Académie National de Pharmacie de France
Ordem dos Farmacêuticos du Portugal

Les noveaux enjeux de la securité et du risque des medicaments

(New chalenges on drug safety)

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AIBILI

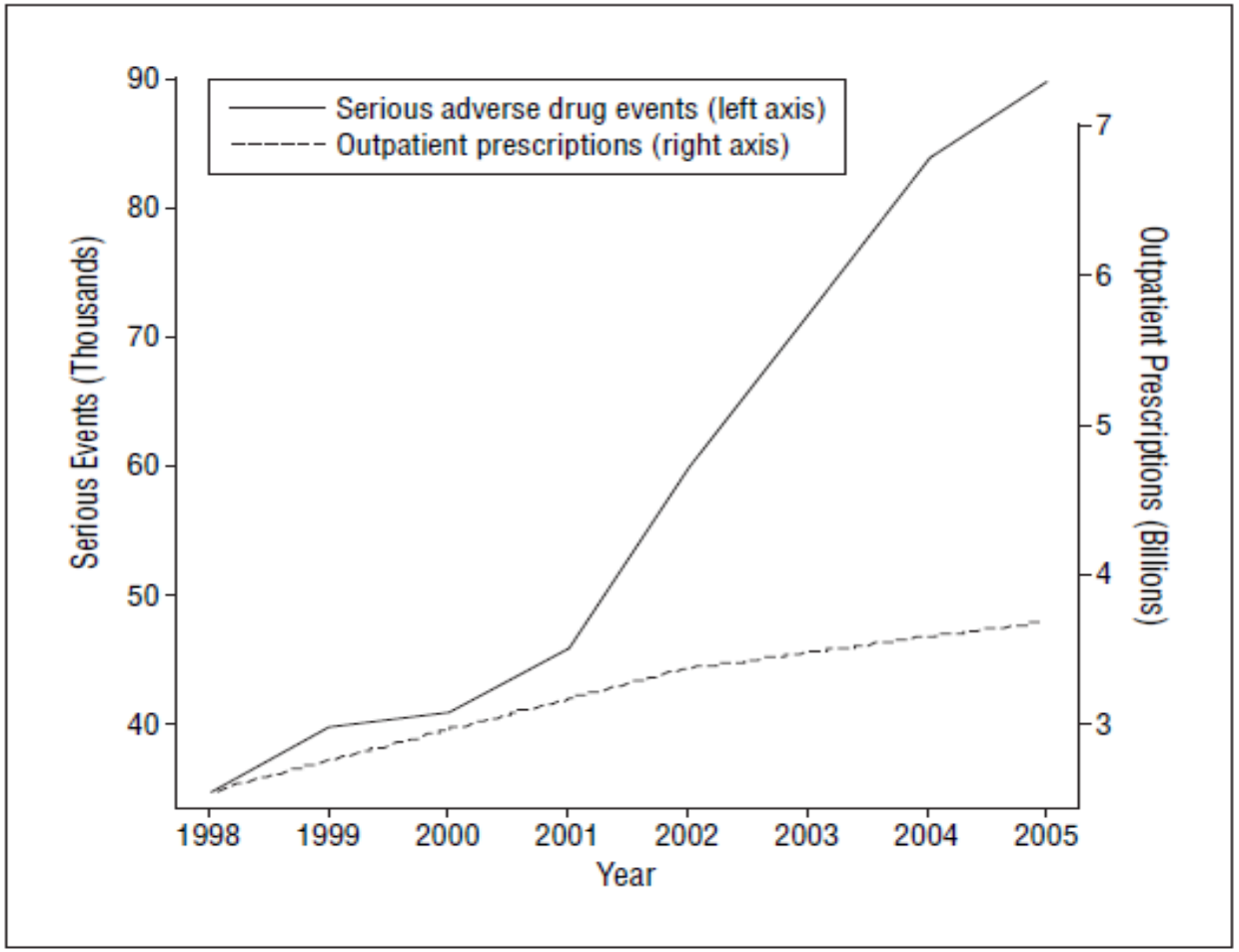

Figure 1. Reported serious events vs outpatient prescriptions, 1998-2005.

