

Is once a week enough?

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Is Once a Week Enough?

To the Editor:

Etanercept, infliximab, and adalimumab, are the 3 anti-tumor necrosis factor- α (TNF- α) agents widely used for the treatment of aggressive rheumatoid arthritis (RA). Etanercept (Enbrel) is a fully humanized soluble recombinant TNF receptor p75 Fc fusion protein¹, which until recently was routinely given by subcutaneous injection 25 mg twice weekly. Etanercept 50 mg once weekly was licensed in the UK for the treatment of RA on April 28, 2005. The use of etanercept 50 mg once weekly in patients with RA² and ankylosing spondylitis³ has been shown to have similar clinical outcomes, safety, efficacy, and pharmacokinetic profiles as compared to etanercept 25 mg twice weekly^{2,3}. This preparation is becoming more popular, as patients only need injections once weekly.

We conducted an observational study during the summer of 2006 at the Rheumatology Department, Stoke Mandeville Hospital, Aylesbury, UK. We retrospectively audited the clinical notes of patients diagnosed with RA who had been treated successfully with etanercept 25 mg twice weekly and subsequently switched to 50 mg once weekly. We set out to prove the null hypothesis that there was no difference in clinical outcome regardless of the etanercept dosing regime used in our cohort of patients.

The cohort consisted of 15 patients, all female. The mean age was 50.3 years (range 36–60). These patients had been successfully treated with etanercept 25 mg twice weekly in accord with British Society for Rheumatology guidelines⁴. Disease Activity Score-28 (DAS-28) were analyzed before and 3 months after switching to etanercept 50 mg once weekly. All patients in the cohort had been switched to the once-weekly regimen due to personal choice. Five patients (31.3%) were found to deteriorate when switched to etanercept 50 mg once weekly. The mean DAS-28 was 3.19 (SD \pm 1.20) while taking 25 mg twice weekly, and 5.48 (SD \pm 1.16) while taking 50 mg once weekly. The increase in DAS-28 score was statistically significant ($p = 0.019$). Statistically significant increases were seen in both the swollen joint score ($p < 0.009$) and visual analog scale (VAS) pain score ($p < 0.041$), but not the erythrocyte sedimentation rate (ESR; $p < 0.067$) or tender joint count ($p < 0.065$). In 11 patients (68.7%), disease activity remained stable when switched to the once-weekly regimen. Mean DAS-28 scores were 3.57 (SD \pm 1.21) and 3.07 (SD \pm 1.59) while taking 25 mg twice weekly and 50 mg once weekly, respectively. The reduction in DAS-28 score was not statistically significant ($p = 0.181$). The

5 patients who deteriorated switched successfully back to their original dosing regime.

Our results show that one-third of patients treated with etanercept 25 mg twice weekly for RA deteriorated when switched to etanercept 50 mg once weekly. One argument would be that the patients' deterioration could be due to the patients' perception of having only one injection a week, when previously they were having 2. However, studies have shown that the maximum influence that the VAS score can have on the DAS-28 is 1.2, and that there was no change in the overall management when the VAS was excluded from the DAS-28 calculation⁵.

Despite both etanercept dosing regimes satisfying the primary requirements for bioequivalence testing⁶, comparable clinical outcomes were not seen in our small cohort of patients. The study group used by van der Heijde, *et al*³ and Keystone, *et al*² was interestingly etanercept treatment-naive, in contrast to our cohort of patients. This may be the reason for the disparity in the results of our study. A larger study group may also have shown statistically significant changes in the ESR and tender joint count. Further, we can postulate from our results that patients who fail to respond adequately to etanercept 50 mg once weekly may respond to etanercept 25 mg twice weekly.

Our experience rejects the null hypothesis. This small observational study suggests that patients well controlled on etanercept 25 mg twice weekly may experience loss of disease control if they considered switching to etanercept 50 mg once weekly. Larger studies are needed in this area, but clinicians should be aware of our interesting and relevant findings, and proceed with caution if considering switching a patient with controlled RA taking etanercept 25 mg twice weekly to 50 mg weekly.

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Dr. Keystone replies

To the Editor:

Bawa, *et al* report an interesting but small study of 15 patients who

switched from etanercept 25 mg subcutaneous twice per week to 50 mg once per week. This report is the first to address the issue of switching from 25 mg twice a week to 50 mg once-weekly dosing. The authors demonstrated that one-third of patients switching from 25 mg twice per week to 50 mg weekly exhibited a flare. However, the sample size was too small to provide an accurate assessment of the proportion of patients who might experience flare on the 50 mg dose. Although our previous study of 420 patients demonstrated comparable responses with the 25 mg twice per week dose and the 50 mg once-weekly dose, the therapeutic paradigm of our study differs from that of Sundee, *et al*, since, as they point out, the 50 mg once-weekly dose was used only after a good response was achieved with the standard 25 mg dose. This difference in therapeutic strategies between the 2 studies precludes drawing direct comparisons, as Sundee, *et al* pointed out.

