there was less radiologic progression of disease in patients receiving anakinra.

Patients receiving anakinra experienced significant increases in productive days of work and domestic activity after 6 months. Patients who continued for another 6 months of anakinra treatment showed even further increases compared to the first 6 month period. Cohen et al investigated the efficacy in patients with RA of MTX plus 5 different doses of anakinra, ranging from 0.04 to 2.0 mg/kg/day. There were a significantly greater proportion of patients achieving ACR 20 response that received the 1 and 2 mg/kg/d doses at both 12 and 24 weeks.

Toxicity/Safety

81% of patients receiving the higher doses had mild site reactions, which resulted in a 10% withdrawal. Infections requiring antibiotics were similar between placebo and treatment groups.

Leflunomide (ARAVA)

Leflunomide is a novel isoxazol drug. In vitro studies have shown it is a prodrug and is quickly metabolized to its' main active metabolite (A771726, referred to as M1). This metabolite reversibly inhibits the enzyme dihydroorotate 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 between 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 100mg per day for 3 days is used to facilitate 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 (three 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.

Efficacy

The onset of leflunomide's effects have been evident 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 52/100 patients treated with 10 mg 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 46% improvement in patients treated with methotrexate (7.5 - 15 mg/week) (37). A 24-week trial revealed patients treated with sulfasalazine at 2g/d improved 56% compared to 55% improvement in patients treated with leflunomide (39). Patients with rheumatoid arthritis treated with leflunomide for 12 months have been demonstrated to have retardation in progression of X-ray damage (40).

Toxicity

The most common adverse reaction has been gastrointestinal symptoms, occurring in 10-27% of patients (diarrhea, anorexia, abdominal pain, dyspepsia, gastritis and elevation 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; there are no long-term studies to assess its carcinogenicity or effect on fertility in humans.

In conclusion, we now have available some very effective medications with which to treat inflammatory arthritis. With the important concepts of treating JIA and RA early and aggressively we now need to decide when to use the new highly effective biologics. Despite their enormous cost, wouldn't the impact on patients and society as a whole be greater if used early in disease rather than after joint damage has already occurred and other agents have failed? Maybe used very early, combination treatment including biologics and MTX could result in lasting remissions of disease with less joint damage, less disability and lost income with less amounts of total medication required.

BIBLIOGRAPHY

1. Wallace CA. The Use Of Methotrexate In Childhood Rheumatic Diseases. *Arthritis Rheum* 1998;41 (3):381-391
2. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept In Children With Polyarticular Juvenile Rheumatoid Arthritis. *N Engl J Med* 2000;342:763-769.

3. Takei S, Groh D, Bertstein B, et al. Safety And Efficacy Of High Dose Etanercept in Treatment Of Juvenile Rheumatoid Arthritis. *J Rheumatol* 2001;28 (7):1677-80.
 4. Reiff A, Takei S, Sadeghi S, et al. Etanercept Therapy In Children With Treatment-Resistant Uveitis. *Arthritis Rheum* 2001;44 (6):1411-1415.
 5. Lipsky PE, Desiree MD, Van Der Heijde FM, et al. Infliximab And Methotrexate In The Treatment Of Rheumatoid Arthritis. *N Engl J Med* 2000;343:1594-1602.
 6. St. Clair EW, Wagner CL, Fasanmade AA, et al. The Relationship Of Serum Infliximab Concentrations To Clinical Improvement In Rheumatoid Arthritis. *Arthritis Rheum* 2002;46 (6):1451-1459.
 7. den Broeder AA, Joosten LAB, Saxne T, et al. Long Term Anti-Tumour Necrosis Factor (alpha) Monotherapy In Rheumatoid Arthritis: Effect On Radiological Course And Prognostic Value Of Markers Of Cartilage Turnover And Endothelial Activation. *Annals Of The Rheumatic Diseases* 2002;61 (4):311-318.
 8. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. *Arthritis Rheum* 1998;41 (12):2196-2204.
 9. van Vollenhoven RF, Harju A, Bratt J, et al. Treatment With Infliximab Or Enbrel and Employment Status Article #163. Annual Scientific Meeting Arthritis & Rheumatism Abstract Supplement, San Francisco California, 2001;44(9):S80.
 10. Warner AE, Huston KA, Scott TE, et al. Community Experience With Infliximab Infusion Reactions, Article #181. Annual Scientific Meeting Arthritis & Rheumatism Abstract Supplement, San Francisco California, 2001;44 (9):S83.
 11. Jerdan DA, Pritchard CH. A Prospective Study Of Adverse Drug Events During Infliximab (Remicade) Infusion Article #185. Annual Scientific Meeting Arthritis & Rheumatism Abstract Supplement, San Francisco California, 2001;44 (9):S83.
-