Editorial

Why Are Only 50% of Courses of Anti-Tumor Necrosis Factor Agents Continued for Only 2 Years in Some Settings? Need for Longterm Observations in Standard Care to Complement Clinical Trials

In this issue of *The Journal*, Duclos, Gausec, Dougados, and colleagues at the Cochin Hospital in Paris report analyses of the largest series of courses of anti-tumor necrosis factor (anti-TNF) agents at one site in patients with inflammatory arthritides[1]. The proportion of 975 courses that were continued in 770 patients at 6, 12, and 24 months was 64%, 50%, and 39%, respectively. No significant differences were seen between the 3 available agents, etanercept, infliximab, and adalimumab. Courses of anti-TNF agents were continued longer in the 38% of patients with ankylosing spondylitis than in the 57% of patients with rheumatoid arthritis, and courses were continued longer if no concomitant disease modifying antirheumatic drug (DMARD), including methotrexate (MTX), was taken[1].

The authors recognize that results in their report, termed the "Cochin report," differ from those reported in clinical trials[1], in which a combination of anti-TNF agent with MTX invariably had greater efficacy than either agent as monotherapy[2-4]. Further, a study from Sweden indicated continuation of 88% of etanercept plus MTX courses at 24 months versus 73% of etanercept-only courses at 24 months, and 57% of infliximab plus MTX courses versus 35% of infliximab courses[5].

Perhaps DMARD therapy serves as a marker for more severe clinical status and is often discontinued when the patient is improved in the Cochin clinical setting. In contrast, many rheumatologists, including the authors of this editorial, continue MTX in most patients who take anti-TNF agents, generally indefinitely[6]. In some senses, the question about the use of concomitant DMARD with anti-TNF therapies addresses physician attitudes and actions as well as patient status.

If reports of clinical trials and results in some clinical settings indicate that anti-TNF agents have had greater apparent efficacy compared to findings of the Cochin report, as recognized by the authors[1], we may ask why 50% of courses they studied were continued for 2 years or less:

1. The Cochin report data may not be generalizable

The authors note that some rheumatology centers have reported high remission rates in patients treated with anti-TNF agents in standard clinical care[5,7,8]. In a study of 200 patients in The Netherlands, 50% of courses of anti-TNF therapy were continued for 37 months[7]. In reports from Sweden 77% of etanercept courses were continued after 20 months[9] and 24 months[10]. Analyses in Germany suggested that continuation after 12 months was about 75%[11]. An abstract from Denmark[8] indicated that 70% of courses of anti-TNF agents were continued for 1 year, and 50% for 134 weeks. A recent abstract from Sweden indicated continuation at 24 months of 72% of etanercept courses, 59% of infliximab courses, and 50% of adalimumab courses; however, continuation of first courses of the 3 anti-TNF agents was similar, at 80%, after 1 year[12]. Stern and Wolfe reported that 75% of courses of infliximab were continued for 2 years in 2 cohorts from Dallas and the entire United States[13], although these patients may be selected for returning mailed questionnaires every 6 months.

Taken together these reports suggest somewhat higher rates of continuation of anti-TNF agents in other clinical settings versus those seen in the Cochin study, although results are in a range similar to other studies. Continuation rates may also in part reflect attitudes and actions of rheumatologists and patients, which may differ widely in different clinical settings.

The Cochin database does not include analyses of MTX courses. Reports from the United States in 1990[14] and in 1992[15] indicated that 50% of courses of MTX were continued over 5 years, and more recently in one setting, that 80% of courses were continued over 5 years[6]. Although it is not possible to gain definitive information from comparisons of data from different settings and different eras, these reports may suggest higher rates of continuation of MTX courses versus those seen for anti-TNF agents in the Cochin report.

See Retention rates of TNF blockers in daily practice in 770 rheumatic patients, *page 2433*

2. Many patients treated with anti-TNF agents already had extensive joint damage

Patients with RA usually have some degree of ongoing reversible inflammatory activity indefinitely, so most can benefit from antiinflammatory therapies even after many years of disease. However, currently many patients treated with TNF agents have significant longterm joint damage (in addition to inflammatory activity[16]) that will not necessarily respond to anti-TNF therapy. Moreover, patients who have irreversible longterm joint damage often are less likely to experience control of pain and other symptoms compared with patients with reversible damage. In the Paris study no association between disease duration and continuation of courses was seen; however, duration of disease is a poor surrogate for joint damage.

