

Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

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Reactions to Infliximab in Patients with Rheumatoid Arthritis

To the Editor:

The recent article about practical experience with infliximab infusion reactions¹ 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 periorbital 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 the administration of infliximab after most reactions without further difficulties. Although we are prepared for more serious reactions in the office, infliximab and other biological infusions have been generally well tolerated and accepted by patients in a private rheumatology practice.

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REFERENCE

1. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol* 2004;31:1912-7.

Dr. Keystone replies

To the Editor:

The experience reported by Dr. Prupas is of considerable interest.

With regard to the duration of infliximab infusion, we are interested to learn of his experience with a shortened duration of infusion. His experience is consistent with recent data from a Centocor-sponsored study.

With regard to the use of antihistamines, our experience as described¹ suggests that antihistamines may not be helpful, particularly as a pretreatment regimen. We still use antihistamines for more serious reactions of the kind described by Dr. Prupas. We have also had experience with patients developing severe back pain. These symptoms have subsided spontaneously with discontinuation of the infusion. Whether intravenous antihistamines would shorten the course of the symptom requires further study.

Finally, we certainly concur with Dr. Prupas that 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 withdraw therapy on this account. Infliximab is well tolerated and accepted by patients in an academic rheumatology center.

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REFERENCE

1. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol* 2004;31:1912-7.

To the Editor:

We read with great interest the article by Wasserman and colleagues¹ on infusion related reactions to infliximab in patients with rheumatoid arthritis (RA). The authors did not assess any potential correlation between the frequency of infusion reactions and clinical response. However, some evidence of the relationship between infusion reactions and clinical response could be observed in the first 14 weeks. With regard to demand for escalating the infliximab dose from 3 mg/kg to 5 mg/kg at Week 14, the patients are separated into 2 groups, responders and nonresponders. The difference in the number of patients experiencing at least one infusion reaction during the first 14 weeks between the 2 groups may be significant.

The authors mention that there was no relationship between infusion reactions and prednisone dose. However, it is not reported if there was any difference in infusion reactions between patients with prednisone treatment and those without.

The results of study showed that pretreatment with antihistamine failed to reduce the frequency of infusion reactions in patients without previous reactions at infusions 3 and 4. However, other forms of pretreatment, such as steroids, may be more beneficial than diphenhydramine.

Although there are no reports of studies of infliximab treatment in patients with RA that indicate the association of infusion reactions with clinical response and standard steroid therapy, the trials of infliximab in patients with Crohn's disease (CD) have revealed some interesting results. In a prospective observational study of infliximab infusions in patients with CD², the duration of response to subsequent infusions decreased once an infusion reaction occurred. In the ACCENT I trial³, the incidence of infusion reactions was 23% among CD patients receiving steroids alone, compared with 32% of patients not taking corticosteroids or immunosuppressives. Further, premedication with a high dose of intravenous corticosteroids seems to reduce the frequency of infusion reactions. In a study of

CD patients reported by Farrell, *et al*⁴, 6 of 39 (15%) patients with 200 mg intravenous hydrocortisone premedication experienced infusion reactions, in comparison to 10 of 41 (24%) patients with no hydrocortisone premedication. Perhaps 2 doses of oral corticosteroids administered 12 hours and 2 hours before infliximab infusion are more effective in reducing the frequency of infusion reactions. A 2-dose premedication regimen of oral corticosteroids (methylprednisolone 32 mg) roughly 12 and 2 hours before administration of intravenous contrast material provides more significant protection against contrast reactions than a single-dose premedication regimen 2 hours before contrast administration⁵.

In any case, the important point is that infliximab is well tolerated in patients with RA. Infusion related reactions are mild, and few patients stop therapy due to infusion reactions.

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REFERENCES

1. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol* 2004;31:1912-7.
2. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601-8.
3. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002;359:1541-9.
4. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003;124:917-24.
5. Lasser EC, Berry CC, Talner LB, et al. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med* 1987;317:845-9.

Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients with Rheumatoid Arthritis

To the Editor:

I read with interest the article by Hoekstra, *et al* on the bioavailability of higher doses of methotrexate (MTX)¹. In the introduction the authors write that "pharmacokinetic studies in adult patients with rheumatoid arthritis (RA) show comparable bioavailability of oral and parenteral MTX in doses up to 25 mg weekly." However, most studies performed with doses ranging from 10 to 25 mg have shown a significantly reduced bioavailability of oral MTX compared with parenteral MTX. For example, in the study by Herman, *et al*² the bioavailability of 10 mg oral MTX ranged from 25% to 100%, with a mean of 73%; in the study by Auvinet, *et al*³ the bioavailability of 15 mg oral MTX ranged from 45% to 80% (mean 60%); Oguey, *et al*⁴ found a mean absorption rate of 67% (range 28–94%) with 15 mg, and in the study by Korber⁵, administering 25 mg, the absorption rate was 73% (range 42–129%). These data show that the bioavailability of oral MTX also in doses less than 25 mg weekly is highly variable and significantly lower compared to parenteral administration.

