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.

Contact. **The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail:jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Is the STAR Trial Really a Safety Trial?

To the Editor:

The results of the STAR trial (Safety Trial of Adalimumab in Rheumatoid Arthritis) by Furst and colleagues[1] are of much interest to the rheumatology community. However, I think they merit further discussion.

It is surprising the authors designate this well designed efficacy study a safety study. In the 1999 study of Moreland, *et al*[2], a tumor necrosis factor-α (TNF-α) antagonist, etanercept, was shown to be superior to placebo among patients with rheumatoid arthritis (RA) who had poor response to traditional disease modifying antirheumatic drugs (DMARD) in a trial in which the failing DMARD had been discontinued at entry. The STAR trial now shows, very usefully, that the addition of a TNF-α antagonist, this time adalimumab, to traditional DMARD is superior to the addition of placebo, again among a group of patients who had poor response to traditional DMARD therapy.

There are also some important issues related to the interpretation of the safety data. (1) The authors say that "A sample size of 300 patients per group was determined to demonstrate a specific adverse effect of 1%, or less, with a 95% confidence." This statistical reasoning is valid only if no adverse effects are observed[3]. It only puts an upper confidence limit to a zero observation and is not of much use to search for statistically significant differences in the frequencies of rare events between the 2 arms of a drug study. (2) The frequencies of the most feared side effects of the TNF-α antagonists, i.e., lymphoma, serious infections, and demyelinating disease, appear, fortunately, to be relatively small. Thus, thousands of patients need to be studied for properly powered clinical trials to probe the real safety of a new agent like adalimumab, and it is probably best to depend on postmarketing surveillance data to appreciate the real importance of these side effects in clinical practice. It is disappointing not to find any discussion of this phenomenon in the STAR report. (3) The authors use the annual incidence rates of serious infections in the general population of patients with RA as a comparator for the infections they observed in their study group. As suggested for lymphomas[4], this appears unjustified. As with lymphomas, the onset of tuberculosis[5] — and for that matter of demyelinating disease, as well[6] — occurs, in many patients, only within months of use of TNF-α antagonist. To use the presumably random annual incidence among a group not using TNF-α antagonists as a comparator unjustifiably dilutes the frequency, and thus the real importance of the drug side effects.

It is timely and healthy to question the real value of the controlled clinical trial as the ultimate guide for evidence based practice of medicine[7,8]. Sometimes, however, it is not the "controlled clinical trial," but its interpretation that needs to be put on trial.

HASAN YAZICI, MD, Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Aksaray, 34303 Istanbul, Turkey. E-mail: hyazici@attglobal.net

REFERENCES

1. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563-71.
2. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
3. Yazici H, Biyikli M, van der Linden S, Schouten HJ. The 'zero patient' design to compare the prevalences of rare diseases. Rheumatology Oxford 2001;40:121-2.
4. Yazici H. Lymphomas after tumor necrosis factor antagonist therapy: comment on the article by Brown, et al. [letter]. Arthritis Rheum 2003;48:2389.
5. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122-7.
6. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44:2862-9.
7. Dieppe P, Szebenyi B. Evidence based rheumatology [editorial]. J Rheumatol 2000;27:4-7.
8. Pincus T. Guidelines for monitoring of methotrexate: "evidence-based medicine" outside of clinical trials. Arthritis Rheum 2003;48:2706-9.

Dr. Furst replies

To the Editor:

I very much appreciate the thoughtful comments of Dr. Yazici. The study was conducted to obtain "real-world" safety data (similar to typical clinical practice). This data would include adalimumab with 0–3 or more disease modifying antirheumatic drugs (DMARD), nonsteroidal antiinflammatory drugs, or corticosteroids. The lenient entry criteria allowed for a more heterogeneous patient population and did not allow for true efficacy to be determined because of the small size of many groups. In that context, the sample size of 300 patients per group did allow us to determine at least one adverse event in a particular organ system of interest, with a 1% incidence at 95% confidence limit, and this would serve as a signal for further testing (i.e., precisely as Dr. Yazici commented—a confidence limit for zero observations).

And, in agreement with Dr. Yazici, the study was not powered or intended to obtain an incidence of rare events. It was simply to see if relatively common adverse events occurred in a population of adalimumab treated patients taking various DMARD. The number of adverse events expected relates only to relatively common events, not rare events such as serious infections, lymphomas, or demyelinating disease. It is also for this reason that very few statistical conclusions were made regarding adverse events. The efficacy will be further analyzed in an exploratory analysis in the future. Thus, we believe our interpretation and discussion of this trial

are appropriate to its stated purposes and it was designed appropriately for those purposes.

DANIEL E. FURST, MD, Division of Rheumatology, Department of Medicine, UCLA, Rehabilitation Center, Room 32–59, 1000 Veteran Avenue, Los Angeles, California 90095-1670, USA

Niacin-like Reaction to Infliximab Infusion in Systemic Juvenile Rheumatoid Arthritis

To the Editor:

Infliximab is a chimeric human/mouse monoclonal antibody that binds to tumor necrosis factor-α and has been used with success in pediatrics for ankylosing spondylitis, psoriatic arthritis, and sarcoid arthritis. The multicenter clinical trial for its juvenile rheumatoid arthritis (JRA) indication is currently under way. We and others have been using infliximab off-label for the treatment of refractory pediatric rheumatic diseases for the past few years.

