Title:

Post Marketing Safety Registries in Dermatology: how do we identify important safety issues as quickly as possible?

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Abstract

Given that pre-marketing studies are usually relatively short and assess a limited number of patients and comorbidities, post marketing information about drug safety needs to be collected. The ideal safety source would evaluate a large number of patients under ‘real world’ circumstances, be simple and comprehensive, relatively inexpensive and fulfill ethical requirements. Registries, if well-designed, can accomplish most of these requirements and may emerge as one of the most important post-marketing safety sources.

Introduction

Post-marketing safety concerns are not a new issue. Since early 1960s when thalidomide was reported to be associated with teratogenicity, the concept of post-marketing surveillance has been progressively considered more important. Physicians have to face concerns regarding potential drug-related toxicity more frequently with growing number of medications. In dermatology, the introduction of modifiers of biologic response in the treatment of chronic inflammatory cutaneous conditions, such as psoriasis, has brought this question to the forefront. Case reports of Progressive Multifocal Leukoencephalopathy occurring after rituximab therapy and, more recently, efalizumab, some of which were fatal, illustrate the importance of safety studies and surveillance not only in pre-marketing phases of drug development, but also in post-marketing settings. Some of these examples raise the obvious question of how these adverse events could have been missed in thousands of patients in clinical studies performed before drug approval. In terms of investigational studies, randomized clinical trials (RCT) are considered the gold standard study design because of their advantages. However, these very same advantages can become limitations when one tries to extrapolate the results of a RCT with very restricted settings, a small number of participants, a limited profile of co-morbidities, concomitant therapies and age ranges into a more broad general population. Moreover, their length is frequently insufficient to assess long-term safety issues.

Given the importance of conveying new therapies into clinical practice, while assuring patient’s safety, regulators from different nations such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) currently require post-marketing pharmacovigilance activities in addition to pre-marketing clinical trials.

Post-Marketing Safety data sources

Post-marketing surveillance consists of different sources of safety data, including clinical trials, voluntary reports, patients’ databases and registries. Pharmaceutical companies can commit to actively watch for safety issues after drug approval (PMSC) and, in certain situations, these post-marketing studies are required by regulatory agencies, including when there has been a fast approval of the drug or to ascertain safe use in children.

Bognet et al showed that a large proportion of dermatology-related PMSC were pending or delayed, meaning that they were not initiated or were behind the original schedule during the analysis. The authors point that there is strong discouragement for producers to recognize safety problems.

Clinical Trials

Investigator or sponsor-initiated clinical trials performed post-marketing have similar advantages and limitations to the ones performed during the pre-marketing phases. They can be a result of post-marketing study commitment and can be performed as a RCT or a phase IV study. Unfortunately,
head-to-head trials comparing different therapeutic options are infrequent as they are expensive in account of the large sample size necessary for this type of studies. Moreover, the possibility of finding out that a new drug is as or less efficacious than a standard of care typically is not very attractive to pharmaceutical companies.

**Voluntary Reports**

Once a drug has been marketed, newly observed associated events, such as side effects, drug interactions and improvement of other comorbidities can spontaneously be reported to regulatory agencies, pharmaceutical companies and medical community in general. Although this source is cumulative and includes events occurring in ‘real world’ situation, prevalence or incidence of these events cannot be estimated because the number of reports may not represent the total number of events and the total population exposed is typically not known. In addition, inadequate information often impairs evaluation of a definite cause and effect association, especially there concomitant drugs and/or when the adverse effect is unanticipated or delayed. If the event is not remarkably unusual or disastrous or the relation to the drug is not clear, it is unlikely to be spontaneously reported.\(^6\)

**Databases**

Administrative or claims databases are another source of safety information. They can represent an important resource and can help generate hypotheses. However coding issues and incompleteness of clinical data can reduce credibility of safety information based on this source by itself.\(^7\) Another limitation is generalizability in cases where the information has been collected from a particular sample (e.g. inpatients), not reflecting the effect in a more general population that could be potentially exposed and ascertainment bias in medically engaged populations.