Moore TJ et al. *Arch Intern Med* 2007; 167 (16):1752-1759

Summary

- Post-marketing safety evaluation of medicines
- Safety signal generation
- Exposure
- Grading evidence on the safety arm
- Second generation pharmacovigilance
- Genetics/genomics of drug safety

Post-marketing safety evaluation of medicines

- Spontaneous reporting:
  - Clinical monitoring of patients
    - Culture of safety
  - Reporting suspected ADR´s
    - Culture of underreporting
  - Causality assessment
    - Validated methods and quality assessement
      - Global introspection/decisonal algorithms
      - Severity and previous knoweledge

· U C ·

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ORIGINAL REPORT

Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel†

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SUMMARY

Purpose To compare the results of causality assessments of reported adverse drug reactions (ADR's) obtained from decisional algorithms with those obtained from an expert panel using the WHO global introspection method (GI) and to further evaluate the influence of confounding variables on algorithms ability in assessing causality.

Method Two hundred sequentially reported ADR's were included in this study. An independent researcher used algorithms, while an expert panel assessed the same reports using the GI, both aimed at evaluating causality. Reports were divided into three groups according to the presence, absence or lack of information on confounding variables.

Results For the total sample, observed agreements between decisional algorithms compared with GI varied from 21% to 56%, average of 47%. When confounding variables were taken into account, agreements varied between 41% and 69%, average of 58%; 8% and 65%, average of 46% and 15% and 53%, average of 42% accordingly to the absence, lack of information or presence of confounding variables, respectively. The extend of reproducibility beyond chance was low for the total sample (average Kappa = 0.26) and within the groups considered.

Conclusion The overall observed agreement between algorithm and GI was moderate although poorly different from chance, confounding variables being a shortcoming of algorithms ability in assessing causality.

KEY WORDS — pharmacovigilance; adverse drug reaction; causality assessment; algorithm; global introspection

ORIGINAL RESEARCH ARTICLE

Drug Safety 2006; 29 (8): 697-702
0114-5916/06/0008-0697/$39.95/0

Can Decisional Algorithms Replace Global Introspection in the Individual Causality Assessment of Spontaneously Reported ADRs?

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Abstract

Aim: The usefulness of algorithms for assessing the causality of suspected adverse drug reactions (ADRs) has yet to be established and, since the validation of causality algorithms depends upon their sensitivity and specificity, our study was carried out to evaluate these measures.

Method: In this study, an expert panel assessed causality of adverse reports by using the WHO global introspection (GI) method. The same reports were independently assessed using 15 published algorithms. The causality assessment level 'possible' was considered the lower limit for a report to be considered to be drug related. For a given algorithm, sensitivity was determined by the proportion of reports simultaneously classified as drug related by the algorithm and the GI method. Specificity was measured as the proportion of reports simultaneously considered non-drug related. The analysis was performed for the total sample and within serious or unexpected events.

Results: Five hundred adverse reports were studied. Algorithms presented high rates of sensitivity (average of 93%, positive predictive value of 89%) and low rates of specificity (average of 7%, negative predictive value of 31%).

Conclusion: Decisional algorithms are sensitive methods for the detection of ADRs, but they present poor specificity. A reference method was not identified. Algorithms do not replace GI and are not definite alternatives in the individual causality assessment of suspected ADRs.

