ARTHRITIS & RHEUMATISM
Vol. 50, No. 1, January 2004, pp 334–340

LETTERS

DOI 10.1002/art.11475

A brief history of Wegener's granulomatosis: on limited, localized, and generalized forms of the disease: comment on the article by the Wegener's Granulomatosis Etanercept Trial Research Group

To the Editor:

We read with interest the recent report by the Wegener's Granulomatosis Etanercept Trial (WGET) Research Group on differences between what they defined as "limited" and "severe" forms of WG with regard to clinical features, antineutrophil cytoplasmic antibody (ANCA) serology, and biopsy findings (1). In his original report on 3 patients with a previously unrecognized new disease entity, Friedrich Wegener concentrated on vasculitic features, but soon he stressed the importance of granuloma formation in what became known as Wegener's granulomatosis in the 1950s (2). Later, a study by Fienberg suggested that WG may start as granulomatous disease in the respiratory tract, and that vasculitis may evolve subsequently (3).

Meanwhile, numerous clinical and experimental studies have demonstrated that interaction of ANCA with neutrophils leads to endothelial damage, subsequent vasculitis, and leukocyte recruitment, but the relationship between vasculitic and granulomatous lesions needs to be further clarified (for review, see ref. 4). As has been noted in earlier studies (5), the WGET Research Group detected ANCA (by immunofluorescence) and anti–proteinase 3 antibodies (PR3 ANCA) (by enzyme-linked immunosorbent assay) less frequently in patients with limited disease than in patients with generalized WG (1). This may reflect true differences of disease stage, but further methodical improvements, such as use of capture ELISA or detection of ANCA directed against the pro form of PR3, may be more sensitive in the early stages of the disease and to changes in disease activity (6).

Carrington and Liebow introduced the term limited WG to characterize predominant involvement of the lungs in the absence of kidney involvement (7). Some patients may present with isolated meningocerebral inflammation or ophthalmic involvement without renal manifestations and the absence of ANCA (8). The European Vasculitis Study Group (EUVAS) refined the term limited WG by determining 2 subgroups previously subsumed under the category of limited forms. The determination of subgroups was based on clinical and pathologic considerations in order to define disease stages. Localized WG was defined as WG restricted to the upper and/or lower respiratory tract. Early systemic WG included any organ involvement except renal, or imminent vital organ failure. Finally, generalized WG included renal involvement and/or imminent organ failure. Two other subgroups, namely, severe renal and refractory disease, were defined to cover the spectrum of disease and to enroll patients into appropriate stage-adopted treatment trials (9).

It is obvious that the WGET Research Group's definition of limited WG as the absence of an immediate threat necessitating aggressive therapy, and that of severe WG as all other patients (1), differs from the EUVAS definitions and may cause confusion. Whereas the EUVAS defined disease stages (9), the WGET Research Group defined 2 groups of patients according to disease activity at the time of enrollment (1). As a consequence, the WGET Research Group's definitions of limited WG (1) will include patients who are grouped to localized, early systemic, or even generalized WG according to the EUVAS definitions (9), as long as the disease activity is not organ- and/or life-threatening. The same patient will be classified as having severe WG according to the WGET Research Group's definition when aggressive therapy is needed to control organ- and/or life-threatening disease manifestations (1). Studies will be difficult to compare when different definitions are used to characterize patients.

Recent experimental data support the assignment of patients according to disease stages rather than considering only disease activity. Abundant interferon (IFNγ) expression is seen in granulomatous lesions of the respiratory tract in localized WG but not in generalized WG (4,10). Predominance of Th1-type chemokine receptor CCR5 expression on memory T cells may favor stronger recruitment of Th1-type cytokine-secreting cells into inflammatory lesions in localized WG compared with generalized WG (11). Certain cellular subsets such as IFNγ– and tumor necrosis factor α–producing peripheral blood and granuloma CD4+ CD28− T cells may play an important role in granuloma formation (12). Changes in the cytokine balance may cause or accompany disease progression (4,10–12). Infectious agents such as *Staphylococcus aureus,* other environmental influences, or the autoantigen itself are thought to play a role in triggering and/or maintaining disease activity in WG on the basis of a genetic predisposition to an exaggerated Th1-type response (13,14).

