Commentary

Monitoring Drug Safety in Rheumatoid Arthritis Prevention Trials

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ABSTRACT

This commentary discusses issues particular to drug safety monitoring in prevention trials. Although the general approach to safety assessment applies across all clinical trials, prevention trials pose special challenges given that the patient population is currently asymptomatic or experiencing only mild symptoms of the targeted disease. This sways the risk-benefit analysis balance toward minimal acceptable risk. Definition of the predisease state with validated biomarkers or other assessment tools is essential. The timing and required length of exposure to the disease intervention to produce an effect requires special methodologic considerations. In addition, prevention trials generally have a longer duration with higher dropout rates. As a result, there is an enhanced focus on lessening patient burden in regard to data collection and finding ways to minimize the safety signal to noise ratio to enable product causality assessment. To meet these challenges, clinical safety monitoring in prevention trials involves 3 essential steps: safety planning, systematic data collection and evaluation, and transparent communication of safety information. We discuss some of these issues using historical experience with primary prevention cardiovascular trials and then focus on unique issues surrounding patient populations at risk for rheumatoid arthritis. (*Clin Ther*. 2019;41:1366–1375) © 2019 Published by Elsevier Inc.

Keywords: drug safety monitoring, rheumatoid arthritis, prevention trials, safety information communication.

INTRODUCTION

Clinical trial safety monitoring is at the heart of ethical trial design, and the risk-benefit analysis of an investigational medicinal product (IMP) is fundamental to further treatment development. Ensuring clinical trial safety effectiveness involves three essential steps: safety planning, systematic data collection and evaluation, and communication of the resultant safety information.[1] (see Tables 1 and 2)

The first of these steps is generating a safety plan based on the demographic characteristics of the study population, the underlying disease profile, the pharmacokinetic and toxicologic properties of the IMP, and known or suspected risks related to product class. The objective of the safety plan is to adequately characterize the product's risks through systematic data collection. In addition, patient risk during clinical development is addressed through appropriate protocol participant exclusion criteria, safety monitoring, and toxic effect management. As safety data from ongoing clinical development emerge and are assessed, safety signals may be detected, which require further evaluation. The sponsor needs to then clearly communicate information about identified adverse drug reactions and any proposed risk minimization measures. Risk minimization measures may include modification of protocol-specified exclusion criteria, enhanced safety monitoring, or additional toxic effect management. This holds true for both therapeutic and prevention trials, with the latter involving a relatively healthier

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Table I. Special considerations for prevention trials.

Healthier population:
→ Skews risk-benefit ratio towards minimal acceptable risk

Longer trial duration:
- Added complexity: emerging comorbidities and new concomitant medication use over time
- Increased signal to noise ratio challenging safety and efficacy data interpretations
- Potential bias attributable to higher dropout and drop-in rates

Address through:
Careful selection of study population at (high) risk for developing disease (eg, clear "predisease" biomarkers) to maximize benefit

Table II. Considerations in rheumatoid arthritis prevention trials.

- **Careful selection of study population** with preclinical disease/high risk of developing disease (biomarkers)
- **Special risks:** Study population with preclinical disease may have associated comorbidities; interventions are typically immunomodulatory →address in **study inclusion/exclusion criteria, risk minimization measures and toxicity management**

Cardiovascular events
Infections, including opportunistic infections and tuberculosis
Renal toxic effects
Malignant tumor
Autoimmune diseases

Additional: transaminase elevations, anemia, neutropenia, lymphopenia

Address through:
1) Reduce patient burden for clinical trial participation
2) Carefully consider potential data bias in developing statistical analysis plan
- Cardiac Adjudication Committee
- Data Monitoring Committee

population, low acceptable risk and patient burden, and longer trial duration.

Safety Planning

Planning for safety monitoring occurs during clinical trial development. The safety monitoring plan will evolve over time with the generation of more safety information and as the IMP is evaluated for new indications or in new patient populations. In general, the same safety monitoring principles apply to both therapeutic and preventive trials. A critical consideration is the design of the prevention trial and the timeframe of intervention in relation to disease onset, which typically leads to longer trial duration.[2,3] With prolonged follow-up, product causality assessment for reported adverse events (AEs) (any undesirable medical occurrence in a clinical trial participants) becomes more difficult with increasing changes in concomitant medications, comorbid conditions, and potentially variable intervention adherence.