**Registries**

A registry is a systematic collection of data, an observational study that evaluates patients presenting with the same characteristic (disease, drug, etc). It aims to assess efficacy and safety of different therapeutic approaches can be compared under a ‘real world’ situation, not only between patients but also in the same patient, due to its longitudinal quality. Ideally, the presence of a large number of patients allows detection of more subtle events. It also allows identification of specific subgroups of patients that could either benefit from or who do not respond to a given therapeutic regimen. Comparison between multiple therapeutic agents and cost-effectiveness analysis are also possible.\(^8\)

Conversely, some limitations are evident. Time constraint can pose a barrier for physicians, especially when data for multiple patients has to be entered. Another weakness is the possibility of confounding by indication where drugs with similar indications are prescribed to groups of patients with different prognosis or risk profiles.\(^9\) For example, patients with psoriasis included in biologics registries are likely to have more severe disease and poorer outcomes than psoriatic patients treated with other treatment modalities. Finally, ethical concerns regarding release of personal information have to be adequately addressed and patients have to be informed which sensitive information will be included and how confidentiality will be provided.

There is a trade off between mandatory and voluntary registries. The quality of data for mandatory registries may not be as good; on the other hand, voluntary registries have better quality data but are more likely to have biases.

**Registries in Dermatology**

In dermatology, with the advent of new biologic therapies, particularly for psoriasis, well-established safety registries are a high priority. Some lessons that should be learned from the rheumatology experience with biologics registries are that all enrolled patients ideally should remain on the registry, regardless of therapeutic maintenance.\(^9\) This is very important in analyzing delayed events. Given that there is no randomization, an appropriate control group can be a challenge. This group can be
internally (comparing patients with similar disease severities but different therapies) or externally selected (matching control from cancer registries, hospital admission records, clinical trial results, etc). Confounding factors have to be accounted for. It is also important that reports containing safety information be generated regularly.

PsONet is an example of psoriasis registry. It was created in order to perform joint analysis of data from different registries in European countries. In some of these countries, the biologics registries are fully developed. The objective of combining data from different registries is to increase power – especially for rare events, such as lymphomas or opportunistic infections and help establishing a routine across different nations. Nevertheless the evaluation of the combined data can overlook some nuances of each individual registry, therefore close attention should be paid to them separately. Financial support for these large population-based registries is provided by collaboration between national academies of dermatology, government and industry.

Although extremely important, the implementation of safety registries has not yet occurred in many countries. In Latin America, we were able to identify one dermatology safety registry. It was developed in Rio de Janeiro- Brazil and includes patients with psoriasis that have been treated with biologic therapy since 2006. This important concept should be incentivized in different nations, contributing to the recognition of safety issues in different populations.

Discussion

Registries are important tools in evaluating short and long-term management of patients with chronic diseases. In order to maximize their task, registries must be established in ‘real world’ settings, allowing for comprehensive information to be acquired as well as practicality. The simpler the data capture procedure is, the more likely healthcare professionals are to contribute consistently. After the practice has been introduced for a given disease or drug, it becomes easier to expand it creating new registries. Delineating benefits and pitfalls in previously created registries is crucial in this process.

Future directions could include the enhancement of automated systems. Data mining, a technique able to capture meaningful information from large problematical databases and to transform that into a signal, could be used to identify patterns and outstanding findings in these datasets. In the era of electronic health records and health information and communication technology, access to complete organized health information would ideally be immediate and easy, facilitating safety assessments. Other important goals are to track enrolled patients that discontinued therapy and follow them as closely as possible and to translate the data and signals acquired with these safety sources into clinical routine with the purpose of improving patient’s care.
References

Conflict of Interest

ABK is on the Steering Committee for the PSOLAR and Obeve-5 registries, funded by Centocor and Amgen, respectively. XTL has no conflicts of interest to declare.