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Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability

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SUMMARY

Objectives: **To evaluate agreement between causality assessments of reported adverse drug reactions (ADRs) obtained from decisional algorithms, with those obtained from an expert panel using the WHO global introspection method (GI), according to different levels of imputability and to evaluate the influence of confounding variables.**

Method: **Two hundred reports were included in this study. An independent researcher used decisional algorithms, while an expert panel assessed the same ADR reports using the GI, both aimed at evaluating causality. Reports were divided according to the presence, absence or lack of information on confounding variables.**

Results: **The rates of concordance between assessments made using the algorithms and GI according to levels of imputability were: 45% for 'certain', 61% for 'probable', 46% for 'possible' and 17% for drug unrelated terms. When confounding variables were taken into account, the rates of concordance for the 'absence of information', 'lack of information' and 'presence of confounding variables' in the 'certain' group were 49, 69 and 7%, respectively. The corresponding values for the 'probable' group were 80, 68 and 24% and 30, 51 and 51%, respectively for the 'possible' group.**

Conclusion: **Full agreement with global introspection was not found for any level of causality assessment. Confounding variables were found to be associated with low levels of agreement between decision algorithms and the GI method compromising the algorithms' sensitivity and specificity.**

Keywords: **adverse drug reaction, algorithm, causality assessment, global introspection, pharmacovigilance**

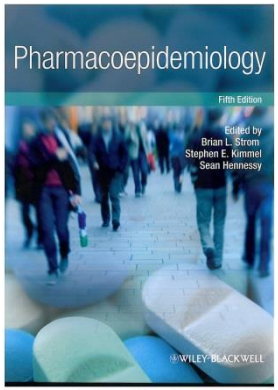
INTRODUCTION

Causality assessment of reported adverse drug reactions (ADRs) is an important component of pharmacovigilance, particularly for regulatory purposes, as they contribute to making better evaluations of the risk-benefit profiles of medicines.

The 'Núcleo de Farmacovigilância do Centro', NFC – the central Portugal regional pharmacovigilance unit – started the collection of ADR reports from family physicians and community pharmacists in January 2001. Its regulatory responsibilities mandate the causality assessment of reported ADRs. As a component of the adopted standard operating procedures of the Portuguese pharmacovigilance system, the global introspection (GI) based on the World Health Organization scale of imputability (1) is used despite criticisms that the method is subjective and imprecise as it is mainly based on expert clinical judgements (2, 3).

Several decisional algorithms have been published with the claim that the scoring systems proposed are more explicit and therefore less susceptible to bias (2–4). However, none of the algo-

Causality



types will be described, chosen as illustrative examples and because they have been widely described in various publications. Agbabiaka and colleagues in a 2008 review concluded that "there is still no method universally accepted for causality assessment of ADRs."[61]

Unstructured clinical judgment/global introspection

Probably the most common approach to causality assessment is unstructured clinical judgment. An expert is asked to review the clinical information available and to make a judgment as to the likelihood that the adverse event resulted from drug exposure. However, it has been amply demonstrated that global introspection does not work well, for several reasons.[9]

First, cognitive psychologists have shown that the ability of the human brain to make unaided assessments of uncertainty in complicated situations is poor, especially when assessing the probability of a cause given an effect, precisely the task of causality assessment.[62] This has been clearly demonstrated for the evaluation of suspected adverse reactions. Several studies have used pharmacologists to review sus- Comparing their individual evalu- udies documented the extent of nt and illustrated, thereby, how l introspection is as a causality od.[17,18,19,63,64]

al introspection is uncalibrated. "possible" might mean the same r assessor's "probable." This has strated in a study of one pharma- y's spontaneous report reviewers, a verbal and numerical scale.[22] shortcomings of global introspec- y assessment method for adverse ussed in detail by Lane, Hutchinson, ers.[9,27,64–68] Despite these concerns, tion for evaluation of adverse s to be used. Most notably, the WHO Centre for Drug Monitoring, which collects the spontaneous reports from national centers worldwide, has published causality criteria ranging from "certain" to "unassessible/unclassifiable" that essentially represent six levels of global introspection, though they generally incorporate consideration of the more standard criteria for causality.[69] The Portuguese central pharmacovigilance unit (Nucleo de Farmacovigilancia do Centro) utilizes this WHO global introspection method, in part based upon a comparison of results from evaluation of 200 cases by algorithm methods and the WHO global introspection method. They found a relatively moderate to high degree of correspondence of judgments for the reactions more likely associated.[70]

teria for causality.[69] The Portuguese central pharmacovigilance unit (Nucleo de Farmacovigilancia do Centro) utilizes this WHO global introspection method, in part based upon a comparison of results from evaluation of 200 cases by algorithm methods and the WHO global introspection method. They found a relatively moderate to high degree of correspondence of judgments for the reactions more likely associated.[70]

