

# Some Concerns about Adverse Event Reporting in Randomized Clinical Trials

Yusuf Yazici, M.D.

## Abstract

*Reporting of adverse events (AEs) in randomized clinical trials (RCTs) is often lacking and with limited application in the real world, as RCTs are of short duration, include small numbers of patients, and are selective for subjects lacking in comorbid conditions. It is not surprising that new and unexpected safety concerns emerge with any new drug after it has been launched and used by many more patients. Part of the problem is inherent to the way safety data are reported in RCTs. This article focuses on some of the shortcomings of AE reporting in RCTs, especially those involving tumor necrosis factor (TNF) inhibitors. Discussion focuses on reporting of "time-to-event" issues, use of standardized incidence ratios for comparison to normal population or disease controls, use of "patient-years" when reporting AEs, and the problem of adequate sample size and power calculations that are lacking in safety outcome data trials.*

Adverse event (AE) profiles of treatments are of great concern to patients and physicians, with some studies suggesting, at times, that perceived risk may be greater than actual risk. Most of the data that leads to a new drug coming on the market are from randomized clinical trials (RCTs). Reporting of AEs in RCTs, especially of new drugs, is frequently incomplete or inadequate.<sup>1</sup> RCTs are efficacy trials by design and are not powered to look at AEs, especially rare AEs. The main platform for assessing AEs is long-term follow-up databases or cohorts. However, safety data from RCTs are frequently used as evidence for a lack

of difference in AE between active treatments and control arms, despite of being an appropriate conclusion. This report focuses on several problems in AE reporting related to the use of the following in RCTs: 1. reporting of time-to-event, 2. use of standardized incidence ratios, 3. use of "patient-years" when reporting AEs, and 4. adequate sample size.

## Time to Adverse Event Reporting

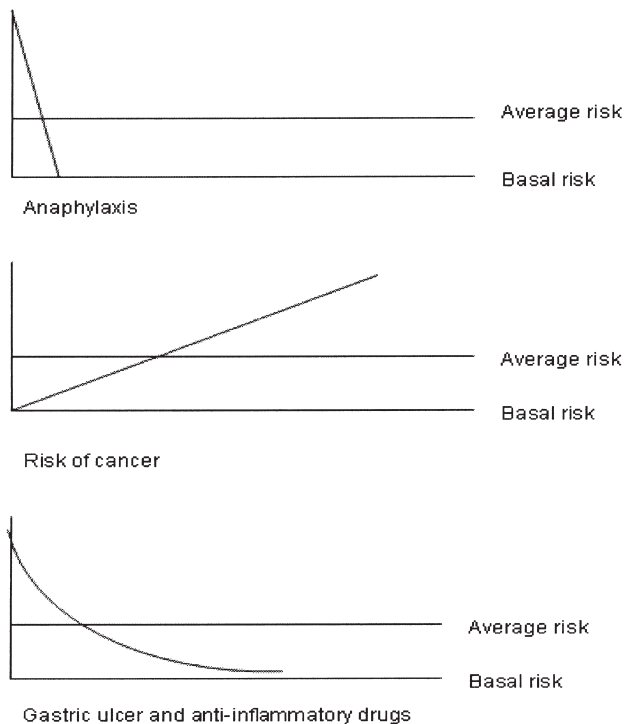
Specificity of when an AE occurs (time-to-event) in an RCT is important to note and report. Time-to-event, as a concept, is closely related to causality and can provide information for the practicing physician when he or she is faced with the next patient starting the medication studied in the RCT in question, as the physician would have a better idea of when an AE might occur in that patient.<sup>1</sup> It is important to remember that cumulative risk, which is commonly reported in RCTs, may be similar between two treatments at the end of study period, but the instantaneous risk might be different for these drugs (Fig. 1).<sup>2</sup>

Average risk does not reflect the true risk faced by patients, especially when decisions are being made at the beginning of a treatment. If risks were reported with the time element included, then the physician would have a clearer understanding of what to expect at each stage of treatment: initiation, follow-up, and possibly chronic use.