Rheumatology clinical trials generally exclude people in functional "class IV" RA[17], but this status is unusual in ambulatory patients at this time in an era of total joint replacement. Nonetheless, many of the patients may have extensive joint damage. It is unfortunate that measures of damage generally are not included in clinical trials, and results are not analyzed according to the presence or absence of significant damage to possibly serve as an exclusion criterion or potentially adjust for joint damage.

3. Some patients who receive anti-TNF agents have fibromyalgia as their primary clinical problem

About 10–20% of patients with RA may have extensive fibromyalgia (FM)[18], which will reduce or eliminate the likelihood of substantial improvement and lead to discontinuation within 1 or 2 years of therapy. Again, the presence of FM generally is not considered in inclusion or exclusion criteria for RA clinical trials. Most rheumatologists might be unlikely to enroll a patient with extensive FM in a trial. Nonetheless, no adjustment is made for FM in reporting results of clinical trials.

4. Selection for patients with severe inflammatory activity into clinical trials

Most early trials of anti-TNF agents selected incomplete responders to MTX to continue MTX with the biologic agent or a placebo. This "add-on" trial design[19] might be expected to select for patients who have more severe inflammatory activity than the general population of patients seen in clinics. Indeed, in some settings, only a small minority of patients seen were eligible for such trials[20-22]. Patients with higher levels of inflammatory activity might be more likely to respond to an intervention that reduces inflammation. Therefore, a higher proportion of patients who meet eligibility criteria for clinical trials would be expected to respond to any therapy.

5. Availability of 3 anti-TNF agents

Three anti-TNF therapies are available, so that a patient or clinician who is unhappy with one anti-TNF agent can switch to another agent. Therefore, an analysis of continuation of *any* anti-TNF agent might be of considerable interest, i.e., what is the likelihood of someone who begins anti-TNF to continue to take any anti-TNF agent? For example, in a report from Sweden, treatment with any TNF agent was continued in 84% of patients after 2 years and 75% after 5 years[12]. In the Cochin report[1], only 205 of the 770 patients appeared to have more than one course of an anti-TNF agent, so most of the data appear to reflect results with any anti-TNF agent.

6. Expense of anti-TNF agents

The expense of anti-TNF agents may inhibit their being continued over long periods. In general, once administrative hurdles to administer anti-TNF agents are overcome, the therapy is continued, particularly if there is a good response. However, some patients in the USA attribute discontinuation to financial reasons. The Cochin report does not mention possible financial influences on discontinuation of therapies.

The Cochin observations reinforce the importance of data from observational studies in standard clinical care to supplement data from clinical trials. Essays concerning limitations of randomized controlled clinical trials conducted in various disciplines have been published[23-26], including several editorials in *The Journal*[27-30]. Patient selection, short timeframe, fixed dosage schedules, and many other limitations may explain why results in clinical care may differ from those in clinical trials. It is recognized that many different designs other than the randomized clinical trial are needed in research concerning clinical care[31-34]. Nonetheless, in the rheumatology and general medical communities, the limitations of clinical trials remain underrecognized, while their results remain overemphasized as almost the only source of "evidence-based medicine"[30].

Data from clinical trials cannot be used by the rheumatologist to choose a specific agent when managing an individual patient with RA, as many choices are supported by "evidence." Therefore, longterm analyses, such as those performed by the Cochin group, are required to inform clinicians concerning the optimal management of individual patients. Databases or registers to study longterm outcomes of RA have been established in many locales, including the United States[35-39], United Kingdom[40], Germany[11,41], Norway[42], Sweden[9,12,43,44], Finland[45], Denmark[8,46], and elsewhere.

In longitudinal databases of patients with RA, it may be of value to include a measure of joint damage such as joint deformity on radiographic and/or physical examination, as well as assessment of the presence of FM. Further, such studies should include patients treated with MTX, and all patients with RA, including those with suspected disease. Indeed, a longterm observational study is most informative

if all consecutive patients are included, rather than a selection for any particular therapy[47].