Adult clinical trials for infliximab have identified serious adverse reactions mainly associated with infection and hypersensitivity. In the ATTRACT study in which different regimens of infliximab plus methotrexate (MTX) were compared to MTX plus placebo, upper respiratory infections (34% vs 22%), sinusitis (17% vs 6%), and pharyngitis (11% vs 6%) were seen more frequently with infliximab[1]. In the MedWatch postmarketing surveillance report, disseminated tuberculosis was noted to be increased in patients with RA treated with infliximab[2]. In addition, acute infusion reactions including fever, chills, cardiopulmonary reactions, pruritis, and/or urticaria or anaphylaxis have consistently been reported[3]. Overall, however, the consensus is that the drug is safe.

We describe 3 children we treated with infliximab for refractory systemic JRA who developed an initially drastic, yet ultimately benign, niacin-like effect, which may have been poorly recognized in pediatrics.

Our infliximab protocol includes premedication with acetaminophen (10 mg/kg/dose) and diphenhydramine (1 mg/kg/dose) given 1 hour before infusion of the drug. Two patients with systemic arthritis who had received infliximab successfully, as well as one who had not, developed a previously undescribed side effect. They experienced cutaneous erythematous flushing over the face and chest and intense chest tightness during the first few minutes of the infusion. The vital signs remained stable thus no hypotension, tachycardia, or hypoxia was noted. Examination revealed no wheeze and no stridor. Upon discontinuation of the infusion, the flushing quickly resolved. For the first 2 patients, several premedications were added upon subsequent attempts, including dexamethasone, prednisone (on both the day previous and the day of medication), and albuterol nebulizer treatments. These interventions failed to prevent the reaction. A niacin-like reaction was suspected and ASA (10 mg/kg/dose with a maximum of 325 mg) was substituted for acetaminophen in the premedication protocol. After ASA was added, no further episodes were observed. We were able to slowly taper nearly all of the additional premedication drugs that were secondarily added without difficulty in Patients 1 and 2. Patient 3, who reacted at the first infusion, was immediately treated with ASA after the initial reaction and was rechallenged successfully after 30 minutes.

Niacin, a water-soluble B vitamin, has been identified as a hypolipidemic agent, via reduction of triglyceride synthesis. Its use has been hindered by side effects, one of which is intense flushing. This dermatological effect is dose-related and is described as severe skin reddening, associated with warmth, mainly over the face, neck, and ears within 2 hours of ingesting the drug[5]. Studies have linked this effect to vasodilatation of cutaneous vessels from an endogenous release of prostaglandin D_2 (PGD_2)[4]. The skin has been shown to be a major site of PGD_2 release after ingestion, although the specific cell from which PGD_2 is released is unknown[6]. Pretreatment of patients receiving niacin with cyclooxygenase inhibitors has been shown to significantly lessen the cutaneous effects of this drug, most likely secondary to PGD_2 inhibition[7]. A single dose of ASA 325 mg is the most effective in blocking this reaction.

Our 3 patients exhibited symptoms similar to a previously described niacin-like effect not yet widely recognized with infliximab therapy. After treating these patients with 162–325 mg of ASA 1 hour prior to infusion, there was a dramatic improvement in their symptoms. Other investigators have reported a similar observation. A "red man syndrome" was described in a total of 5 patients with Crohn's disease treated with infliximab[8,9]. When the infusion rate was decreased or the drug stopped, the symptoms improved.

It is intriguing that all our cases were patients with systemic JRA. This apparent association may be caused by more frequent use of infliximab in patients with the systemic subset. The finding of a similar adverse event among patients with Crohn's disease suggests a drug-related more than a disease-related effect. By changing the premedication protocol for infliximab when necessary to include ASA, we may enable the continuation of a successful therapy for patients with juvenile arthritis that is difficult to treat.

MARA BECKER, MD, Pediatric Rheumatology Fellow; CARLOS D. ROSÉ, MD, CIP Professor of Pediatrics; GAIL McILVAIN-SIMPSON, MSN, RN, CSN, Division of Rheumatology, Department of Pediatrics, duPont Hospital for Children, Thomas Jefferson University, Wilmington, Delaware, USA

REFERENCES

1. Lipsky PE, van der Heijde DMFM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594-602.
2. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098-104.
3. Centocor, Inc. Infliximab package insert. Malvern, PA: Centocor, Inc.
4. Wilkin JK, Fortner G, Reinhardt LA, Flowers OV, Kilpatrick SJ, Streeter WC. Prostaglandins and nicotinate-provoked increase in cutaneous blood flow. Clin Pharmacol Ther 1985;38:273-7.
5. Wilkin, JK. Why is flushing limited to a mostly facial cutaneous distribution? J Am Acad Dermatol 1988;19:309-13.
6. Morrow JD, Awad JA, Oates JA, Roberts LJ. Identification of skin as a major site of prostaglandin D2 release following oral administration of niacin in humans. J Invest Dermatol 1992;98:812-5.
7. Gibbons LW, Gonzalez V, Gordon N, Grundy S. The prevalence of side effects with regular and sustained-release nicotinic acid. Am J Med 1995;99:378-85.
8. Lobel EZ, Korelitz BI, Warman JI. Red man syndrome and infliximab [letter]. J Clin Gastroenterol 2003;36:186.
9. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr 2000;137:192-6.