Most patients with localized WG progress to generalized disease, but some do not, for as yet unknown reasons. Clinical and experimental evidence suggest that there are further differences between PR3- and myeloperoxidase-positive WG, ANCA-negative WG, and patients displaying features of 2 granulomatous diseases (for review, see ref. 15). Analyzing the differences will help to better tailor therapies and target specific effector mechanisms at different disease stages and in different subgroups of patients.

Peter Lamprecht, MD
Wolfgang L. Gross, MD
University Hospital of Schleswig-Holstein and Rheumaklinik Bad Bramstedt
Luebeck, Germany

1. The Wegener's Granulomatosis Etanercept Trial Research Group. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis Rheum 2003;48:2299–309.
2. Wegener F. Ueber eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. Beitr Pathol Anat 1939;102:36–68.
3. Fienberg R. The protracted superficial phenomenon in pathergic (Wegener's) granulomatosis. Hum Pathol 1981;12:458–67.
4. Savage CO, Harper L, Holland M. New findings in pathogenesis of antineutrophil cytoplasm antibody-associated vasculitis. Curr Opin Rheumatol 2002;14:15–22.
5. Nölle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. Ann Intern Med 1989;111:28–40.
6. Russell KA, Fass DN, Specks U. Antineutrophil cytoplasmic antibodies reacting with the pro form of proteinase 3 and disease

activity in patients with Wegener's granulomatosis and microscopic polyangiitis. Arthritis Rheum 2001;44:463–8.
7. Carrington CB, Liebow AA. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 1966;41:497–527.
8. Reinhold-Keller E, de Groot K, Holl-Ulrich K, Arlt AC, Heller M, Feller AC, et al. Severe CNS manifestations as the clinical hallmark in generalized Wegener's granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA): a report of 3 cases and a review of the literature. Clin Exp Rheumatol 2001;19:541–9.
9. Jayne D. Update on the European Vasculitis Study Group trials. Curr Opin Rheumatol 2001;13:48–55.
10. Muller A, Trabandt A, Gloeckner-Hofmann K, Seitzer U, Csernok E, Schonermarck U, et al. Localized Wegener's granulomatosis: predominance of CD26 and IFN-γ expression. J Pathol 2000,192: 113–20.
11. Lamprecht P, Erdmann A, Mueller A, Csernok E, Reinhold-Keller E, Holl-Ulrich K, et al. Heterogeneity of CD4 and CD8+ memory T cells in localized and generalized Wegener's granulomatosis. Arthritis Res Ther 2003;5:R25–31.
12. Komocsi A, Lamprecht P, Csernok E, Mueller A, Holl-Ulrich K, Seitzer U, et al. Peripheral blood and granuloma CD4+ CD28− T-cells are a major source of interferon-γ and tumor necrosis factor-α in Wegerner's granulomatosis. Am J Pathol 2002;160: 1717–24.
13. Popa ER, Stegeman CA, Kallenberg CGM, Cohen Tervaert JW. Staphylococcus aureus and Wegener's granulomatosis. Arthritis Res 2002;4:77–9.
14. Sneller MC. Granuloma formation, implications for the pathogenesis of vasculitis. Cleveland Clin J Med 2002;69 Suppl 2:SII40–43.
15. Lamprecht P, Trabandt A, Gross WL. Clinical and immunological aspects of Wegener's granulomatosis (WG) and other syndromes resembling WG. Isr Med Assoc J 2000;2:621–6.

DOI 10.1002/art.11490

Reply

To the Editor:

We appreciate the opportunity to discuss the points raised by Lamprecht and Gross and to emphasize some of the conclusions of our article. As we stated in both the introduction and discussion sections of our report, the existence of different clinical phenotypes within WG has been recognized for several decades. In addition, as we noted (see refs. 40–45 in our report), studies of T cell subsets, cytokine expression, and chemokine levels provide some (albeit incomplete) pathophysiologic basis for the existence of such subsets. We noted in our concluding paragraph that in addition to the limited and severe subset designations used for the purpose of assigning conventional treatments in our clinical trial, "It is possible that other WG subsets exist, and that our appreciation of these subsets will become more refined as our understanding of this disease advances."

