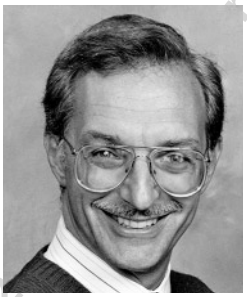
Editorial

Observational Cohort Studies and Well Controlled Clinical Trials — We Need Them Both!



In this issue of *The Journal*, Stern and Wolfe describe 2 studies: one is a retrospective record review of 394 patients out of 552 started on infliximab; the other examines results from 1324 usable responses from 1886 patient questionnaires in a longterm cohort study supervised and analyzed by Dr. Wolfe[1]. The studies document that the dose of infliximab rose from 3.6 mg per kg to about 5 mg per kg during 2 years' treatment. Fourteen percent of patients had discontinued the infliximab by one year and 25% had discontinued the drug by 2 years.

This work supports and extends data from published clinical trials[2-4]. The trial studies have documented increased responses with increasing doses and showed that, despite significant differences in pharmacokinetics, increasing concentrations of infliximab led to increasing response[2-4]. One important difference between the clinical trials and the studies by Stern and Wolfe is that the latter represent observational studies in real-life conditions, with patients and physicians changing doses or stopping therapy in response to various clinical conditions. The fact that the 2 methodologies, randomized clinical trials (RCT) and observational studies, support each other emphasizes the complementary nature of these research strategies.

As noted above, cohort studies and retrospective chart reviews represent real-life experience. With large numbers, one can try to compensate and control for a number of factors such as age, disease duration, rheumatoid factor positivity, etc., to develop a form of control for the population of interest. Further, the studies are relatively inexpensive. On the other hand, because the patients are observed in real-life conditions, they are not randomized to any given treatment, and evaluations of efficacy are open and uncontrolled. Observational studies and retrospective chart reviews do not control for inherent biases associated with most response variables such as the joint count and Health Assessment Questionnaire (HAQ) disability index and the biases inherent in dosing changes. For example, the reason that doses were changed was said to be for "insufficient clinical response," but the definition of "insufficient clinical response" will clearly be different for different physicians and different patients, making this measure very difficult to "get one's hands around." Intuitively, the use of "time on drug" seems a useful measure but, again, its definition is relatively inexact and differs from patient to patient and practice to practice.

And while the large numbers and longer followup period may allow greater generalizability, this is not necessarily the case. In Stern and Wolfe's study, for example, 33% of patients did not answer the questionnaire and those who did were somewhat older, had lower HAQ disability indices, and used less prednisone than those who did not ($p < 0.05$ for all of these). Similarly, patients with concomitant fibromyalgia used increased doses of infliximab compared to those who did not have fibromyalgia — mean dose 0.9 mg per kg higher (although not statistically significant). Again, in cohort studies, missing data can be a problem that impairs the generalizability. In Study 1, 29% of patients were missing data on disease duration. Since disease duration has been claimed by some to relate to responsiveness (less responsiveness with longer disease duration)[5], the lack of these data could conceivably decrease generalizability in Study 1.

RCT are necessary to prove drug efficacy and often necessary to define some dosing ranges and to determine the frequency of relatively common adverse events. In RCT, particularly double-blind trials, a number of biases inherent to open, observational studies are minimized. Usually criteria for dose increases, if allowed, are carefully defined, and biases in evaluations of response are minimized. Similarly, background medications are very carefully defined, and often minimized, as are concomitant illnesses. On the other hand, this means that patients are often "pristine" without concomitant illnesses or excluded medications, which are the rule in real life. Oh, and by the way,

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randomized clinical trials are *very* expensive. RCT rarely reflect real life, and consequently, the results from observational studies and RCT cannot be predicted to be the same.

It is nearly axiomatic to say that no study is perfect. While true of the study by Stern and Wolfe, I believe that their observations make a valid and clinically useful point. As is frequently the case, observational studies and RCT are complementary, each yielding valuable information.

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