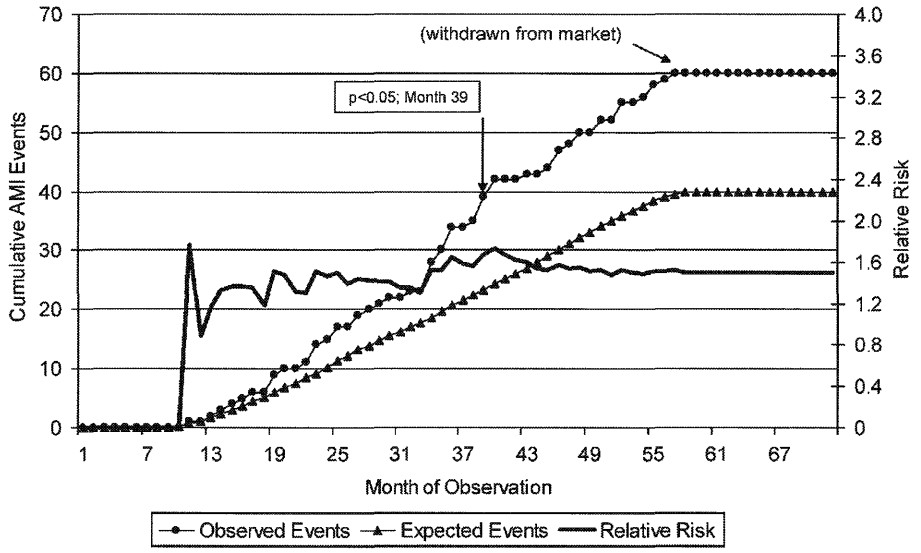

Figure 1. Observed and expected outcomes for rofecoxib users compared to naproxen users: 2000–2005. Outcome: acute myocardial infarction. Adjusted for age, sex and health plan

included in the analyses, thereby influencing the timing of signal detection. For example, shortening the exposure and diagnosis-free interval will include more people in the analyses at the expense of incorporating less of their prior exposure and diagnosis experience.

Signal detection using sequential analysis is closely tied to population size; in general the more people included the faster a signal will be detected or the surveillance will be stopped. For example, all things being equal, doubling the population should halve the time to signal detection. Specification decisions also impact cohort size and those decisions therefore must balance the desire to include as many people in the analyses as possible with the potential for confounding and bias by comparing disparate groups.

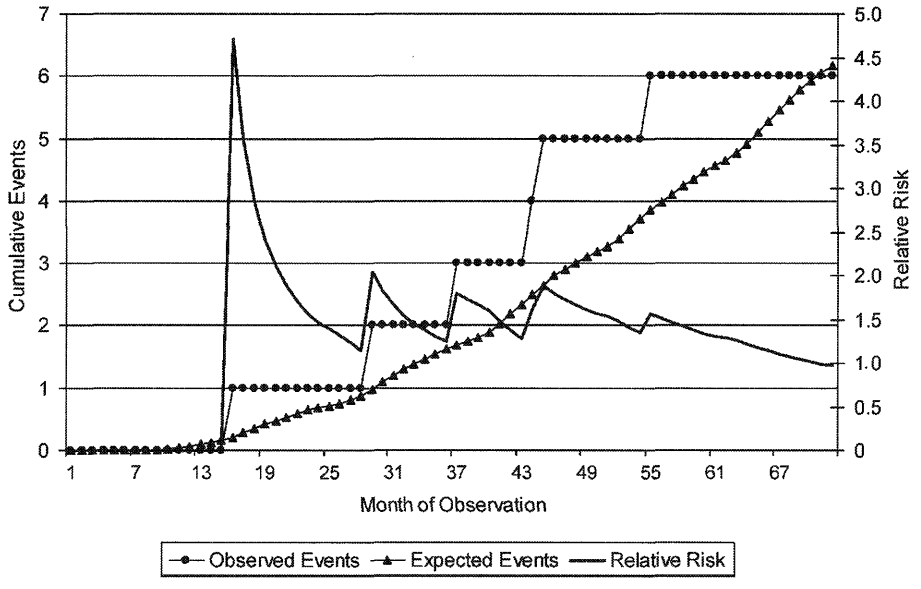

Figure 2. Observed and expected outcomes for cetirizine users compared to non-users: 2000–2005. Outcome: thrombocytopenia. Adjusted for age, sex and health plan