All efforts to delineate phenotypic differences among WG disease subsets are commendable, including those of the EUVAS (1). Most investigators would agree that, to date, none of these efforts is perfect. Patients classified as having early systemic disease under the EUVAS definition, for example, might include those whose ear/nose/throat, skin, joint, and lung manifestations of WG have been present for years. Such patients would hardly qualify as having early disease. Because the current understanding of disease pathophysiology remains incomplete, all attempts at classifying large groups of WG patients into discrete subsets—including our own—will inevitably lead to some inconsistencies and misclassifications.

The approach that we used for the classification of patients in the WGET was developed through the consensus of a group of expert clinicians and investigators and was based on work done previously by others in the field. As we discussed in our report, our patients were not an inception cohort (i.e., a group of patients with newly diagnosed disease who were followed up for years to determine the natural history of their disease). In spite of the specific purpose for which the WGET patient cohort was assembled and characterized, our use of the terms limited and severe led to some novel observations about this disease. Patients with limited disease were nearly a decade younger at the time of disease onset compared with patients with severe disease (41 years versus 50 years; $P = 0.005$). Despite their younger age at the time of disease onset, patients with limited disease had longer disease duration, a greater likelihood of having previous disease exacerbations following periods of remission, and a higher prevalence of destructive upper respiratory tract disease at the time of enrollment. Patients with severe disease also had a strikingly higher likelihood of previous thyroid disease, particularly either Graves' disease or Hashimoto thyroiditis, compared with those with limited disease (15% versus 0%; $P = 0.003$). Finally, among patients with severe disease, only 33% were female, compared with 58% of patients in the group with limited disease ($P = 0.002$). These sex differences were confirmed among a larger group of WG patients (n = 778) who were screened for the trial but not enrolled.

Consistent with observations made by other investigators (2), patients in our clinical trial cohort with limited WG were also less likely than those with severe WG to have ANCA. Lamprecht and Gross imply that other techniques for detecting ANCA (e.g., the capture ELISA technique or measurement of antibodies against the pro form of PR3) might be more sensitive in early stages of the disease. We believe that the use of such techniques is unlikely to resolve the differences in these disease subsets with regard to ANCA prevalence, but agree with their alternative explanation, namely, that the consistent variations in ANCA prevalence among the limited and severe disease subsets reflect the true differences between these groups of patients and confirm the importance of defining these differences further. We also note that although the measurement of antibodies to the pro form of PR3 might be more useful in detecting the presence of active disease, the use of this technique would not be more sensitive than the measurement of ANCA reacting with the mature enzyme (3).

We agree that differences in patient classifications across different types of studies render more difficult the interpretation of clinical trial reports. Therefore, it is of utmost importance that the patient populations studied in trials be described as thoroughly as possible. We believe that our article will make subsequent reports of WGET results more transparent and easier to interpret and compare with the results of other trials.

We concluded our report with an observation and 2 questions: "At this point in time, the distinction between limited and severe disease is clearly important with regard to

the choice of treatment. Is the distinction between limited and severe WG also important from the standpoint of response to therapy and that of prognosis? What might differences in the selection of target organs tell us about pathogenetic mechanisms? These are questions that can be resolved only by future investigations." When our understanding of disease subsets, the factors that affect prognosis, and anticipated responses to treatment is perfect, there will be no controversy about how to classify patients for the purposes of clinical studies. Until that time, readers and investigators must consider each set of definitions on its own merits and draw their own conclusions.

John H. Stone, MD, MPH
Janet T. Holbrook, PhD
Andrea Tibbs
Johns Hopkins University
Baltimore, MD
Gary S. Hoffman, MD
The Cleveland Clinic Foundation
Cleveland, OH
Nancy B. Allen, MD
E. William St.Clair, MD
Duke University
Durham, NC
John C. Davis, MD, MPH
University of California, San Francisco
Peter A. Merkel, MD, MPH
Boston University
Boston, MA
Ulrich Specks, MD
The Mayo Clinic Foundation
Rochester, MN
Robert F. Spiera, MD
Beth Israel Medical Center
New York, NY
For the WGET Research Group

1. Jayne D. Update on the European Vasculitis Study Group trials. Curr Opin Rheumatol 2001;13:48–55.
2. Nölle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. Ann Intern Med 1989;111: 28–40.
3. Russell KA, Fass DN, Specks U. Antineutrophil cytoplasmic antibodies reacting with the pro form of proteinase 3 and disease activity in patients with Wegener's granulomatosis and microscopic polyangiitis. Arthritis Rheum 2001;44:463–8.