Anti-TNF agents provide a major advance to the rheumatology community — the senior author of this editorial has reported that 37% of his patients with RA have been treated with biologic agents[48]. Since many patients with severe disease activity will require anti-TNF therapy, TNF agents will invariably appear superior to MTX and other DMARD in randomized trials in which a combination of anti-TNF and MTX is compared to MTX monotherapy. Nonetheless, many patients may be adequately treated with MTX — the highest reported levels of remission in the rheumatology literature are seen in the FinRACo[49] and TICORA[50] trials in patients who did not receive anti-TNF therapy, and longterm minimal radiographic progression has been documented in many patients prior to anti-TNF therapy[51,52].

The most important principle in standard clinical care of RA at this time is not necessarily which agent is used, but how early "tight control" is established[50,53]. Frequent visits that include quantitative assessments[54] are helpful to recognize which patients are responders or nonresponders to different DMARD, so that anti-TNF therapy may be initiated prior to substantial damage. The Cochin group has accomplished much. Further studies from these and additional databases from many locales, including standard clinical care, will further inform rheumatologists in their efforts to improve outcomes for patients with RA.

THEODORE PINCUS, MD,
Professor of Medicine,
Division of Rheumatology and Immunology,
Vanderbilt University Medical Center,
Nashville, Tennessee;
YUSUF YAZICI, MD,
NYU Hospital for Joint Diseases,
New York, New York, USA;
RONALD van VOLLENHOVEN, MD,
Karolinska University Hospital,
Karolinska Institute,
Stockholm, Sweden.

Supported in part by grants from the Arthritis Foundation and the Jack C. Massey Foundation.

Address reprint requests to Dr. T. Pincus, Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, 203 Oxford House, Box 5, Nashville, TN 37232-4500.

REFERENCES

1. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of TNF blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33:2433-9.
2. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
3. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
4. St. Clair EW, van der Heijde DMFM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-43.
5. Kristensen L, Geborek P, Saxne T. Adherence to therapy of etanercept and infliximab during first anti-TNF treatment course in rheumatoid arthritis patients [abstract]. Ann Rheum Dis 2005;64 Suppl III:431.
6. Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T. Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. Ann Rheum Dis 2005;64:207-11.
7. Flendrie M, Creemers MCW, Welsing PMJ, den Broeder AA, van Riel PLCM. Survival during treatment with tumor necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 2003;62 Suppl II:ii30-ii33.
8. Ostergaard M, Unkerskov J, Krogh NS, et al. Poor remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept — results from the nationwide Danish "Danbio" database [abstract]. Ann Rheum Dis 2005;64 Suppl III:59.
9. Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002;61:793-8.
10. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 2005;64:246-52.
11. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005;64:1274-9.
12. van Vollenhoven RF, Cullinane Carli C, Bratt J, Klareskog L. Six-year report of the STURE registry for biologicals in rheumatology: satisfactory overall results, but plenty of room of improvement [abstract]. Arthritis Rheum 2005;52 Suppl:S135.
13. Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol 2004;31:1538-45.
14. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17:994-1002.
15. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. J Rheumatol 1992;19:1885-94.
16. Callahan LF, Pincus T, Huston JW III, Brooks RH, Nance EP Jr, Kaye JJ. Measures of activity and damage in rheumatoid arthritis: Depiction of changes and prediction of mortality over five years. Arthritis Care Res 1997;10:381-94.
17. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659-62.
18. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004;31:695-700.
19. Boers M. Add-on or step-up trials for new drug development in rheumatoid arthritis: a new standard? Arthritis Rheum 2003;48:1481-3.
20. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in