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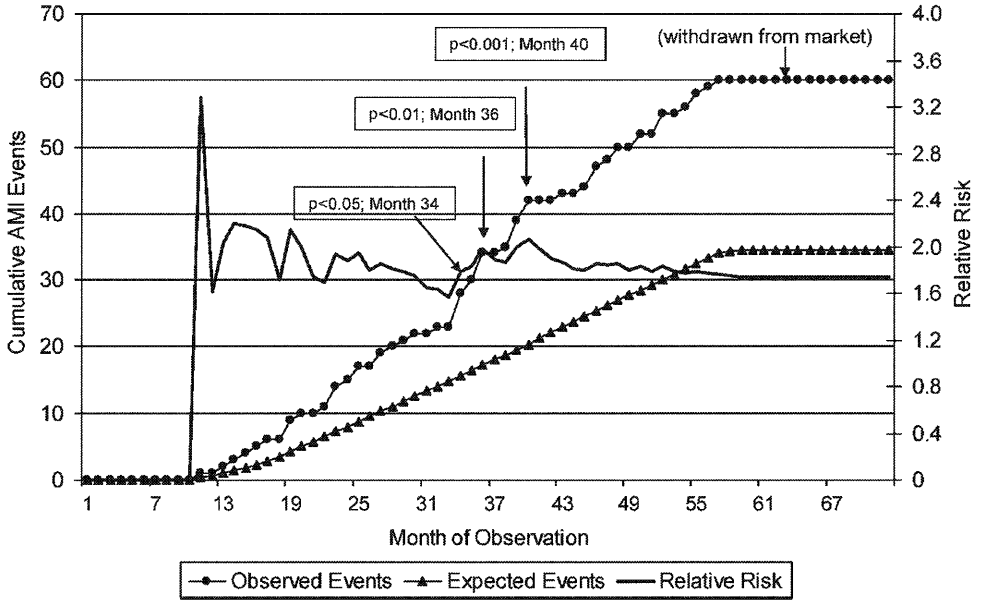

Figure 3. Observed and expected outcomes for rofecoxib users compared to non-users: 2000–2005. Outcome: acute myocardial infarction. Adjusted for age, sex and health plan

Identification of an exposed population

We focused on incident users who had no exposure to the drug of interest or any comparator drugs for the 6 months before the incident dispensing. Our decision to include only incident users was meant to approximate the intended application of the methodology—the prospective monitoring of a newly marketed product. Although excluding prevalent users helped avoid some biases (e.g., survivor bias),[9] it is an open question as to whether prevalent users could also be used for this type of analysis. Our choice of a 6-month exposure-free period is likely conservative and other periods could be reasonable based on drug-specific or other factors. In addition, we did not stratify by dosage; we believe that this level of precision will be important in confirmatory studies but less so in signal detection.

Selection of comparators

We compared the users of each drug of interest to an active comparator cohort of health plan members exposed to a drug or drug class used to treat similar conditions as well as a group that comprises all non-users of the drug of interest. Although we controlled for age, sex and health plan variation, we did not specifically control for treatment selection bias, including confounding by indication, or co-morbidities, incorporating an active comparator was intended to address these issues and should be considered whenever possible. However, the selection of the comparator may introduce other treatment selection biases that must be considered. For this reason, it may be desirable to perform simultaneous evaluation of different comparator groups to help interpret signals. In any event, additional adjustment for confounding is likely to be a useful refinement of this method.