DOI 10.1002/art.11477

Leflunomide and anti–glomerular basement membrane glomerulonephritis: comment on the letter by Bruyn et al

To the Editor:

We read with interest the recent report by Bruyn et al of anti–glomerular basement membrane (anti-GBM) glomerulonephritis in a patient with leflunomide-treated rheumatoid arthritis (1).

It would be even more interesting, nonetheless, to remind readers that leflunomide was formerly shown to have therapeutic effects in anti-GBM glomerulonephritis in animal models. Using rabbit antiserum against rat GBM, Ogawa et al (2) induced glomerulonephritis similar to Goodpasture's syndrome in rats. Those investigators reported that administration of leflunomide had therapeutic effects on proteinuria as well as inhibitory effects on the glomerular IgG and C3 deposits (2,3).

Although genetic predisposition to anti-GBM disease might be cited as the reasoning to reconcile with a somewhat enigmatic disparity, variable dosing (or, more precisely, the active metabolite level) of leflunomide could also have been implicated. With respect to the role of leflunomide in preventing renal allograft rejection, for instance, cytotoxic T lymphocytes were inhibited at a high drug concentration, but the opposite effect was shown at a low concentration (4).

If there is one thing that can be said with certainty about the paradox between the foregoing observations, it is that we still have incomplete understanding of them.

Kai Ming Chow, MD
Cheuk Chun Szeto, MD
Prince of Wales Hospital
The Chinese University of Hong Kong
Shatin, Hong Kong, China

1. Bruyn GAW, Veenstra RP, Halma C, Grond J. Anti–glomerular basement membrane antibody–associated renal failure in a patient with leflunomide-treated rheumatoid arthritis [letter]. Arthritis Rheum 2003;48:1164–5.
2. Ogawa T, Inazu M, Gotoh K, Hayashi S. Effects of leflunomide on glomerulonephritis induced by antibasement membrane in rats. Agents Actions 1990;31:321–8.
3. Ogawa T, Inazu M, Gotoh K, Inoue T, Hayashi S. Therapeutic effects of leflunomide, a new antirheumatic drug, on glomerulonephritis induced by the antibasement membrane antibody in rats. Clin Immunol Immunopathol 1991;61;103–18.
4. Hoskin DW, Taylor RM, Makrigiannis AP, James H, Lee TD. Dose-dependent enhancing and inhibitory effects of A77 1726 (leflunomide) on cytotoxic T lymphocyte induction. Int J Immunopharmacol 1998;20:505–13.

DOI 10.1002/art.11491

Reply

To the Editor:

We thank Chow and Szeto for their interest in our report of anti-GBM antibody–associated renal failure in a patient with rheumatoid arthritis (RA) who was treated with leflunomide. They mention correctly that high-dose leflunomide paradoxically has been shown to be effective for both prevention and treatment of artificially induced anti-GBM glomerulonephritis in rats (1). In addition, leflunomide has been shown to have efficacy in experimentally induced tubulointerstitial nephritis (2). Chow and Szeto offer genetic predisposition, a dose-dependent pathologic mechanism, or a combination of these, as possible explanations.

First, we would like to emphasize once again that we have speculated on a possible yet unproven relationship.

Unfortunately, because we do not store sera from our patients for a long period of time, we were unable to exclude the possibility of prior existence of anti-GBM autoantibodies in our patient. Conversely, induction of autoantibodies is neither confined to nor unique for leflunomide. It is well known that other agents for the treatment of RA (e.g., tumor necrosis factor α blockers) can induce autoantibodies to a variety of nuclear antigens (3). The brunt of these autoantibodies are not pathogenetic, because they do not lead to a clinical syndrome. Why some autoantibodies are pathogenetic while others are not is unclear.

We certainly agree with the final conclusion of our colleagues Chow and Szeto that, at the present time, our knowledge about the exact mechanism of leflunomide in RA, including the optimal dosing scheme, is still insufficient.