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Glucocorticoid Treatments and Rheumatoid Arthritis

To the Editor:

In the April issue of *The Journal*, Caplan, *et al*¹ report a retrospective database analysis on glucocorticoid treatment in rheumatoid arthritis (RA). Their data show that a substantial proportion of the patients with RA are treated with prednisolone at any time during their course of disease. They also could show a correlation between the use of glucocorticoids and a poorer outcome of the disease. This seems not surprising, though, as one would expect the chance of doctors finding indication for prescribing glucocorticoids is greater among patients with the highest disease activity. In concordance with this, the authors themselves state that the association may be due to confounding by association.

Other aspects of glucocorticoid treatment in rheumatoid patients are economic and demographic factors and the patients' attitudes to glucocorticoid treatment. These factors might influence the course of RA and the decision to use glucocorticoids or not. To my knowledge, the access to modern disease modifying antirheumatic drugs (DMARD) including biologic anti-tumor necrosis factor treatment is not in all countries equal at all levels of society. These factors might also influence another finding of Caplan, *et al*, namely that rheumatologists have different practices in prescribing glucocorticoids to their patients. This might to some extent be attributed to differences in economic, educational, and demographic characteristics of the patient populations.

In their report, Caplan, *et al* do not specify whether intraarticular or intramuscular glucocorticoid injections were recorded and corresponding prednisolone doses estimated and included in the analysis. In most European rheumatologic centers I know of, parenteral glucocorticoid injections are often used as early bridge therapy to gain quick control over the rheumatic inflammation while the effect of DMARD is awaited, and to treat flares of disease activity. This might not be the case in the US, but if a substantial proportion of the patients in the study by Caplan, *et al* received parenteral glucocorticoids without this being recorded and included in the analysis, the conclusions of the study might be severely hampered.

OLE SLOT, MD, Department of Rheumatology, Hvidovre Hospital, DK-2650 Hvidovre, Denmark. E-mail: ole.slot@hvh.regionh.dk

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Dr. Wolfe, et al reply

To the Editor:

We thank Dr. Slot for his letter. In our study we did not include isolated intramuscular corticosteroids, which would have increased corticosteroid use by around 1%.

We are certainly aware of individual cases where corticosteroids are used instead of DMARD therapy because of costs. However, the more important issue is whether this is a common occurrence and one that influenced the results of our study. Access to treatment in the US is complex, being dependent not only on household income but also on individual health insurance contracts. There are thousands of different health insurance contracts, and distinguishing their benefits and differences in the research that we presented is not possible. Only 1.9% of participants had neither private nor government health insurance. We do have data on household income, however, and such data might serve as a surrogate for access to care.

But even here the relationship between access to care and income is complex, as income is correlated with age, sex, RA severity, and education. To fully answer Dr. Slot's question, an inception cohort study would be necessary. However, an approximate answer may be helpful. We matched patients by Health Assessment Questionnaire score in a conditional logistic regression, and further adjusted for age, sex, and education level. An increase in total household income of \$10,000 US did not significantly decrease the risk of corticosteroid use (odds ratio 0.99, 95% confidence interval 0.97–1.00, $p = 0.121$). In sensitivity analyses that employed other analytic methods, similar results were found. Therefore our data do not provide support for the hypothesis that income (as a surrogate for access to care) influences prednisone prescription.

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Problems with Franco-American Systemic Sclerosis Study

To the Editor:

In their article comparing American and French patients with systemic sclerosis (SSc), Meyer, *et al*¹ report increased topoisomerase I antibodies in the French patients, and describe mild and localized disease in that population. American patients, by contrast, were found to have higher levels of anti-RNA polymerase III antibody, and more arthritis and tendon friction rubs. The clinical findings, in particular, are questionable due to the retrospective design of the trial, the potential for interobserver variability, and statistical flaws.

Although the authors state "data were collected prospectively and abstracted for this study retrospectively," the data go back to 1986 for the American cohort, and 1975 for the French patients, suggesting a retrospective chart review process. Moreover, a third of the French patients were examined by dermatologists, which may explain the relative absence of joint disease as a finding. The Americans, examined by rheumatologists entirely, would be expected to have more joint disease. This difference may reflect interobserver variability, or even cross-cultural differences in practice styles.

