

Assessing the Safety of Biologic Therapies in Rheumatoid Arthritis: The Challenges of Study Design

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ABSTRACT. Clinical trials have shown the anti-tumor necrosis factor- α (TNF- α) drugs to be safe and efficacious for the treatment of rheumatoid arthritis (RA). However, since their release for general use, reports have raised concerns about potentially serious complications including tuberculosis, lymphoma, and cardiac failure. It must be remembered that patients with RA are already at increased risk of many of these complications, due both to their underlying inflammatory disease activity and the immunosuppressing effects of many conventional disease modifying antirheumatic drugs. It is unknown whether anti-TNF- α therapies are putting patients at increased risk of adverse events above what might already be expected. Data on the frequency of these adverse events have come predominantly from 3 sources: followup of subjects recruited to clinical trials, spontaneous adverse event reporting to national pharmacovigilance systems, and surveillance of patients treated in routine practice. Each of these study designs plays an important role in assessment of new drugs. However, each also has limitations, which must be considered when interpreting adverse event rates. (J Rheumatol 2005;32 Suppl 72:48-50)

Key Indexing Terms:

BIOLOGICAL THERAPY

ADVERSE EFFECTS

RHEUMATOID ARTHRITIS

Anti-tumor necrosis factor- α (TNF- α) drugs have been shown to be very effective for rheumatoid arthritis (RA), with upwards of 70% of patients in clinical trials (CT) who have failed other disease modifying antirheumatic drug (DMARD) therapy achieving at least a 20% improvement in their disease activity and up to 30%–50% achieving a 50% improvement¹⁻⁴. These drugs were shown to be relatively safe during CT, with a minimal amount of observed side effects. Blockade of this cytokine, however, may have effects beyond the suppression of synovial inflammation. There is concern that such effects might be associated with the development of severe adverse events, including tuberculosis⁵, lymphoma⁶, demyelination⁷, and congestive heart failure⁸.

It must be remembered that patients with RA are already at increased risk of many of these complications, due to both their underlying inflammatory disease activity and the immunosuppressing effects of many conventional DMARD. Mortality rates are increased in RA compared to the general population, with a substantial proportion of this excess explained by cardiovascular disease⁹. The rates of non-Hodgkin's lymphoma and Hodgkin's disease have been shown to be 2–3 times that of the general population¹⁰. Patients with RA have also

been shown to have an increased risk of serious infections¹¹, including tuberculosis (TB)¹². Interpreting rates of adverse events occurring in patients receiving anti-TNF- α therapy must take these baseline risks into account.

SOURCES OF ADVERSE EVENT INFORMATION

Data on the frequency of these adverse events have come predominantly from 3 sources: followup of subjects recruited to CT, spontaneous adverse event reporting (AER) to national pharmacovigilance systems, such as the US Food and Drug Administration Medwatch system¹³, and the surveillance of patients treated in routine practice.

CLINICAL TRIAL DATA

Clinical trials are considered by many to be the gold standard for assessing the efficacy of new therapies. However, study design may be limited in determining the risk of a new drug in routine practice. One specific issue is that the subjects recruited to CT are, by the nature of the recruitment process, different from those who will subsequently be treated with the investigated agents in clinical practice. Therefore, patients who receive new therapies during general use may be at a different risk of adverse events than those in CT.

CT are also limited by their sample size. Although powered to detect a statistically significant difference in efficacy, CT are not usually large enough to detect an increase in rare adverse events, such as TB. With estimated TB rates of 7 cases per 100,000 in the general Canadian population¹⁴, one would have to observe thousands, not hundreds, of patients receiving anti-TNF- α to accurately predict an increased risk. Owing to both financial and time restraints, CT are not equipped to do this.

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Finally, relatively short study durations limit the observation of latent adverse events, particularly malignancy, in CT. Cases of transitional cell carcinoma of the bladder have been observed up to 18 years following therapy with cyclophosphamide¹⁵. It is not known if similar risks will be observed with the anti-TNF- α agents.

SPONTANEOUS ADVERSE EVENT REPORTS

AER are an easy method to assess AE once a drug has been released for general use. Possible new AE, whether related to the drug or not, can be highlighted to the appropriate regulatory authorities and pharmaceutical companies. Although this method of ascertaining AE is potentially useful, it is relatively inefficient for following large groups of patients treated with a new drug and has many limitations.

Under-reporting is a significant issue with AER. The process of the AER relies on the ability of a clinician to recognize a new illness as an AE and report it to the appropriate authorities. There is no governing body that audits this process¹⁶. It is felt that only 1%–5% of all suspected AE are reported¹⁷. However, with increasing reports in the literature of possible associations between a drug and an outcome, AER will rise. It has been noted that the highest rate of AE reporting is at the end of the second year of marketing. There is often a subsequent decline in AER, despite any changes in drug usage¹⁶.

It is difficult to accurately calculate incidence using AER, as the true number of exposed patients is essentially unknown. Finally, without an appropriate comparison group, AER cannot be used to calculate relative risk. Therefore, while having the advantage of covering a wide population and being useful for detecting very rare events, AER can function only to generate signals of potential safety issues.

OBSERVATIONAL COHORT STUDIES

One of the best ways of closely following drug performance in clinical practice is to develop large drug registries. All patients who have been prescribed a new therapy can be systematically followed and rates of adverse events calculated. Although ideal in theory, large drug registries are expensive, time-consuming, and have limitations.

The biggest challenge is to find an appropriate comparison group. Patients with severe chronic RA have been shown to have an increased mortality risk, particularly from malignancy, infections, and cardiovascular disease. These same patients may be more likely to receive new biologic therapies. It becomes difficult to disentangle risk of the new drug from that of the underlying disease in patients who develop serious AE. It is important when calculating risk that the comparison cohort have similar baseline characteristics so that expected event rates can be accurately calculated.

ADDRESSING LIMITATIONS OF STUDY DESIGN Anti-TNF- α therapy and RA

CT still provide the most accurate and scientific evidence for the efficacy of new therapies and play a very important role in the development of new drugs. However, in routine clinical practice, a different safety profile may emerge. Numerous possible explanations have been discussed for this observed discrepancy between the *efficacy* and *effectiveness* of anti-TNF- α drugs in RA. Several countries within Europe (including the UK, Sweden, Germany, and Spain), as well as the US National Databank for Rheumatic Diseases, have established registries that will address these methodological issues. However, it is likely to be some years before robust answers are available on the magnitude of any risk associated with exposure to anti-TNF- α agents.

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