Algorithm/criterial method with verbal judgments

The subsequent attempts to address the limitations of global introspection have resulted in the proliferation of methodologic approaches (see Venulet *et al.*[22] and Herman[23] for reviews and examples of these methods and the appendix in Herman[23] which includes a complete bibliography; also see summaries in Herman and Fourrier[71] and Agbabiaka *et al.*[72]). These methods range from simple flow charts posing ten or fewer questions to lengthy questionnaires containing up to 84 items. However, they share a common basic structure essentially based on the original work by Karch and Lasagna[12] and Irey[10,11]—the timing of the adverse event in relation to administration of the drug, alternative etiological candidates, previous recognition of the event as a possible adverse reaction to the drug, the response when the drug is discontinued (dechallenge), and the response when the drug is subsequently re-administered (re-challenge). Information relevant to each factor is elicited by a series of questions, the answers to which are restricted to "yes/no" (and, for some methods, "don't know").

These approaches have advantages when compared to global introspection,[64] since there is a great improvement in the consistency of ratings among reviewers. Because the consideration of each case is segmented into its components (e.g., timing, confounding diseases, etc.), this also allows for a better understanding of areas of disagreement. However, there is still considerable global introspection required to make judgments on the separate

Post-marketing safety evaluation of medicines

- Spontaneous reporting
  - Added dificulties for pharmacists ?

    - Community pharmacy
      - Lack of access to relevant information (clinical and lab)
    - Hospital pharmacy
      - Low performance on safety monitoring

Outcomes From the First 6 Years of Operation of the Central Portugal Pharmacovigilance Unit

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Diogo Mendes, PharmD, MSc,† and Carlos Alves, PharmD, PhD*†*

Objectives: The aim of this study was to analyze and characterize the outcomes of the Central Portugal Regional Pharmacovigilance Unit over a 6-year period.

Methods: Spontaneous reports received between January 2009 and December 2014 were considered. The annual reporting ratios were estimated. The cases were characterized according to their seriousness, previous description, causality assessment, reporting professional, pharmacotherapeutic groups of the suspected drugs, and type of adverse drug reactions most frequently reported.

Results: The Pharmacovigilance Unit received 1277 reports that contained 3222 adverse events. In 2014, the reporting rate was estimated at 124 reports per million inhabitants. Sixty-five percent of the reports were assessed as serious. Seventy-three percent of the cases were assessed as being at least possibly related with the suspected drug. Physicians reported 49% of the cases. The suspected drugs most frequently reported were "anti-infectives for systemic use" (n = 494, 38%). The most frequently reported adverse events were "general disorders and administration site conditions" (n = 667, 21%).

Conclusions: Despite the continuous efforts carried out by the Central Portugal Regional Pharmacovigilance Unit in promoting spontaneous reports of suspected adverse drug reactions, the results, although representing a contribution to the postmarketing safety monitoring of drugs, are still modest illustrating the need to promote the adherence of health-care professionals to the pharmacovigilance system and to increase their reporting rates of suspected ADRs.

Key Words: spontaneous reports, safety outcomes, pharmacovigilance, adverse drug reactions

(*J Patient Saf* 2016;00: 00–00)

Frequent and well-recognized ADRs are potentially observed in randomized controlled studies. However, rare and long-term latency reactions are detected with difficulty in such studies because of their structural limitations. Therefore, most evidence on harm is obtained from postmarketing surveillance.[8,9] Spontaneous reporting is a valuable method to identify rare and serious ADRs with an acute onset and occurring with a close temporal relationship between the start of the treatment or after a dosage increment.[8,9] Spontaneous reporting systems operate with a relatively low cost, allowing monitoring all drugs in market during their entire life cycles and covering the whole patient population.[10] The less likelihood of reporting ADRs with long-latency period or the lack of data in the reporting schemes are, nevertheless, some of the limitations of this method that should be noted.[11]