Finally, the authors properly undertake to do a Bonferroni adjustment, a statistical method of raising the bar necessary to achieve significance when doing multiple comparisons, but then ignore their own statistical process in discussing their findings. For example, the introductory abstract states, "French lcSSc patients...more often had radiographic evidence of pulmonary fibrosis (57 vs 30%)," without acknowledging that this difference was only significant to a p value of 0.014 (Table 3), and that a threshold of 0.0036 would be necessary to be statistically significant. Either a finding is significant or it is not, once the methodology is spelled out. The authors cite "data not shown," (p. 106), and "Unpublished data," (p. 108) as evidence for milder disease among French patients, rather than building a case based on refutable argumentation.

In summary, the Meyer, *et al* article finding milder disease among French scleroderma patients is significantly compromised by confounding variables, interobserver variability, and lack of recognition that this was a retrospective trial, ignoring the Bonferroni adjustment that was employed, and making speculative statements based on unpublished data.

SCOTT T. ANDERSON, MD, PhD, FACR, Clinical Associate Professor of Medicine, Division of Rheumatology, University of California at San Francisco, San Francisco, California, USA.

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Dr. Meyer replies

To the Editor:

The letter from Dr. Anderson contains interesting comments about our recent article comparing American and French patients with SSc¹. For clarification, the French patients with SSc have a higher frequency of limited cutaneous involvement (not localized) and among American patients a higher proportion have anti-RNA polymerase III antibody (not antibody levels).

The American data are definitely prospective, as a 100% sample of first and followup visits on patients with SSc has been entered into the Pittsburgh Scleroderma Databank beginning in 1980. No retrospective chart review was necessary. We used 1986-88 patients because all patients with SSc entered during this 3-year period had a full panel of serum autoantibody tests. The data on French patients were obtained by retrospective chart review of a series of consecutive patients with frozen (-20°C) blood samples, all of whom were seen or followed by a single investigator (Dr. Meyer), thus minimizing interobserver variability. We compared definitions used for symptoms and signs between the 2 centers and when they were not directly comparable, e.g., proximal muscle weakness on examination, we did not include these comparisons in the tables. Thus we made an honest attempt to report only comparable SSc manifestations.

It is true that French patients with SSc were not referred exclusively to the Rheumatology Department at Bichat University Hospital in Paris. However, all 127 French patients reported by us were examined and followed in the Rheumatology Department and none were referred from Dermatology. We do not deny the retrospective nature of the data and the potential for interobserver variability. We commented on these points in the Discussion section.

To explain the discrepancy between pulmonary fibrosis frequencies between the 2 centers, we considered and discussed referral bias in Pittsburgh and differences of recruitment of SSc patients to Dermatology versus Rheumatology at Bichat. The latter data have not been published, but comparison of 30 patients in each of these 2 Bichat departments has shown a higher frequency of pulmonary fibrosis, gastrointestinal abnormalities, and cardiovascular involvement in patients seen in the

Rheumatology Department. All 3 of these differences were statistically significant, and thus our statement is not speculative but rather evidence-based. If anything, these results would further support milder SSc among French patients.

With regard to Bonferroni adjustment, we agree that $p < 0.05$ is not significant, as noted at the bottom of Tables 3 and 4. In the Abstract we specifically used the term "more often" to describe differences in pulmonary fibrosis frequency rather than using "significantly more often," which we would have used if the Bonferroni-adjusted p value was less than 0.0036. We do not believe that this sentence, as written, is misleading.

Despite likely interobserver variations in data collection regarding symptoms and examination findings, we stand by our conclusion that, in these 2 populations, SSc is milder in French patients. We welcome a prospective study to confirm or refute this observation.

OLIVIER C. MEYER, MD, Professor of Rheumatology, Rheumatology Unit, Bichat Hospital, Paris, France.

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Jean-Martin Charcot: Rheumatology in Philately

To the Editor:

As a philatelic rheumatologist I have appreciated a rare article about rheumatology in philately, published in 1992¹. In that interesting article, R.A. Greenwald presented a small collection of rheumatology related stamps; the second example portrays "Jean Martin Charcot...certainly the most prominent neurologist of the 19th century..." Charcot spent more than 30 years of his career at the Hôpital Salpêtrière and there he established the great School of Neurology; in 1868 he gave the first detailed description of the relationship between loss of sensation and arthropathy, and he described the joint lesions of syphilis caused by this complication². For this reason, neuropathic osteoarthropathy was named after him, "Charcot joint disease."