George A. W. Bruyn, MD, PhD
Cees Halma, MD, PhD
Joris Grond, MD, PhD
Medisch Centrum Leeuwarden
Leeuwarden, The Netherlands

1. Ogawa T, Inazu M, Gotoh K, Inoue T, Hayashi S. Therapeutic effects of leflunomide, a new antirheumatic drug, on glomerulonephritis induced by the antibasement membrane antibody in rats. Clin Immunol Immunopathol 1991;61:103–18.
2. Thoenes GH, Sitter T, Langer KH, Bartlett RR, Schleyerbach R. Leflunomide (HWA 486) inhibits experimental autoimmune tubulointerstitial nephritis in rats. Int J Immunopharmacol 1989;11: 921–9.
3. De Rycke L, Kruithof E, Van Damme N, Hoffman IE, Van den Bossche N, Van den Bosch F, et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum 2003;48:1015–23.

DOI 10.1002/art.11498

Intravenous immunoglobulin and placental transport of anti-Ro/La antibodies: comment on the letter by Kaaja and Julkunen

To the Editor:

We read with interest the letter by Kaaja and Julkunen on the role of intravenous immunoglobulin (IVIG) in the prophylaxis of fetal congenital heart block (CHB) (1). In response, Buyon and colleagues discussed potential mechanisms by which IVIG may reduce anti-Ro/La antibody–mediated tissue damage including, antiidiotypic regulation, induction of inhibitory Fc receptors, and inhibition of placental anti-Ro/La antibody transport (2). We now provide evidence for the placental Fc receptor blockade hypothesis in vivo, by utilizing a murine passive transfer model in which anti-Ro/La antibodies are transported across the placenta and bind to apoptotic cells in the fetal heart (3).

We conducted a study in which time-mated pregnant BALB/c mice were injected with either 1.5 gm/kg of IVIG (Intragam P; CSL, Melbourne, Victoria, Australia) (n = 4) or saline control (n = 4) via the tail vein at day 14 of gestation (E14). At E15, mothers were injected intraperitoneally with 0.5 ml of a human anti-Ro/La serum, and maternal and fetal IgG anti-Ro/La levels were measured by recombinant antigen enzyme-linked immunosorbent assay following killing at E17 (3). Dual TUNEL and human IgG staining was performed on frozen sections of fetal hearts, and the proportion of apoptotic cells with bound IgG was counted in a blinded manner by 2 observers, as previously described (3).

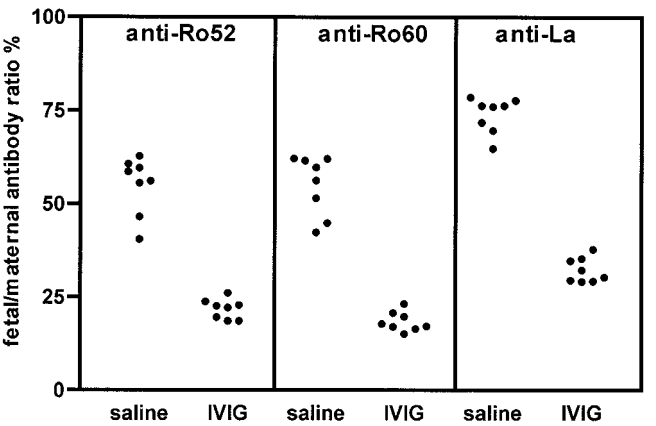

Figure 1. Transplacental passage of maternal anti-Ro/La antibodies on day 17 of gestation (E17) following administration of intravenous immunoglobulin (IVIG) or saline control on E14 and injection of mothers with human anti-Ro/La serum on E15. Each dot represents the fetal/maternal antibody ratio for an individual fetus compared with its mother.

Fetal:maternal ratios of anti–Ro 52, anti–Ro 60, and anti-La levels were significantly lower in fetuses of mothers infused with IVIG compared with fetuses of the saline-injected mothers ($P < 0.001$ for each specificity, by Mann-Whitney U test) (Figure 1). IVIG similarly inhibited placental transfer of anti–double-stranded DNA (anti-dsDNA) antibodies following injection of mothers with a high-titer human anti-dsDNA serum (data not shown). We next investigated whether the IVIG-associated reduction in anti-Ro/La placental transport affected the formation of IgG-apoptotic cell complexes in the fetal hearts. In the IVIG-treated fetuses there was a significant decrease in the proportion of TUNEL-positive cells bound with IgG (131 of 285 [46%]) compared with controls (171 of 263 [65%]) ($P < 0.01$ by chi-square test). No inhibition of placental anti-Ro/La transfer was observed following injection of the mothers with an equimolar amount of the $F(ab')_2$ fraction of IVIG in place of whole IVIG, indicating that the inhibition of placental transfer is mediated by the Fc fragment of pooled IgG (data not shown).