The main source of postmarketing information on drug safety to national pharmacovigilance systems are spontaneous reports of suspected ADRs.[10] Although multiple sources of evidence support regulatory decisions' undertaken by authorities, spontaneous reports ADRs have supported most of the drugs' withdrawal and label changes to date.[11–14] However, the underreporting of ADRs, which can be as high as 90%, may delay the identification of important safety issues.[15]

The Portuguese pharmacovigilance system began its activity in 1992, as a central structure. Regional pharmacovigilance units covering the Portuguese Health Administration System (Northern, Central, Lisbon area, and Southern) have been established in 2000, allowing the approximation to the health-care professionals.[16]

The update of new information and knowledge on drug's safety profile generated within the Central Portugal Regional Pharmacovigilance Unit activity to provide the reporters with the

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Safety Monitoring of Ophthalmic Biologics: A Systematic Review of Pre- and Postmarketing Safety Data

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Abstract

Purpose: The present study evaluates the safety of the biologics approved for the treatment of ocular diseases.
Methods: The European medicines agency Website was searched to identify biologics with approved ophthalmologic therapeutic indications. A systematic search was performed using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the International Clinical Trials Registry Platform up to December 2013. Pre-marketing, phase III randomized controlled trials (RCT), postmarketing clinical trials, observational longitudinal studies, and case reports involving adverse events (AE) were included. Methodological quality was assessed by Downs & Black checklist. All European spontaneous reports of AE included in the Eudravigilance up to December 2013 were also considered. AE were classified as ocular (related and non-related with the injection procedure) and non-ocular (related or non-related with vascular endothelial growth factor inhibition). Incidences of all reported AEs were estimated.
Results: Pegaptanib, ranibizumab, and aflibercept were identified as ophthalmic biologics. Fourteen premarketing RCT, 7 postmarketing clinical trials, 31 observational studies, along with 31 case reports and 7,720 spontaneous reports were identified and included in this study. Both in pre- and postmarketing settings, ocular AEs were more frequent than non-ocular AEs. Premarketing safety data inform the most common AEs. Postmarketing studies suggest an increased number of events such as retinal pigmented epithelium tears (0.6%–24%), thromboembolic events (0.8%–5%), and mortality (2.8%–4%).
Conclusions: This study highlights the need to properly evaluate the risk for rare, serious, and long-term AEs, such as thromboembolic events, since they can lead to imbalances in the benefit-risk ratio of biologics in ophthalmology.

Safety signal generation

- Explicit and objective methologies
  - Disproportion analysis
  - Combining disproportion analysis with exposure
    - The role of databases
      - Pharmacovigilance databases
      - DRG databases
      - Other administrative databases

The Role of Disproportionality Analysis of Pharmacovigilance Databases in Safety Regulatory Actions: a Systematic Review

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Abstract: *Introduction*: Disproportionality analysis (DA) of adverse drug reactions spontaneous reporting (SR) databases is used to identify signals of disproportionate reporting (SDR). The objective of this study was to identify the generation of SDR in the published literature and whether it led to regulatory action.

Methods: A systematic literature search in MEDLINE and Cochrane Central Register for Controlled Trials (CENTRAL) in a 10-year period, from 2005 to 2014, was conducted, to identify studies designed to detect drug safety signals through the use of disproportionality measures applied to spontaneous reporting databases of adverse drug reactions.

Results: Seventy three studies were included. The number of publications has been rising over the study time period. Forty nine studies focus on drug-event combinations. Large international and smaller national or regional databases were identified. The disproportionality measures applied included frequentist and Bayesian methods and some studies used more than one method. SDRs were identified in more than ninety percent of the studies. Ten studies were found to be confirmatory of previous regulatory decision.