rheumatoid arthritis. Arthritis Rheum 2003;48:313-8.
21. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. J Rheumatol 2003;30:1138-46.
22. Gogus F, Yazici Y, Yazici H. Inclusion criteria as widely used for rheumatoid arthritis clinical trials: patient eligibility in a Turkish cohort. Clin Exp Rheumatol 2005;23:681-4.
23. Feinstein AR. An additional basic science for clinical medicine: II. The limitations of randomized trials. Ann Intern Med 1983; 99:544-50.
24. Freireich EJ. The randomized clinical trial as an obstacle to clinical research. In: Varco RL, Delaney JP, editors. Controversy in surgery. Philadelphia: WB Saunders; 1983:5-12.
25. Pincus T. Rheumatoid arthritis: disappointing long-term outcomes despite successful short-term clinical trials. J Clin Epidemiol 1988;41:1037-41.
26. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? J Clin Epidemiol 2001;54:541-9.
27. Pincus T, Stein M. What is the best source of useful data on the treatment of rheumatoid arthritis: Clinical trials, clinical observations, or clinical protocols? J Rheumatol 1995;22:1611-7.
28. Urowitz MB. How do I know thee...? Let me count the ways. The varieties of medical evidence. J Rheumatol 2001;28:2373-4.
29. Buchanan WW, Kean WF. Evidence based medicine: the median is not the message. J Rheumatol 2001;28:2371-2.
30. Pincus T, Tugwell P. Shouldn't standard rheumatology clinical care be "evidence-based" rather than "eminence-based," "eloquence-based" or "elegance-based"? J Rheumatol 2007; In press.
31. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490-7.
32. Glasziou P, Vandenbroucke J, Chalmers I. Assessing the quality of research. BMJ 2004;328:39-41.
33. Tugwell P, Shea B, Boers M, et al. Evidence-based rheumatology. London: BMJ Publishing Group; 2004.
34. Sackett D, Haynes RB, Guyatt G, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. 3rd ed. Philadelphia: Little, Brown and Company; 2006.
35. Bruce B, Fries JF. The arthritis, rheumatism and aging medical information system (ARAMIS) — still young at 30 years. Clin Exp Rheumatol 2005;23 Suppl:S163-S167.
36. Wolfe F, Michaud K. A brief introduction to the National Data Bank for Rheumatic Diseases. Clin Exp Rheumatol 2005;23 Suppl:S168-S171.
37. Kremer JM. The CORRONA database. Clin Exp Rheumatol 2005;23 Suppl:S172-S177.
38. Sokka T, Pincus T. An early rheumatoid arthritis treatment evaluation registry (ERATER) in the United States. Clin Exp Rheumatol 2005;23 Suppl:S178-S181.
39. Yazici Y. A database in private practice: the Brooklyn outcomes of arthritis rheumatology database (BOARD). Clin Exp Rheumatol 2005;23 Suppl:S182-S187.
40. Silman A, Klareskog L, Breedveld F, et al. Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR Surveillance Register for Biological Compounds. Ann Rheum Dis 2000;59:419-20.
41. Zink A, Niewerth M, Zeidler H. The national database of the German Collaborative Arthritis Centres: II. Treatment of patients with rheumatoid arthritis. Ann Rheum Dis 2001;60:207-13.
42. Kvien TK, Heiberg MS, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23 Suppl:S188-S194.
43. Askling J, Fored CM, Geborek P, et al. Swedish registers to examine drug safety and clinical issues in RA. Ann Rheum Dis 2006;65:707-12.
44. van Vollenhoven RF, Askling J. Rheumatoid arthritis registries in Sweden. Clin Exp Rheumatol 2005;23 Suppl:S195-S200.
45. Sokka T. Rheumatoid arthritis databases in Finland. Clin Exp Rheumatol 2005;23 Suppl:S201-S204.
46. Hetland ML. DANBIO: a nationwide registry of biological therapies in Denmark. Clin Exp Rheumatol 2005;23 Suppl: S205-S207.
47. Moses LE. The series of consecutive cases as a device for assessing outcomes of intervention. N Engl J Med 1984;311:705-10.
48. Pincus T, Yazici Y, Yazici H, Kavanaugh AF, Kremer JM, Wolfe F. Radiographic benefit without clinical improvement in infliximab-treated patients with rheumatoid arthritis: comment on the article by Smolen et al. Arthritis Rheum 2005;52:4044-5.
49. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.
50. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
51. Pincus T, Ferraccioli G, Sokka T, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology Oxford 2002;41:1346-56.
52. Sokka T, Kautiainen H, Häkkinen K, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. J Rheumatol 2004;31:1073-82.
53. Pincus T, Gibofsky A, Weinblatt ME. Urgent care and tight control of rheumatoid arthritis as in diabetes and hypertension: better treatments but a shortage of rheumatologists. Arthritis Rheum 2002;46:851-4.
54. Pincus T, Yazici Y, Bergman M. Saving time and improving care with a multidimensional Health Assessment Questionnaire: 10 practical considerations. J Rheumatol 2006;33:448-54.