It is perhaps less well known that Charcot's doctoral thesis was devoted to gout and chronic rheumatism, and indeed in his famous book *Leçons Cliniques sur les Maladies des Vieillards* he is credited with the first description of both rheumatoid pericarditis and hand deformations. He also left a lasting imprint on the study of rheumatic diseases, proposing nosologic distinctions that are widely accepted today³. In that article, Lagier reports that Charcot's son, Jean-Baptiste, the arctic explorer and physician, was also represented on a stamp. This is a rare example — father and son, both physicians and both depicted on stamps for quite different achievements. This aspect has also been noted by Haas in 2001⁴.

However, Greenwald made a mistake. The stamp illustrated in his article (Figure 1), instead of depicting the father and neurologist, Jean-Martin Charcot (1825-1893), shows his son the explorer, Jean-Baptiste (1867-1936). Figure 2 shows the only stamp dedicated to Jean-Martin Charcot,



Figure 1. Jean-Baptiste Charcot (1867-1936), the son, the explorer. Commemorative stamp released in 1961 on the 25th anniversary of his death at sea in 1936. (From Greenwald RA. *J Rheumatol* 1992;19:1458-61).



Figure 2. Jean-Martin Charcot (1825-1893), the father, the neurologist. In the background is the famous Paris hospital, La Salpêtrière, where he spent more than 30 years of his career. The stamp was issued in 1960.

who has given his name to an arthropathy and to an island (Charcot Island, in Antarctica, was dedicated by the son to his father).

Jean-Baptiste became a doctor to give satisfaction to his father. But he devoted all his spare time to ships and to the sea; at the age of 35, he declared, "I'm nothing more than my father's son," and deserted medicine to become a well known polar explorer, sailing in his famous ship, *Pourquoi pas?* ("Why not?"). Yet he was influenced by his early background, and commenting on his lifetime experience he associated it with the education and scientific method of the hard and inflexible school of his father. He went down with his ship during a storm off northern Iceland in 1936. For his achievements in exploration he was honored by France and Britain with several postage stamp issues, exceeding his famous father in the philatelic field.

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Book Review

Osteoarthritis, 4th edition

Roland W. Moskowitz, Roy D. Altman, Joseph A. Buckwalter, Victor M. Goldberg, Marc C. Hochberg, editors. New York: Lippincott Williams & Wilkins, 2006. 528 pages. \$149.00 US.

Osteoarthritis is the definitive text covering all aspects of this vital rheumatologic area. The authors have been and remain leading figures in the treatment and research of osteoarthritis (OA). This is the 4th edition of this text, the first appearing in 1984. As noted in the preface, this is the shortest interval between editions, attesting to the rapid pace of our understanding of OA as a disease and cartilage as a target, not only with respect to basic and clinical aspects, but also to its impact on society. This book serves the needs of rheumatologists, basic investigators in the field, as well as orthopedic surgeons, physiatrists, and primary care physicians with a clinical interest in OA.

The text is well organized, divided into major subsections: Basic Considerations; General Aspects of Diagnosis; General Aspects of Management; and Surgical Considerations. New methodologies of imaging, an evidence-based presentation of complementary and alternative medicine, and new frontiers in surgery are 3 areas that expand on what was written in the previous edition. The increasing roles of magnetic resonance imaging and newer methodologies are effectively presented. Chapters on genetics and on animal models and a section on noninvasive biomarkers are well written and add to the excellent and ever-expanding chapter on etiopathogenesis. The growth of our understanding of these areas as described in these chapters points to the possibility of disease-modifying pharmacotherapeutics. The book finishes with several chapters dealing with regional considerations (upper extremity, hip, etc.).

Osteoarthritis is well written and well referenced. It is thoughtful and complete. This book is indispensable and necessary to the student of osteoarthritis.

Jerry Tenenbaum, MD, FRCPC, Professor of Medicine, University of Toronto; Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, Ontario; and Victoria Women's Health Centre, Victoria, British Columbia, Canada.

Correction

Roldan R, Morote G, del Carmen Castro M, Miranda MD, Moreno JC, Collantes E. Efficacy of bosentan in treatment of unresponsive cutaneous ulceration in disabling pansclerotic morphea in children. *J Rheumatol* 2006;33:2538-40. In the Abstract and in the last paragraph of the first page of the report, the dose of bosentan is given as 31.25 mg qid; however, "qid" (4 times per day) is incorrect. The correct dosage is "qd" (once per day). We regret the error.