Conclusion: It was not found any safety signal issued by drug regulatory agencies exclusively generated by DA. More research devoted to this issue is needed, since the value of these methods on drug safety signaling and their impact on drug regulation actions remains to be established.

Keywords: Adverse drug reactions, disproportionality analysis, safety signal generation, spontaneous reports, systematic review, regulatory actions.

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Safety profiles of adalimumab, etanercept and infliximab: a pharmacovigilance study using a measure of disproportionality in a database of spontaneously reported adverse events

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Keywords: **adverse events, biologics, pharmacovigilance, reporting odds ratio, rheumatoid arthritis, spontaneous reporting**

SUMMARY

What is known and objective: **Despite being effective, the biologics approved for treating rheumatoid arthritis have been associated with serious adverse events. This study is aimed at comparing the safety profiles of adalimumab, etanercept and infliximab by analysing the disproportionalities of the associations between the different adverse events and the different biologics in the Portuguese spontaneous reporting database.**

Methods: **Adverse events spontaneously reported to the Portuguese pharmacovigilance system (PPS) between 2009 and 2011 were included. Adverse events were classified according to MedDRA® in the primary system organ class. The reporting odds ratio (ROR) and its 95% confidence intervals (CI) were calculated for each biologic regarding the various categories of adverse events. Microsoft Excel® was used to perform all the calculations.**

Results and discussion: **The PPS received 12167 adverse events reported for all drugs, of which 741 were reported for biologics: 157 for adalimumab, 132 for etanercept and 452 for infliximab. Compared with the all other drugs, adalimumab, etanercept and infliximab were all disproportionately associated with 'infections and infestations' (ROR: 6·65, 95% CI: 4·50–9·83; ROR: 2·74, 95% CI: 1·56–4·81; ROR: 2·95, CI 95%: 2·16–4·02, respectively) and with 'neoplasms benign, malignant and unspecified' (ROR: 7·23, 95% CI: 3·92–13·33; ROR: 6·26, 95% IC: 3·12–12·57; ROR: 3·94, 95% CI: 2·41–6·44, respectively), etanercept with 'general disorders and administration site conditions' (ROR: 2·08, 95% CI: 1·44–3·02) and infliximab with 'immune system disorders' (ROR: 5·17, 95% CI: 3·50–7·64), 'respiratory, thoracic and mediastinal disorders' (ROR: 1·80, 95% CI: 1·31–2·48) and 'investigations' (ROR: 1·82, 95% CI: 1·19–2·78). When interpreting the results one should take into consideration the number of patients exposed and should not only rely on the number of adverse events reported.**

What is new and conclusion: **Although the disproportionalities found for adalimumab and etanercept may suggest strong associations with particular adverse events, caution is needed when drawing conclusions on the association between infliximab and the adverse events analysed. In the light of the present findings, these results deserve further evaluation.**

WHAT IS KNOWN AND OBJECTIVE

The approval of several biologics and their use in clinical practice in the past few years has considerably improved the treatment of rheumatoid arthritis (RA) and other inflammatory conditions. Despite being effective, biologics have been associated with serious safety problems.[1] The evaluation of their safety profile is influenced by specific characteristics, including a high potential for immunogenicity.[2–4] Further, the predictability of preclinical to clinical data is limited for biologics.[4,5] Although there is relatively good concordance with animal models used for the premarketing safety evaluation of small molecules, in biologics such animal models may have more limitations with regard to human relevance. Because biologics are highly targeted molecules, differences in physiological processes or biologic pathways may limit pharmacologic relevance.[6] In addition, each biologic has a particular safety profile which is characterized by different types of adverse events. As an example, a network meta-analysis of randomized controlled trials of biologics for RA found that adalimumab and infliximab were more likely than etanercept to result in withdrawals related to adverse events.[7] The results of other meta-analysis, which included randomized controlled trials of biologics vs. placebo, revealed an increased likelihood of an injection or infusion reaction with infliximab, etanercept or golimumab, whereas adalimumab and certolizumab did not statistically significantly differ from the controls in this respect.[8]

