Reconciling Subject Differences in Recruitment to Clinical Trials and Clinical Practice

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ABSTRACT. The special interest group on Reconciling Subject Differences was centered around the issue that the results from randomized clinical trials do not predict response to therapies in clinical practice, and around the hypothesis that this might be explained by differences in subjects selected for clinical trials compared to those treated in routine practice. (J Rheumatol 2005;32:2475–6)

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ANTI-TUMOR NECROSIS FACTOR-α INHIBITORS
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The special interest group (SIG) on Reconciling Subject Differences was centered around the issue that results from randomized clinical trials do not predict response to therapies in clinical practice, and around the hypothesis that this might be explained by differences in subjects selected for clinical trials compared to those treated in routine practice. This SIG was attended by about 20 participants.

The group reviewed current data from recent pivotal randomized controlled trials (RCT) of the anti-tumor necrosis factor-α (TNF-α) agents etanercept, infliximab, and adalimumab, in patients with rheumatoid arthritis (RA). They have shown these new therapies to be very efficacious in patients with long-standing, refractory disease. Typically, at least 60% of patients who had failed other disease modifying antirheumatic drug (DMARD) therapy achieved at least a 20% improvement in their disease activity, and 30%–50% achieved a 50% improvement[1-6]. These responses occurred with relatively few serious adverse events. However, although a large majority of patients treated with the doses recommended or studied in the RCT do respond, there are reports from at least 2 cohorts of patients treated with infliximab in general rheumatology practice demonstrating that over 50% of patients required alterations in dose or schedule of this drug to maintain its initial efficacy[7,8].

The reason for these discrepancies between RCT results and actual clinical practice was thus the main topic for discussion. One specific issue is that the subjects recruited to RCT are, by the nature of the recruitment process, different from those who will subsequently be treated with the investigated agents in clinical practice. Specific questions addressed included:

1. Do patients receiving anti-TNF-α therapies in routine clinical practice differ from patients recruited to RCT?
2. Are the outcomes observed in clinical practice different from those expected based on results from RCT?
3. Is there any evidence that these patient differences have an influence on outcome?

Much of the discussion that followed focused on the inclusion and exclusion criteria of the anti-TNF-α trials for RA and how patient differences may affect outcome.

There was a group consensus that patients recruited to RCT do differ substantially from those treated in clinical practice. There was specific focus on the following issues:

1. Socioeconomic status (SES): Subjects recruited to RCT are likely to be of higher SES, which may be associated with a better outcome and may be related to higher compliance or greater expectation of success;
2. Comorbidities: Recruitment of subjects to RCT selectively excludes those with comorbidity, which might have increased their likelihood of adverse events and hence premature stoppage of therapy;
3. Cotherapies.

The strict inclusion and exclusion criteria enforced during RCT also influence the nature of the patients recruited, limiting them to a very select group that differs from the larger population who will eventually receive these drugs. Differences in outcome may therefore stem from the nature of the recruitment process itself.

There was less agreement about whether results from RCT and clinical practice are actually different, although results presented during the SIG did suggest that there is a less favorable response among patients receiving the drugs in clinical practice. For several reasons, including those stated above, a large placebo response may be associated with

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participation in a RCT that could overinflate expectations of eventual efficacy of these drugs in clinical practice. It is important, therefore, to look at the actual outcomes (e.g., swollen joint count, tender joint count, erythrocyte sedimentation rate) among the responders, rather than at composite scores, to better understand how effective these drugs may be.

What is not yet known is which factors will predict response to anti-TNF-α therapies, if any. Current ongoing longitudinal observational studies in clinical practice are including predictors of response in their analysis. However, the RCT offers the best experimental evidence for drug efficacy, and therefore it would be ideal to measure predictors of response in this setting. Possible plans for future research in this area would include access to individual patient data from RCT such that a more detailed analysis of outcome, including predictors, can be performed.

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