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

1. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose MTX comparing oral and subcutaneous administration in patients with RA. *J Rheumatol* 2004;31:645-8.
2. Herman RA, van Pedersen P, Hoffman J, Furst DE. Pharmacokinetics of low dose methotrexate in rheumatoid arthritis patients. *J Pharm Sci* 1989;78:165-71.
3. Auvinet B, Jarrier I, Le-Lavier F, Pegon Y, Turcant A, Allain P. Comparative bioavailability of methotrexate given orally or intramuscularly in rheumatoid arthritis [letter]. *Presse Med* 1992;21:822.
4. Oguey D, Kolliker F, Gerber NJ, Reichen J. Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 1992;35:611-4.
5. Korber H, Iven H, Gross WL. Bioavailability and pharmacokinetics of methotrexate and its metabolite 7-hydroxy-MTX after low dose MTX (25 mg) in patients with chronic rheumatoid diseases [abstract]. *Arthritis Rheum* 1992;Suppl 35:S142.

Dr. Hoekstra replies

To the Editor:

We thank Dr. Rau for his comment on our article¹. 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 study² 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 to 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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REFERENCES

1. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose MTX comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol* 2004;31:645-8.
2. Seideman P, Beck O, Eksborg S, Wenneberg M. The pharmacokinetics of methotrexate and its 7-hydroxy metabolite in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1993;35:409-12.



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 tissue¹. 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 sclera¹⁻². Despite its episodic nature, RP is a progressive disease and most patients have significant disabilities during later stages, including impairments in hearing and vision, as well as cardiorespiratory problems¹. Treatments are not standardized and generally consist of nonsteroidal antiinflammatory drugs and/or immunosuppressive therapies such as corticosteroids, methotrexate (MTX), or cyclophosphamide. Treatment may relieve the immediate symptoms of RP, but longterm therapy does not generally prevent disease progression, and prognosis is usually poor².

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 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 combination 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^{1,2}. 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 tissues¹. An animal model of experimental collagen-induced arthritis resembles RP³ 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 longterm systemic steroid therapy. There are currently 4 reports of successful treatment of RP symptoms, including laryngotracheal chondritis with respiratory complications⁴, scleritis⁵ arthritis⁶⁻⁷, and chondritis⁷ 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 longterm progression of this disease. Longterm studies are clearly warranted.

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REFERENCES

1. Molina JF, Espinoza LR. Relapsing polychondritis. *Best Pract Res Clin Rheumatol* 2000;14:97-109.
2. Letko E, Zafirakis P, Baltatzis S, Voudouri A, Livir-Rallatos C, Foster CS. Relapsing polychondritis: a clinical review. *Semin Arthritis Rheum* 2002;31:384-95.
3. Cremer MA, Rosloniec EF, Kang AH. The cartilage collagens: a review of their structure, organization, and role in the pathogenesis of experimental arthritis in animals and in human rheumatic disease. *J Mol Med* 1998;76:275-88.
4. Mpfu S, Estrach C, Curtis J, Moots RJ. Treatment of respiratory complications in recalcitrant relapsing polychondritis with infliximab. *Rheumatology* 2003;42:1117-8.
5. Cazabon S, Over K, Butcher J. The successful use of infliximab in resistant relapsing polychondritis and associated scleritis. *Eye* 2005;19:222-4.
6. Matzkies FG, Manger B, Schmitt-Haendle M, et al. Severe septicemia in a patient with polychondritis and Sweet's syndrome after initiation of treatment with infliximab. *Ann Rheum Dis* 2003;62:81-2.
7. Saadoun D, Deslandre CJ, Allanore Y, Charlier C, Pham X-V, Kahan A. Sustained response to infliximab in 2 patients with refractory relapsing polychondritis. *J Rheumatol* 2003;30:1394-5.

Corrections

Guillemin F, Billot L, Boini S, Gerard N, Ødegaard S, Kvien TK. Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:778-86. The mathematical definition of standard error of measurement should be

$$\text{SEM} = \sqrt{\frac{\sum (\text{score } 1 - \text{score } 2)^2}{2 * n}}$$

We regret the error.

S. Kumagai, S. Kawano, T. Atsumi, et al. Vertebral fracture and bone mineral density in women receiving high dose glucocorticoids for treatment of autoimmune diseases. *J Rheumatol* 2005;32:863-9. The name of the sixth author of this article should be Yoshinori Kanai. We regret the error.