We conducted a study looking at AE reporting in TNF (tumor necrosis factor) inhibitor and COX-2 inhibitor RCTs.<sup>1</sup> All RCT trials of TNF and COX-2 inhibitors were reviewed for availability of AE reporting, time-to-event data, and other methods of reporting AEs. There were 70 studies (44 with TNF inhibitors and 26 with COX-2 inhibitors); 91% were industry sponsored. Only one-third of the studies reported time-to-AE data within a table, in the text, or by illustration, using a Kaplan-Meier curve. No better reporting was noted for serious adverse events (SAEs). When SAE details were reported, only selected cases were mentioned, and there was

Yusuf Yazici, M.D., is Assistant Professor of Medicine, New York University School of Medicine, and in the Division of Rheumatology, Department of Medicine, NYU Hospital for Joint Diseases, NYU Medical Center, New York, New York.

Correspondence: Yusuf Yazici, M.D., 246 East 20th Street, New York, New York 10003; yusuf.yazici@nyumc.org.



**Figure 1** Risk of adverse events related to drug exposure. (From: Nies AS. Principles of therapeutics. In: Hardman JG, Limberd LE (eds): *Goodman and Gilman's The Pharmacological Basis of Medical Therapeutics*, (10th ed). New York: McGraw-Hill, 2001, pp. 45-66, with permission.)

no uniform method of discussing the data. This review of TNF and COX-2 RCTs, two frequently used medications in rheumatology, showed that time-to-event information is frequently not reported.

### Standardized Incidence Ratios

In the same review,<sup>1</sup> eight of 17 TNF trials reporting malignancy used the Surveillance, Epidemiology, and End-Results (SEER; National Cancer Institute, Rockville, Maryland) database as the comparison group in the normal population. SEER normal population data assumes an even distribution of events in any given year, and the data is commonly presented as occurring over a 12-month period. Trials may also provide quarterly or any other preferred time period data, but these are rarely used or reported.

When TNF trials report data, time-to-event information is largely ignored and rarely reported. However, if the SEER database is to be used as a comparator, the distribution and timing of AEs need to be evenly spread over any 12-month period. For example, if the expected number of AEs in the population is 12 malignancies in 1 year, the assumption is that one malignancy is seen each month. If 12 malignancies were observed in TNF users and it was reported that “there were no significant differences” among TNF users and SEER database, this should not be immediately interpreted as one malignancy occurred each month in the study. For example, reports of lymphomas in TNF users show that over 60% of

malignancies happen in the first 4 to 6 months.<sup>2</sup> The same has been demonstrated for serious bacterial infections.<sup>3</sup> So, for the sake of this example, if six malignancies occur in the first 3 months and the remaining six occur in the next 9 months, if these data were compared with the quarterly rates of incidence in the SEER database (three per quarter), then the incidence of malignancy with TNF inhibitors would be twice the expected risk. The risk is actually higher than this when RCT data are analyzed.<sup>1</sup>

Knowing the early, increased risk for malignancy or any other SAE is very important for the practicing physician. Decision-making that involves risk versus benefit analysis and treatment decisions would be very different when these SAEs clustered in time rather than when there was an even distribution throughout the year.

In TNF trials,<sup>2,4</sup> most of the malignancies occurred in the first 4 to 6 months, clearly skewing the timing of these SAEs. When this is the case, the SEER database, if it is going to be used, should be used with, minimally, quarterly incidence rates rather than yearly rates.

Another suspect practice is the exclusion of the initial, or up to, 180 days after TNF initiation for analysis of malignancies.<sup>5</sup> The explanation frequently given is that it is not “biologically plausible” to see these early SAEs. When this period is looked at in the control arms, most frequently using methotrexate, no increases in SAEs are seen. The main reason for randomization is to control for these types of unanticipated confounders. Not to include a certain amount of time at the beginning of the study, where increased SAEs can be seen in the active treatment and not in the control treatment, is disingenuous. If the increase was due to a pre-existing condition only coming to light after the treatment is started, and this was unrelated to the TNF inhibitor, then the same rate of events should be seen in the control arms as well; however, this is not the case.

