Bioavailability of higher dose MTX comparing oral and subcutaneous administration in patients with RA.

Rolf Rau

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Reactions to Infliximab in Patients with Rheumatoid Arthritis

To the Editor:

The recent article about practical experience with infliximab infusion reactions was timely and worthwhile. Our experience with just as many patients has been similar. Some differences are worth reporting.

At the Arthritis Center of Reno over 100 patients have been given infliximab for a minimum of 3 years for a total of more than 2000 infusions. Ninety-five percent of the infusions have been office-based. Infusions are done over 1 hour unless there is a history of reactions to the infusion. There has been no increase in infusion reactions.

At the time of a reaction of significance the infusion is stopped and a second intravenous infusion of saline is initiated. Antihistamine is given only rarely. Intravenous steroids have been given a handful of times for severe periocular edema, severe urticarial rash, or respiratory distress (the regular use of intravenous steroids confuses the ability to determine if infliximab or steroid is benefiting the patient). Once the reaction resolves, the infusion is restarted at a slower rate and is usually tolerated well. Three patients have developed an acute back pain syndrome characterized by anxiety. This responded well to intravenous antihistamine, but necessitated the discontinuation of infliximab in all 3 patients permanently.

Restarting infusions at a much slower rate has made it possible to finish infliximab administration in most, but not all patients. We also agree that despite the frequent minor side effects during infusions of infliximab, few patients permanently withdrew therapy on this account. Infliximab is well tolerated and accepted by patients in an academic rheumatology center.

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REFERENCE
The clinical impression of incomplete resorption of oral MTX was the reason we started MTX treatment always by parenteral application in patients with RA: the parenteral route was used with relatively high doses of 25 or 15 mg to ensure the patient received an effective dose. Later, an oral dose sufficient for efficacy could be titrated.

In patients with inadequate response to oral MTX, parenteral administration should be considered.

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REFERENCES

Dr. Hoekstra replies
To the Editor:

We thank Dr. Rau for his comment on our article. Indeed, there have been different studies comparing bioavailability of oral and parenteral methotrexate (MTX) in doses up to 25 mg weekly in patients with rheumatoid arthritis (RA). The mean relative bioavailability (F) of the studies comparing oral and subcutaneous or intramuscular routes of administration of MTX in the dose range of 5 to 25 mg weekly, range from 0.85 to 1.0, more or less comparable.

Dr. Rau is right when he states there are strong interindividual differences that always have to be taken into account. The studies mentioned by Dr. Rau compare intravenous and oral MTX, and they show a reduced bioavailability of oral MTX (range mean F 0.6–0.73). The question is whether the 3 parenteral routes of administration are strictly comparable concerning bioavailability. Seideman, et al’s study7 in 8 patients with RA treated with 15 mg MTX did show this, but other studies in RA are lacking.

We agree with Dr. Rau that, even in the lower dose ranges, you have take a reduced and variable bioavailability into account. The treatment of patients with RA is very much individually determined. Given the data on the bioavailability of MTX and the dose effect relation of oral MTX in doses up to 25 mg weekly, in the lower dose ranges, MTX can well be administered orally. With insufficient response a parenteral route of administration can be considered. The “splitting” of the oral dose may also be an alternative strategy to improve bioavailability, as was observed in our patients with RA taking MTX doses of 25 mg weekly or more (unpublished data).

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Treatment of Relapsing Polychondritis with a Tumor Necrosis Factor Antagonist

To the Editor:

Relapsing polychondritis (RP) is a rare autoinflammatory disorder characterized by recurrent inflammation and destruction of cartilage and connective tissue. Although the etiology of the disease is unknown, the pathogenesis appears to be mediated by an immune reaction to type II collagen, which is abundant in cartilage and the sclera. Despite its episodic nature, RP is progressive and most patients have significant disabilities. Diagnosis is usually poor. Long-term therapy does not generally prevent disease progression, and progressive therapies such as corticosteroids, methotrexate (MTX), or cyclophosphamide. Treatment may relieve the immediate symptoms of RP, but long-term therapy does not generally prevent disease progression, and prognosis is usually poor.