Consequently, safety planning requires a systematic approach to collecting, assessing, and reporting data from the clinical trial.[1] A key objective of safety planning is the early identification of safety signals. A signal is defined by the Council for International

Organizations of Medical Sciences (CIOMS) as "information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."[4] Evaluation of a signal requires the review of relevant safety data from all sources, including reported AEs and safety assessments from the current clinical trial. Examples of other scientific information that is included in signal assessment are the IMP's mechanism of action and safety profile of the class of drugs, potential to exacerbate events associated with the disease indication, preclinical studies evaluating the IMP's effect on major organ systems in animals, animal studies of the IMP's effect on reproductive function and the fetus, and early clinical trial data.[1] An event that is determined to have a causal association with the IMP is termed an *adverse drug reaction* (ADR).[1] Events determined to be ADRs based on the totality of the available safety data are identified or known risks of the study drug.[1] In addition to known or identified risks, potential risks are those undesirable clinical outcomes for which there is evidence to suspect the possibility of a causal relationship; however insufficient data are available to make a final conclusion about product causality. The available aggregate safety information is used to generate a safety plan geared toward risk minimization of any identified or potential risks during the clinical trial.[4]

With collection and interpretation of accumulating data, the safety plan matures into a risk management plan, which includes an anticipated product profile, overview of the epidemiology of the disease indication, a summary of the nonclinical and clinical experience, known or anticipated risks as well as potential risks, and finally plans for risk mitigation.[1,4] When considering the safety profile of any IMP, safety topics of interest need to be delineated for the product and the intended patient population. These safety topics of interest may be related to known product-class issues or theoretical concerns based on the product's mechanism of action, prior clinical trial safety data, known comorbidities of the patient population, or traditional regulatory concerns (such as drug-induced liver toxic effects).

In addition, the following specific safety issues should always be considered: (1) cardiac electrophysiology (QT prolongation specifically poses a risk of sudden cardiac death and is evaluated in early clinical trials with healthy individuals[5]); (2) potential for hepatotoxicity[6]; (3) immunogenicity (especially relevant with the use of biological agents, which pose potential risk of hypersensitivity reactions or immune complex disease)[7]; (4) bone marrow toxic effects[4]; and (5) drug–drug and food–drug interactions.[4]

When interpreting emerging safety data in rheumatoid arthritis (RA) trials, the epidemiology of RA-associated risks must be considered. The risk of infection in patients with RA is approximately 1.5 times higher compared with the general population.[8] This increased baseline infection rate must be considered when interpreting safety data, particularly because RA treatment is typically immunomodulatory in nature. Steroids are often included during flares in this remitting and relapsing multisystem disease. In addition to an increased risk of infection, long-term steroid use is associated with a number of complications, including elevated blood pressure, edema, osteoporosis, diabetes, cataracts, thinning of skin, and psychological effects. Patients with RA also frequently receive methotrexate, which is a mainstay of early RA treatment. Methotrexate therapy is associated with a number of potential multisystem effects, including gastrointestinal, lung, liver, and hematopoietic system.

Patients with RA also have a higher predisposition for other autoimmune diseases, which may manifest before the onset of RA symptoms.[9] In addition, RA may lead to a moderate increase in some malignant tumors (lymphoma and lung), whereas others (colorectal and breast) may have decreased risk in patients with RA compared with the general population.[10] Another comorbidity in this population is renal dysfunction. A recent study found that nearly 20% of patients with RA had renal dysfunction.[11] Renal dysfunction is a risk factor for cardiovascular disease (CVD). Patients with RA already have increased risk of CVD, including thrombotic events.[12] Compared with the general population, the relative risk of myocardial infarction in the RA population has been estimated at 1.69.[13] In patients with RA, the increased CV risk paradoxically may correlate with lower total and LDL-C levels in patients with

higher disease activity, possibly driven by systemic inflammation.[14] Thus, increased lipid levels with RA treatment may not mean increased cardiovascular risk but correction of the inflammatory state. In trials that include populations that are at risk of RA based on biomarker data, it remains to be determined whether the presence of these biomarkers come with the same associated risks as RA. However, the risk for CVD was increased in the 2 years before RA diagnosis,[15] and some studies have found an independent association between a highly specific RA marker, anticyclic citrullinated peptide antibodies, with cardiovascular risk.[16,17]