Expected counts of events were generated using a comparison group identified during the same period as users of the drug of interest (i.e., concurrent controls). Prospective application of this methodology may limit the size of a concurrent control group, especially if the control group is based on an infrequently used product. Therefore, it will be important to carefully balance the benefits of a concurrent control group with the benefits of generating stable expected counts using historical exposure and event data. It also may prove desirable to use the self-control case series method for some drugs with brief exposure intervals.[16,17]

Determination and definition of outcomes

Selection of an appropriate outcome is an important aspect of study implementation. Clinically well-defined outcomes are those that can be identified in

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medical claims data with a high level of certainty and little potential for misclassification. To maximize specificity, we selected outcomes that were clinically serious and that required treatment in an inpatient setting.[6] We specified that each ADE was a 'new' event, defined as not having the same event in the 6 months before the incident dispensing. These outcome decisions must be carefully considered to balance the speed of signal detection with the possibility of false signals. For this demonstration work, we did not confirm diagnoses by review of medical records, and there is likely some misclassification because of this. We anticipate that, in practice, it will be necessary to confirm many of the outcomes identified through diagnosis or procedure codes by review of full text medical records or other means.

Eligible person-time

Classification of eligible person-time into exposed and unexposed categories is substantially more complicated for medications than for vaccines.[6] Drug exposure may be continuous or intermittent over long periods, and may include exposure to multiple agents either in sequence or concomitantly. Assigning days as exposed, unexposed or non-contributed for the sequential analyses requires substantial clinical and methodological consideration to balance the inclusion of more patients versus the potential for confounding and bias; additional work is needed to more thoroughly understand these considerations.

Prospective evaluation of accumulating experience of defined cohorts complements the passive safety surveillance because it addresses the main limitations of spontaneous reporting, that is, no denominator. Whereas spontaneous reporting systems often lack information on the exposed population, our system uses a known population with detailed exposure information, thereby allowing calculation of relative risk among various population cohorts. To the extent that the relevant outcomes are reported within claims-based systems, this method avoids the shortfalls associated with both underreporting and reporting bias.

Key benefits of the methodology relate to its use of routinely collected health plan encounter and dispensing data that are commonly used in epidemiological research, minimal data requirements in terms of needed data elements, the ability to simultaneously apply the methodology within numerous data systems and the use of highly summarized data structure for aggregation across systems and analysis. Most public and private health insurers in the U.S. have data that could support sequential analyses. Because only highly summarized data are needed for analysis, concerns over sharing confidential data and patient confidentiality are minimized. Expanding the available population to publicly funded systems like the Veterans Administration, TRICARE, Medicare and Medicaid and to private health insurers would substantially improve the performance of the methodology by increasing the sample size. This would be especially important for monitoring newly marketed products or those that have limited use.

An important study limitation was the limited number of observed events for most comparisons, including the negative controls and the active comparators. Other limitations relate to the relatively complicated set of decisions that need to be made for implementation, pre-specification of the number of expected events to continue surveillance, reliance on the quality and timely availability of the underlying health plan claims data, the need for enough historical or concurrent comparator data to generate stable expected counts and the need for frequent data updates. Additionally, there is limited practical experience with implementation, analysis and reporting of results. Guidelines will be needed to help investigators establish methodological criteria to address issues of exposure, events and setting a minimum number of observations before accepting a signal. Additional methodologic work that will enhance our understanding of the utility and limitations of this method include assessment of the impact of assessing multiple outcomes for each new drug on the likelihood of identifying a signal, reporting confidence intervals for the relative risk, better delineation of sensitivity and specificity through simulation and comparison of maxSPRT to other sequential methods.

The present study supports the use of a more fully developed version of this method for actively monitoring drug safety. Active surveillance is an important complement to passive safety surveillance as it holds

KEY POINTS

- Sequential analysis of near 'real-time' health plan network data may be useful for drug safety surveillance.
- There are a number of methodological issues associated with drug safety surveillance in health plan networks that must be addressed.
- The automated data needed to conduct near real-time drug safety signal detection are routinely collected by health plans.

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