This report describes the successful treatment of episodic symptoms and cessation of flares with the tumor necrosis factor (TNF) antagonist etanercept in a patient with refractory RP.

The first undiagnosed episode of illness in this patient, a 46-year-old white woman, consisted of a 2-week episode of pain and inflammation involving the bridge of the nose, which had spontaneously resolved. This event occurred approximately 1 year before her presentation with pain and erythema in the left ear, sparing the earlobe. She was originally diagnosed with cellulitis, but antibiotic treatment was ineffective and the symptoms resolved spontaneously after completion of the antibiotic regimen. Three months later, the patient developed scleritis of the right eye and recurrence of pain and inflammation in the left ear, again sparing the earlobe. At that time, she was diagnosed with RP. Other features of RP, including cardiovascular and joint manifestations, were absent. Laboratory tests for antinuclear antibodies and all other lupus serologies were negative. Oral corticosteroids were prescribed (60 mg prednisone daily) and the symptoms resolved; however, when the prednisone dose was tapered to 30 mg daily, the symptoms returned. Azathioprine was added to her therapeutic regimen and titrated up to 150 mg daily. Attempts to taper her prednisone to 30 mg daily were unsuccessful; symptoms of scleritis, with or without ear inflammation, always returned at that dosage. Azathioprine was discontinued after 1.5 months. MTX was added and rapidly titrated up to 20 mg weekly. The patient remained on MTX (20 mg orally per week) and prednisone (varying doses) for 6 months. Scleritis, and frequently pain and erythema of the ear and nose, would recur whenever her prednisone dose was tapered to 25–30 mg daily. Etanercept therapy was initiated at 25 mg subcutaneously (SC) twice weekly (BIW) for her refractory RP, in addition to MTX and prednisone. Her corticosteroid dosage was subsequently tapered and ultimately discontinued without the appearance of flares. She remains on etanercept (25 mg SC BIW) and MTX (15 mg weekly), and has had no recurrence of symptoms in the ensuing year. The level of plasma C-reactive protein (CRP), a marker of inflammation, was slightly elevated (2.6 mg/dl; normal: 0–1.0 mg/dl) during continuation therapy with MTX (20 mg weekly) and prednisone (25 mg daily). Following the initiation of etanercept therapy, CRP levels were reduced to 0.02, 0.05, and 0.03 mg/dl at 3, 6, and 9 months, respectively.

Based on a growing body of evidence, the pathophysiology of RP is apparently mediated by an autoimmune reaction to cartilage components. Autoantibodies to collagen are seen in the serum of patients with RP following an inflammatory episode, and histological studies have suggested the presence of immune complexes in affected tissues. An animal model of experimental collagen-induced arthritis resembles RP and data from this model suggest that the binding of anti-collagen antibodies to cartilage results in complement-mediated inflammation and the release of inflammatory cytokines, including TNF. These studies support the use of biologic therapies designed to modulate TNF function in treatment of RP. Etanercept therapy in this patient resulted in rapid relief of eye and cartilage inflammation, with no recurrence of RP symptoms to date. An additional benefit of instituting this biologic therapy was the subsequent ability to taper her prednisone dosage, reducing the risk of side effects associated with long-term systemic steroid therapy. There are currently 4 reports of successful treatment of RP symptoms, including laryngotracheal chondritis with respiratory complications, scleritis arthritis, and chondritis with an anti-TNF monoclonal antibody, infliximab. These reports, together with the case reported here, strongly suggest that the pathophysiology of RP is mediated by the proinflammatory cytokine TNF. It remains to be seen if anti-TNF therapies will be able to slow or prevent long-term progression of this disease. Long-term studies are clearly warranted.

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REFERENCES
Corrections


\[ SEM = \sqrt{\frac{\sum (score_1 - score_2)^2}{2n}} \]

We regret the error.