Due to their narrow benefit/risk ratios, biologics are used under close supervision of healthcare professionals, who may contribute to increase drug safety knowledge by undertaking the responsibility of spontaneously reporting adverse events. This widely used method of pharmacovigilance is valuable for identifying relatively rare events and providing signals about potentially serious safety problems.[9] Indeed, most benefit/risk ratio re-evaluations of drugs have been supported by post-marketing spontaneous reports of adverse events, thereby confirming the value of such data source.[10]

Spontaneous reporting systems generate large pharmacovigilance databases, which analysis for detecting signals purposes is more efficient using quantitative methods which measure disproportionality.[11] Signals detected by measuring disproportionality of

Exposure

- Methods to assess exposure
  - Indirect methods for its calculation from market data
  - PSUR's
  - Controled exposition (experimental)
  - Measure exposition (observational)

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Clin Rheumatol (2013) 32:1207–1214
DOI 10.1007/s10067-013-2256-9

ORIGINAL ARTICLE

Safety of biologics approved for treating rheumatoid arthritis: analysis of spontaneous reports of adverse events

Diogo Mendes · Carlos Alves · Francisco Batel Marques

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Abstract Despite the effectiveness of biologics approved for the treatment of rheumatoid arthritis, they have been associated with serious adverse events (AEs). Biologics are used under close supervision of health care professionals. In Portugal, they are legally required to report AEs occurring during the treatment. This study aims at investigating post-marketing safety monitoring data of biologics in Portugal by comparing the frequency of spontaneously reported adverse events between 2009 and 2011 with the frequency of such events in the summary of the product characteristics of each biologic. Sales data for biologics were obtained from IMS Health and converted into defined daily doses/1,000 inhabitants/day in order to estimate a proportion of the population treated. The frequency of AEs was estimated as the percentage of patients in which an AE may have occurred. The use of each biologic was estimated for adalimumab at 1,439 patients/year, etanercept 1,944 patients/year, and infliximab 3,211 patients/year. A total of 992 AEs were reported: 207 for adalimumab, 199 for etanercept, and 586 for infliximab. Of the 515 different spontaneously reported AEs, 194 were included for comparisons with the SPCs. Of those, 31 (16 %) were similarly frequent, and 163 (84.0 %) occurred less frequently compared with SPCs' data. These results suggest an insufficient post-marketing safety monitoring of biologics in Portugal.

Keywords Adverse events · Biologics · Pharmacovigilance · Rheumatoid arthritis · Spontaneous reporting

Introduction

Many biologics have been introduced to treat rheumatoid arthritis (RA) in recent years. Those drugs target specific components of the immune system that are involved in the pathologic inflammation cascade [1], such as tumor necrosis factor (TNF) alpha, T cells, B cells, and interleukins [2].

Despite the effectiveness of biologics in treating RA,

Evidence levels

Oxford Centre for Evidence-Based Medicine

Level	Type and study quality
1A	SR/Meta-analysis of RCTs
1B	Indiviual RCT with small IC-95%
2A	SR of coorte studies
2B	Individual coorte study
	Low quality individual RCT
2C	*Outcomes research*
	Ecologic studies
3A	SR of case-control studies
3B	Individual case-controls
4	Série de casos
	Low quality coorte studies
5	Expert opinion

Grading evidence on the safety arm

- Nature of the available evidence, mostly lacking of experimental designs
- Observational data, risk of bias, confounding and heterogeneity of studies
- Cases and case-series (from spontaneous reports and case reports) as a main source of information supporting safety signals generation

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Sources of information used by regulatory agencies on the generation of drug safety alerts

Carlos Alves · Ana Filipa Macedo · Francisco Batel Marques

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Abstract

Purpose The study of the grounds on which data regulatory authorities base their decisions on drug safety evaluations is an important clinical and public health issue. The aim of this study was to review the type and publication status of data sources supporting benefit/risk ratio re-evaluations conducted by the major regulatory authorities on safety issues.