In a preventive trial, the targeted patient population must be thoughtfully selected considering the threshold for tolerating a potential safety signal and adding trial-related patient burden in individuals with preclinical disease. Moreover, robust control groups and clear definitions of preclinical disease and appropriate biomarkers will be vital to the design of RA prevention trials and in interpreting safety risks.[3] Given the cardiovascular comorbidity, an RA prevention trial would benefit from a cardiac adjudication committee—a panel of independent experts blinded to treatment assignment who assess and classify potential cardiovascular events using event definitions in a prespecified charter. The need for expert adjudication of other AEs, such as hepatic events or hypersensitivity reactions, should be considered, depending on the potential risks of the product. In some cases, external adjudication committees may provide judgments regarding the role of study drug in the events (such as hepatic events).

Because of the decreased threshold for tolerating risk in a preventive trial, a data monitoring committee (DMC) is essential. The DMC is independent of the study team and generally includes a statistician and clinical trial experts with appropriate specialty training who analyze the safety and efficacy data of an ongoing clinical trial. The purpose of the DMC is to protect the safety of the study participants. A DMC is particularly helpful in large, long multicenter trials with more potential for safety concerns because of greater overall treatment exposures.[4] In addition, the study design might benefit from DMC input, for example, in the context of preplanned interim analyses for early stopping (for futility or for positive efficacy).[18] Although prevention trials may use lower doses of medication associated with fewer AEs, a DMC typically is still advisable. In an RA prevention trial, a DMC would review the accumulating data unblinded to treatment assignment, enabling them to weigh the risk of drug toxic effects against the efficacy of the intervention. The DMC can thus assist in maintaining a favorable benefit–risk profile for study participants and recommend study discontinuation in the case of unacceptable risks or risks that cannot be mitigated.[1,18]

Data Collection and Evaluation

Data collection for a preventive clinical trial follows the general principles that apply to any clinical trial. Safety monitoring relies on accurate, timely acquisition of comprehensive safety information. A standardized approach, including case report forms, is essential for data collection. Individual AEs are evaluated to determine whether they are serious or nonserious based on regulatory and protocol-specified definitions. Events that result in hospitalization, disability or permanent damage, or a congenital anomaly and those that are fatal, life-threatening, or considered important are serious.[1]

Data collection occurs before the intervention as the participant is enrolling in the study. Baseline risk factor documentation is essential in interpreting subsequent product safety data. Additional disease state–specific information and prior medical history should be collected. In addition to cardiovascular events, malignant tumors and infections (discussed above), transaminase elevations, anemia, neutropenia, and lymphopenia have been observed at a higher rate in the patients with RA or those with approved treatments. The approach to collecting laboratory data relevant to these events should be part of safety planning. Principal investigators are expected to characterize the nature of individual AEs based on reports. To enhance the validity of clinical outcome measures, specified clinical end points may be adjudicated. As noted above, an adjudication committee can be used to systemically classify reported events in a blinded manner to enhance data quality and standardization.[1]

Once the safety data have been collected, the data should be qualitatively evaluated and quantitatively assessed using statistical methods. The type of statistical analyses depends on whether the data are collected categorically or continuously. Examples of

categorical data are AEs, concomitant medications, and medical history.[1] Common ways to analyze AE data are risk difference, relative risk, exposure-adjusted event rate, and Kaplan–Meier survival plot.[1] Laboratory assessments and vital sign measurements are typically collected as continuous data and displayed as box plots, line graphs, and scatterplots.[1] In addition to quantitative data, qualitative approaches are vital to signal analysis. Qualitative analysis requires integration of the aggregated participant safety data and previously identified safety concerns based on understanding of the evolving study profile of the drug and disease characteristics.[1]