### Patient-Years

Patient-years are a common tool for reporting AEs that occur in RCTs and represent a method utilized to define the time frame of AE incidence. However, there are problems with using this method in reporting AEs that do not happen randomly during a trial and may be clustered at certain time points.<sup>6,7</sup> This is especially true of relatively rare idiosyncratic drug reactions, which typically occur early in a treatment course and in only a few individuals. Apart from those few persons with AEs, remaining patients who are prescribed the drug will never have these reactions, no matter how long they use the drug. This situation leads to unduly inflating the denominator of the related incidence ratio when “patient-years” are used, which then leads to potentially the under representation of AE events. Late onset AEs are also apt to be missed when patient-years are used.

In short, only “...when an event is (or is believed to be) likely to occur at any stage during continuous treatment with a drug, can an event rate with a time component (rate per person-year,

etc.) have a true mean.<sup>7</sup> In addition, it is not clear whether more than one event per patient goes into the numerator. If more than one AE per patient is included in a numerator, statistics performed with that incidence ratio will be erroneous. An AE, such as a skin rash, can repeat itself with TNF inhibitor use in any one patient. This leads to over representation of the said individual in tests of significance. In a survey co-conducted by the author,<sup>1</sup> six articles were found that used patient-years when reporting AEs in TNF trials. In addition, it has been recently reported there is a similar, early increased risk of serious infectious AEs in TNF trials.<sup>5</sup>

### Adequate Sample Size

Another concern with RCTs of TNF inhibitors, in fact, a concern with any RCT, is the adequacy of these trials in providing safety data that can be considered conclusive. RCTs are usually of short duration and of limited, selected patients, typically, with few comorbid conditions. This is understandable for studying efficacy outcomes; however, these conditions decrease the external validity of these trials, especially for safety outcomes. Many RCTs are labeled as efficacy and safety trials; however, due consideration for power is provided only for efficacy outcomes. This, in turn, necessitates a discussion of the inadequacy of sample size (a type II error) for identifying harm. This is particularly important in RCTs of TNF inhibitors, as harm related to these agents is still a matter of debate.

A recent survey<sup>8</sup> searched PubMed (U.S. National Library of Medicine, Rockville, Maryland) for all published RCTs examining TNF inhibitors in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The survey recorded the following for all trials: 1. labeling for efficacy, safety, or both; 2. power calculations that were adequately explained; 3. statistical tests of significance for harm; and, finally, 4. presence of any discussion of type II error for harm. Of the 34 articles surveyed, 24 (71%) were labeled as efficacy and safety studies. Among these, 23 (96%) did not include safety as a formal primary or secondary end point. In only two of 24 articles were power calculations provided.

Finally, in only three of 22 (14%) articles, was there any discussion about the inadequate sample size (type II error) relative to detecting harm. Even for efficacy outcomes, the primary point of the RCT, adequate information about power calculation was only given in about two-thirds of published papers. Most of the reports of RCTs evaluating TNF inhibitors in rheumatologic diseases are inappropriately labeled as addressing efficacy and safety. In addition, their lack of power in detecting harm is not adequately discussed.

Along with these problematic issues is an image that is created that if there are no major signals in an RCT regarding the safety of a new drug, it may be assumed that the drug is safe, hence the use of safety in the title or the abstract. It should be clear that real safety data would only be available in postmarketing reports, when the drug is used by many more patients than were enrolled in RCTs and when a siz-

able number of patients with various comorbid conditions are exposed to the drug. Only then can we achieve a better understanding of what AEs to expect and when, and thereby gain adequate knowledge to take meaningful precautions relative to their occurrence and management.

### Conclusions

RCTs are good tools for establishing efficacy of one drug over another or over a placebo control. However, because of their above-mentioned limitations, RCTs provide only limited safety data. This may seem obvious to many, yet data from these RCTs regarding safety are frequently presented as evidence of lack of harm. The true safety profile of any medication can only be understood after the medication has been on the market and used by large numbers of patients. To better study the safety of new drugs, drug companies and regulatory authorities need to establish mandatory registries to follow all patients started on new medications, ideally, not only for safety but also for efficacy. This is the only way to ascertain a new medication is truly an improvement over already available treatments.

### Disclosure Statement

Yusuf Yazici, M.D., participates in the speakers' bureaus of Pfizer, Inc., and Bristol-Myers Squibb; does consulting for Roche, Celgene Corp., and Bristol-Myers Squibb; and is on the advisory boards of Centocor Corp, Bristol-Myers Squibb, Genentech, and Roche.

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