These results provide evidence from a murine model that maternal administration of IVIG inhibits the transfer of potentially pathogenic anti-Ro/La antibodies across the placenta and their subsequent deposition in the fetal heart, most likely by nonspecific blockade of placental Fc receptors. These data provide a rationale for the use of IVIG in the prevention of recurrence of CHB.

Hai B. Tran, PhD
Dana Cavill, BSc
Flinders University
Adelaide, Australia
Jill P. Buyon, MD
Hospital for Joint Diseases
New York University School of Medicine
New York, NY
Tom P. Gordon, MD, PhD
Flinders Medical Centre
Adelaide, Australia

1. Kaaja R, Julkunen H. Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: comment on the editorial by Buyon et al [letter]. Arthritis Rheum 2003;48:280–1.
2. Buyon JP, Kim MY, Copel JA, Friedman DM. Reply. Arthritis Rheum 2003;48:281–2.
3. Tran HB, Macardle PJ, Hiscock J, Cavill D, Bradley J, Buyon J, et al. Anti-La/SSB antibodies transported across the placenta bind apoptotic cells in fetal organs targeted in neonatal lupus. Arthritis Rheum 2002;46:1572–9.

DOI 10.1002/art.11476

Reply

To the Editor:

We thank Dr. Tran and colleagues for providing evidence from a murine model that maternal administration of IVIG inhibits transfer across the placenta of potentially pathogenic anti-Ro/La antibodies. This supports our clinical findings that the recurrence of CHB can be prevented with IVIG and corticosteroid treatment.

Tran et al showed, with a small number (n = 4) of time-mated pregnant BALB/c mice, that injection of IVIG clearly decreased fetal anti–Ro 52, anti–Ro 60, and anti-La levels as well as binding of these antibodies to apoptotic cell complexes in fetal hearts. They claimed that this was attributable to blockade of placental Fc receptors, because no inhibition of placental anti-Ro/La transfer was observed following injection of an equimolar amount of the $F(ab')_2$ fraction of IVIG.

The mode of action of IVIG is complex, involving modulation of the expression and function of Fc receptors (1). The study by Tran et al would also support Fc receptor blockade at the placental level. Among many other immunomodulatory actions, provision of antiidiotype antibodies could explain a decrease in the level of anti-Ro/La antibodies in the maternal circulation. However, there are many unanswered questions. For example, are these antibodies really etiopathogenic (2)? By inhibiting placental transfer of these antibodies are we also decreasing the risk for developing CHB? This is very difficult to prove, because no animal model for CHB is available. One support for a pathogenic role of maternal autoantibodies in the development of CHB is that the onset of bradycardia coincides with heightened placental passage of the IgG type of these autoantibodies (3), and, therefore, inhibition of placental transfer of these antibodies at the right time would be very important. In the future, a large (multinational) clinical study would be needed to confirm the clinical relevance of the findings of Tran and colleagues.

Risto Kaaja, MD, PhD
Helsinki University Hospital
Helsinki, Finland
Heikki Julkunen, MD, PhD
Peijas Hospital
Vantaa, Finland
Helsinki University Hospital
Helsinki, Finland

1. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulins. N Engl J Med 2001;345:747–55.
2. Buyon JP, Kim MY, Copel JA, Friedman DM. Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient [editorial]. Arthritis Rheum 2001;44:1723–7.
3. Tseng C-E, Buyon JP. Neonatal lupus syndromes: pregnancy and rheumatic disease. Rheum Dis Clin North Am 1997;23:31–54.

DOI 10.1002/art.11492

Ultrasound-guided steroid injections in the treatment of hip osteoarthritis: comment on the letter by Margules

To the Editor:

Dr. Margules should be congratulated on his recent letter discussing a study of 510 patients with fluoroscopically guided injections into the hip (1). He states that one of the reasons that corticosteroid injections are not commonly used in hip osteoarthritis (OA) is the technical difficulty in delivering such injections. As a consequence, corticosteroid injection is omitted from current treatment guidelines, although the same procedure is advised for the treatment of knee OA (2).