As noted above, prevention trials are expected to have a longer duration than treatment trials to allow sufficient observation time for intervention efficacy. With longer trial duration, higher dropout and occasionally drop-in rates are expected.[19] Of note, the drop-in rate is the rate associated with the number of participants who received the interventional treatment after initial randomization to the standard-of-care treatment. Dropout rates can only be partially mitigated by reducing patient burden (eg, physician visits, blood tests) in this generally healthier population.[2,19] An imbalance in dropout rates can affect the accumulation of AEs. If the investigational drug is effective in preventing RA, participants in the placebo group may drop out of the study preferentially as they develop the disease or associated symptoms. The earlier dropout in the placebo group compared with the investigational drug group may skew the population that remains for safety analysis. Resulting increased heterogeneity (eg, differences in age, sex, biomarkers, or risk factor) independently may affect AE rates, leading to nonrepresentative results and erroneous safety signals. To determine whether differential dropout or attrition adds bias, identifying the nature of missing data is essential. Data missing at random poses less of a bias risk than data missing not at random (ie, dropout preferentially from one arm because of intervention toxic effects or disease progression), even when dropout rates are similar.[19] These scenarios call for special statistical approaches beyond the scope of this commentary to be considered in the statistical analysis plan, including sensitivity analyses and use of mixed models to reduce bias.[19]

Reporting and Communication of Safety Information

Essential to safety monitoring is the effective reporting and communication of safety information. The unit at the heart of real-time safety reporting is the Individual Case Safety Report (ICSR).[1] To determine the reportability of the ICSR, its validity has to be evaluated, followed by determining the seriousness of the AE, its causal relationship to the IMP, and finally the expectedness of the AE based on the product's current safety reference information.[1] The institutional review board (IRB) is a group that monitors biomedical research with human subjects, and its European equivalent is the Ethics Committee (EC).[1] Unexpected serious events for which the study is judged by the principal investigator or sponsor to have a potential causal relationship are reported to health authorities as per local regulations. The study principal investigator provides an ICSR to the IRB/EC and sponsor within the timeframe outlined in the study protocol. The ICSR includes individual AEs and pertinent clinical details, such as abnormal laboratory values, and must contain 4 elements to be valid: an identifiable patient, an identifiable reporter, an identifiable event, and an identifiable drug.[1] All the AEs in ICSRs are reported by the sponsor as part of the clinical trial and require classification as serious or nonserious,[20] along with a causality assessment, which may be provided by study investigators, the sponsor, or both.[1]

Causality establishes whether an IMP is associated with a particular AE and determines whether it is an ADR. Causality assessment requires well-versed professionals with sharp medical judgment who are able to integrate all available evidence.[21] There are several systematic approaches to aid the identification of ADRs, including the CIOMS working group criteria,[21,22] the Bradford-Hill criteria (a framework of 9 aspects that, despite the evolution of safety science and new statistical methods, have been holding true for >50 years),[23] the Naranjo algorithm (a 10-item point algorithm that divides AEs into definite, possible, probable, or unlikely, which is particularly useful in clinical practice and case reporting),[24] and the World Health Organization Uppsala Monitoring Centre causality assessment (a complex scale that uses elements such as laboratory

parameters and biological plausibility to rank AEs into probable/likely, possible, or unlikely).[25] The CIOMS working group criteria encompass the following[22]: (1) temporal relationship: causality requires that the event happened after the initiation of the IMP and within a reasonable amount of time after discontinuation of IMP, otherwise causality is considered temporally implausible; (2) biological plausibility of IMP association: the mechanism of action of the IMP should be consistent with the possibility of causing the AE, otherwise causality is considered biologically implausible; (3) concomitant medications: does a review of recent or concomitant medications identify a more likely medication associated with the AE? (4) medical history: does the medical history support a different cause of the AE? And (5) dechallenge and rechallenge: dechallenge supports causality if discontinued use of the IMP is associated with resolution of the AE. Although not always feasible, rechallenge can support causality if reintroduction of the IMP leads to reappearance of the AE.[1]