Ultrasonography (US), a safe, noninvasive procedure, may represent a credible alternative to fluoroscopy, especially owing to the lack of radiation exposure associated with the former procedure. In addition, US is able to detect features of OA such as joint space narrowing and osteophyte formation that may help predict the response to treatment. It can also localize collections of fluid within the joint, allowing guided aspiration if infection is a concern. In addition, US can be used to check the accuracy of the injection without the use of contrast and ionizing radiation, as is the case with fluoroscopy.

We now report a prospective study of US-guided injections into the hip joints of patients with severe hip OA, which was undertaken in order to determine the predictive value of US and radiography features. All patients fulfilled the American College of Rheumatology criteria for hip OA (3), had ongoing pain and disability despite use of nonsteroidal antiinflammatory drugs and analgesics, and were on the waiting list for a total hip replacement (THR). Informed consent was obtained, and the study was approved by the local research ethics committee.

The baseline assessment included documentation of analgesic requirements and use of a patient 100-mm visual analog scale (VAS) for pain when walking. Radiographs of the affected hip were scored as mild, moderate, or severe, and US was performed using a standardized technique (4). The hip joint was then injected with 40 mg of triamcinolone and 2 ml of 1% lidocaine under US guidance; all injections were accurately placed.

Followup visits were performed at 2, 6, and 12 weeks when the response to corticosteroid injection (defined as a reduction of >15 mm in the VAS pain score for walking) was noted. Baseline findings on radiography and US were analyzed for any features that might predict the response to treatment.

Eleven patients were recruited, 7 of whom were female; the mean age of the patients was 63 years (range 53–72 years). The mean VAS score for pain at baseline was 78 mm. Six patients had severe OA changes on radiography, and the remaining 5 had moderate OA. Eight patients had an effusion on US (4 with moderate and 4 with severe radiographic OA). Five patients had anterior osteophytes on US (3 with severe and 2 with moderate radiographic OA).

Overall, 6 patients (55%) described a response at 2 weeks, compared with 4 (33%) of 11 patients and 3 (38%) of 8 patients at 6 and 12 weeks, respectively. No patient had improvement in range of motion (ROM) or the Western Ontario and McMaster Universities Osteoarthritis Index (5). There were no complications such as joint infection.

Of the 6 responders at 2 weeks, 2 had severe radiographic OA, but both had US effusion, compared with 4 who had moderate OA (3 of whom had US effusion). At 6 weeks, 3 of 4 responders had moderate radiographic OA, all with US effusion, and these 3 continued to benefit from therapy up to week 12. All 5 patients with an effusion but without osteophytes on US responded at week 2, with 4 (80%) of 5 patients and 3 (75%) of 4 patients continuing to respond at 6 and 12 weeks, respectively. Only 1 of 5 patients (20%) with osteophytes on US responded at 2 weeks.

In this study, severe radiographic OA and osteophytes on US were both (not surprisingly) associated with a poor response to treatment (20%), whereas patients with an effusion but no osteophytes on US had the greatest chance of a sustained response (75%), suggesting that this may be a predictor of favorable response.

In this study, the response to injection was less than that described by Margules (1). However, all of our patients were awaiting THR, suggesting greater disease severity, as highlighted by the lack of improvement in ROM and function. Whether the use of a potentially more potent corticosteroid such as triamcinolone hexacetonide prolongs response (6) is unclear.

Our preliminary evidence suggests that certain patients with end-stage OA who are awaiting THR may benefit from corticosteroid injection, and radiographic and US findings may be used to help predict that response. In addition, US represents a superior means of accurately delivering corticosteroid into the hip joint. A large, randomized controlled trial is required to further investigate these preliminary observations.

Zunaid Karim, MD
Andrew K. Brown, MD
Mark Quinn, MD
Richard J. Wakefield, MD
Philip G. Conaghan, MD
Paul Emery, MD
University of Leeds
Leeds, UK
Philip J. O'Connor, MD
Leeds General Infirmary
Leeds, UK

1. Margules KR. Fluoroscopically directed steroid instillation in the treatment of hip osteoarthritis: safety and efficacy in 510 cases [letter]. Arthritis Rheum 2001;44:2449–50.
2. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–15.
3. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
4. Backhaus M, Burgemester G-R, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641–9.
5. Bellamy N. Outcome measurement in osteoarthritis clinical trials. J Rheumatol 1995;22 Suppl 3:49–51.
6. Kahn C. Use of triamcinolone hexacetonide for the treatment of osteoarthritis of the hip: comment on the letter by Margules [letter]. Arthritis Rheum 2002;45:2546.

DOI 10.1002/art.11493

Reply

To the Editor:

I thank Karim et al for their report on use of US-guided cortisone instillation of the hip. Along with fluoroscopy, US-guided needle procedures can be done with reliable results. Their report addresses the use of US-assisted arthrocentesis, specifically of the hip, in patients with OA. Karim and colleagues clearly state that the use of US for this procedure can accurately direct a steroid preparation into the hip socket. They also report that the patients with joint space effusion had a somewhat better response to the cortisone instillation than did those without effusion.

A question that naturally arises is, "Which is better for hip injection: US or fluoroscopy?" As well, fellowship directors may rightly ask which procedure they should teach. To this end, a comparison (somewhat limited) of the pros and cons of fluoroscopy and US may be useful.

Fluoroscopy provides a much wider field of view compared with US, providing a complete panorama of the hip socket, from the acetabulum to the neck of the femur. It can offer extremely precise needle targeting for narrow joint spaces. I am accustomed to using fluoroscopy, and find it very easy to locate the hip space and insert a needle directly into it. Radiographic contrast can be introduced into the joint space for confirmation of needle location, if desired.

In contrast, fluid collections are invisible. Radiation is required, albeit in very small doses. Expensive equipment in a radiology suite is required, with the consent of hospital authorities—and sometimes radiologists. I am aware that some of my colleagues have the perception that fluoroscopy privileges are granted grudgingly or with resistance. With regard to this matter specifically, I have never met an obstacle. Rheumatologists ordinarily and appropriately perform fluoroscopy.

The circumstances surrounding US are different. This procedure easily lends itself to an (unshielded) office setting. There is no radiation. The costs for the purchase, installation, and training for US are a fraction of those for fluoroscopy, and certain US machines can be operated without an assistant or technologist. Visualization of the joint space is readily obtained because bone structures are highly echogenic. Surface topography, which may include osteophyte take-off, can be seen in fine detail. Fluid collections are readily identified and can be aspirated or incised and drained. US is frequently used when a hip effusion is suspected in a pediatric patient. It is possible that more widespread use of US will reveal more effusions that otherwise might elude the examiner.

However, the field of view obtained with US is extremely narrow. The surface (skin) is off the viewing monitor, because all of the imaging is of deep structures. This makes the location of needle entry a bit more challenging, requiring skin markers (which are available). For those of us who are more comfortable with fluoroscopy, US takes some "getting used to."

I am aware that many rheumatologists perform cortisone instillations into the hip at the bedside, without the use of imaging equipment. When safely done, this is perfectly acceptable. Our discussion of the use of and preference for imaging equipment should not illegitimize bedside hip instillations. However, for the purposes of establishing the value of cortisone instillation into the hip as therapy for OA, the use of one or the other in an academic study is welcome.

Arthrocentesis is a skill expected of a rheumatologist, who can choose whichever of these tools is necessary for completion. Either ultrasonography or fluoroscopy is effective in directing a needle tip into the hip socket. Nonetheless I personally prefer fluoroscopy. The wide field of view and ease of needle insertion make the procedure quick and accurate. Karim and colleagues are to be congratulated for bringing an alternate method of procedure to the forum, and, again, for possibly uncovering a prognostic factor heretofore unknown: OA with effusion may respond with more pain relief to a cortisone instillation than does OA without effusion. Time will tell whether US will enjoy increasingly widespread use. Further discussion and study of these procedural tools are warranted.

Kenneth R. Margules, MD
Finch University
North Chicago, IL
Condell Memorial Hospital
Libertyville, IL

DOI 10.1002/art.11494

Erratum

In the editorial by Hamilton published in the August 2003 issue of *Arthritis & Rheumatism* (pp 2085–2091), it says, "Eighteen cases of TB have been reported among 2,334 patients in premarketing placebo-controlled studies, with no TB-related deaths reported." The sentence (page 2086) should have read, "Thirteen cases of TB have been reported among 2,334 patients in premarketing placebo-controlled studies, with no TB-related deaths reported."

We regret the error.