Once causality is determined, expectedness is assessed against the product safety reference information, which is based on previous clinical experience with the IMP establishing an association of the drug with the event.[1,22] These steps help the sponsor decide whether expedited reporting is required for an AE according to the regulatory guidance that stipulates that for a serious, associated, and unexpected event reporting has to occur within 15 calendar days from the date the sponsor received the ICSR and 7 days for unexpected serious or life-threatening associated reactions.[1,26]

In addition to individual safety reports, aggregate periodic safety reports examining cumulative safety data from clinical trials encompass communications to regulatory agencies (through investigator brochure [IB], development safety update report [DSUR], and informed consent [IC]) and to principal investigators and IRB/EC (through the IB, IC, and ad hoc communications).[1] At the end point of a trial, all safety data are reported in the clinical study report and are used with the efficacy data as the basis for the risk-benefit analysis for an IMP. The IC is the document that provides information on the clinical study and study drug, including safety information to potential participants, and as such it is vital that the language in this communication be understandable by most study participants at a basic health literacy level.[1,27] The IC must cover the description of the clinical trial, the risks and discomforts, the potential benefits, alternative procedures or treatments, participant confidentiality, voluntary participation, and compensation/medical treatment in case of medical injury and requires IRB approval.[1,26] The risks and discomforts section is where safety information must be clearly communicated and explain the potential risks from the IMP and any comparator product used based on information from the IB, protocol, and package label.[1] The IB, in turn, encompasses all the information known about the IMP and is provided by the sponsor to the IRB, principal investigators, and regulatory agencies. Information in the IB covers preclinical and clinical information. The preclinical elements are the physical, chemical, and pharmaceutical properties and formulations of the IMP, data from nonclinical studies, nonclinical pharmacologic properties, pharmacokinetic profile and product metabolism in animals, and toxicologic profile.[1] The clinical data provided in the IB cover the IMP effects in humans, including pharmacokinetic properties and product metabolism in humans, safety and efficacy, marketing, as well as guidance for the investigator.[1] In the IB guidance to investigator, risk minimization recommendations on a population level and for individual participants should be clearly communicated, including protocol-specified exclusion criteria, safety monitoring procedures, and toxic effect management. As clinical trials progress, data on human subjects are accumulated, rendering the IB a dynamic document updated at least yearly to make new information available to principal investigators.

The DSUR is an aggregate, systematic, yearly review of AEs from all clinical trials that involve the particular IMP and is provided by the sponsor to the regulatory agency. The date of first clinical trial authorization for an IMP is called the development international birth date with a yearly data lock point placed on that date. The DSUR is reported within 60 days from the data lock point yearly for the duration clinical trials with the IMP and contains aggregate analysis of deaths, discontinuations, serious unexpected associated AEs, preclinical toxicology studies, literature review, safety information from the same class of drugs, noninterventional study data, completed and ongoing clinical trials, overall safety assessment, interim analysis, conclusion, and a summary of important risks.[1]

Perspectives and Discussion

Safety monitoring in prevention trials requires a systematic approach and exigent assessment of all available safety information for the intervention, both preclinical and clinical. Planning is required at every step in the clinical development program. Quantitative and qualitative information from individual AE reporting as well as aggregate review of data using rigorous statistical methods and expert clinical judgment identify important risks of the IMP and are incorporated into the constantly evolving risk-benefit analysis. This, in turn, requires timely and efficient communication of important new safety information to regulatory agencies, IRBs/ECs, principal investigators, and study participants. Prevention trials are unique because of the enrollment of relatively healthy individuals, which skews the risk-benefit ratio toward minimal acceptable risk and calls for minimization of patient burden. The large size and long duration of prevention trials lead to potentially increased dropout rates and poorer trial adherence rates, which may complicate the safety data assessment by introducing bias, requiring thoughtful statistical approaches in data analysis.[2,19]

Two cardiovascular morbidity prevention trials illustrate some of the challenges associated with safety monitoring in prevention trials. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial focused on prevention of CVD in patients with type 2 diabetes and preexisting cardiovascular risk factors. This study recruited 10,251 participants and assessed 3 approaches to reduction of CVD: strict control of glycemia, strict control of lipids, and strict control of blood pressure.[28] This result was a substantive, rigorous, and complex set of data, with essentially negative results. Bias of result to null is common in prevention trials.[2] Most striking were the results of the strict glycemic control portion of the trial, in which 10,251 individuals were assigned to strict glycemic control versus standard therapy.[29] This trial incorporated rigorous safety monitoring given the known risk of potentially life-threatening hypoglycemia as a serious adverse effect of aggressive blood glucose lowering.[30] During the trial, several approaches were taken to prevent initial episodes of severe hypoglycemia, to monitor the frequency and details of individual episodes that occurred, and to use aggregate information for prevention of recurrence.[30] Part of these actions included extensive individual education at all 77 sites, a trial infrastructure that enabled rapid web-based communication among the sites, and several committees tasked with monitoring and analysis of hypoglycemia cases, most notably an independent 10-member data and safety monitoring board (DSMB).[30] This led to a lower rate of hypoglycemia AEs when compared with other major glycemia trials.[30] The DSMB reviewed the interim results approximately every 6 months and were tasked to monitor the primary outcome and deaths from any cause, ensure the safety of patients, and make recommendations to continue or alter the study design. After reviewing mortality trends as part of preplanned safety analysis, the DSMB recommended discontinuation of the intensive treatment because the risk of increased any-cause death rate outweighed any potential benefit.[29] The rigorous safety monitoring in this trial led to premature discontinuation of intensive therapy after a mean of 3.5 years of follow-up attributable to increased mortality in the intervention group.[29]

The importance of involving an independent data monitoring board (IDMB) is also reflected in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a CVD prevention trial in healthy individuals with normal lipid profiles and elevated levels of the inflammation marker high-sensitivity C-reactive protein.[31] In this clinical trial, 17,802 participants were randomly assigned to receive rosuvastatin or placebo. The trial was stopped after a median follow-up of only 1.9 years based on recommendation from the IDMB because of the intervention significantly reducing the incidence of major cardiovascular events.[31] The IDMB consisted of a group of highly experienced clinical and statistical professionals, and despite premature termination of the trial, statistical analysis remained strong and was verified in the subsequent number-needed-to-treat analyses.[32,33] This trial also prospectively tracked possible risks through trial-monitored AEs, laboratory assessments, and other reported evaluations.[31] Another strength was choosing an excellent biomarker for the intervention such that a healthy population able to benefit from the intervention was identified with little risk and high potential efficacy benefit.[31,32]

The identification of appropriate markers of preclinical disease to identify an ideal study population is of significant importance also in RA prevention studies.[3] As can be seen from reanalysis of the initially disappointing Prospective Registry of Multiplex Testing (PROMPT study, in which 110 patients with undifferentiated arthritis and probable RA were treated with methotrexate and monitored radiographically for joint damage and development of RA,[3,34] refinement of a high-risk group revealed efficacy and changed the risk-benefit analysis.[3,35]

In RA prevention trials, the patient population has preclinical disease, is relatively healthy, and is typically younger than patients with symptomatic disease such that drug exposure may be long term and optimal safety monitoring is essential. Moreover, although there are approaches in RA prevention that attempt to avoid immunosuppression,[36] the cornerstone of RA prevention trials remains immunosuppressive therapy (rituximab,[37] abatacept,[38] hydroxychloroquine,[39] and methotrexate[40]), thus increasing infection risk in a relatively healthy population. It is essential, therefore, that the safety plan in RA prevention take into account the demographic characteristics of the study population, the underlying disease profile, and known or suspected risks related to candidate drugs and drug class. The following safety considerations are recommended in the safety plan of an RA prevention trial: cardiovascular events, including thrombotic events; infections, including opportunistic infections and tuberculosis; renal toxicity effects; and malignant tumors. The addition of an independent cardiac adjudication committee should be considered, and the inclusion of an independent DMC is invaluable for patient safety monitoring and providing guidance during the trial.

CONFLICTS OF INTEREST

Drs Neagu, Weinreich, Doan, and Hendrickson are employees of AbbVie Inc. The content in the manuscript reflects the views of the authors.

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