Methods A website search was carried out to identify all safety alerts published by the U.S Food and Drugs Administration, Health Canada, European Medicines Agency and the Australian Therapeutics Goods Administration. Safety alerts were included if the causal relation between a suspected drug exposure and the occurrence of an adverse event was evaluated for the first time between 2010 and 2012. Type of data sources evaluated by these regulatory authorities, publication status of the data sources and status of the drug label section with respect to updating were evaluated.

Results A total of 59 safety alerts were included in this study. Of these, 33 (56%) were supported by post-marketing spontaneous reports, 24 (41%) evaluated randomized clinical trials, 16 evaluated cohort studies (27%), 13 were case–control studies (22%) and 11 evaluated case report/case series (17%). Twenty-three safety alerts (39%) were issued based. on unpublished evidence, corresponding mainly to post-marketing spontaneous reports. The "Warnings and precautions section" was the drug label section most frequently updated (n=40; 68%).

Conclusion Despite the different lengths of time taken by the different regulatory authorities to come to similar decisions on the same issues—an issue which would seem to deserve further harmonization—post-marketing spontaneous reports have supported most of the benefit/risk ratio re-evaluations, thereby confirming the value of such re-evaluations in detecting unknown adverse events.

Keywords Safety alerts · Data sources · Regulatory agencies · Benefit/risk ratio re-evaluations

Electronic supplementary material The online version of this article (doi:10.1007/s00228-013-1564-y) contains supplementary material, which is available to authorized users.

Grading evidence on the safety arm

- Quantitative metrics:
  - Meta-analysis and
  - Cumulative meta-analysis

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Published online 25 October 2011 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2260

ORIGINAL REPORT

Data sources on drug safety evaluation: a review of recent published meta-analyses

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ABSTRACT

Purpose Meta-analysis is a quantitative approach to summarize the findings from several studies and has been applied with increasing frequency to clinical trials. Because of their sample size and duration limitations, experimental studies (ESs) could not be able to detect late or rare adverse events (AEs), which may be identified in well-designed observational studies (OSs). This study aims to identify and analyze meta-analyses from both ES and OS where safety was found to be an outcome measure.

Methods The meta-analyses inclusion criteria was established as at least one AE as primary outcome. Safety outcomes were considered as the increase in the risk for an AE after a pharmacological intervention. A MEDLINE search for meta-analyses published in the *New England Journal of Medicine*, *The Lancet*, *Journal of American Medical Association*, *British Medical Journal*, *Annals of Internal Medicine*, *PLoS Medicine*, *Annual Review of Medicine*, and *Archives of Internal Medicine*, between October 2005 and September 2010, was carried out.

Results Sixty meta-analyses met the inclusion criteria. Of these, 53 included only ES, 4 included both ES and OS, and 2 included only OS. Of the 6 meta-analyses that included OS, 4 included cohort and case–control studies, and 2 included cohort, case–control, and cross-sectional studies. One meta-analysis did not report the type of studies included.

Conclusions Experimental studies were found to be the main source of meta-analyses on drug safety. The role of meta-analyses in pharmacovigilance is a matter of ongoing debate, and efforts are being made to develop guidelines on the use of meta-analysis in drug safety assessments, to better combine evidence about harms.

KEY WORDS—meta-analysis; pharmacovigilance; adverse events; experimental studies; observational studies

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Apixaban and Rivaroxaban Safety After Hip and Knee Arthroplasty: A Meta-Analysis

Carlos Alves, PharmD[1,2,3], Francisco Batel-Marques, PharmD, PhD[1,2], and Ana Filipa Macedo, PharmD, PhD[1,3]

Abstract

Direct experimental safety comparisons of Xa coagulation factor direct inhibitors, apixaban and rivaroxaban, on their approved therapeutic indications have not been identified. Due to recently raised safety concerns, a meta-analysis was carried out pooling data from studies identified on a Medline and Cochrane Library search in order to better evaluate the safety profile of both drugs. Abstracts from scientific meetings were also searched from 2003 to 2011. Primary and secondary outcome measures were major bleeding and total bleeding, respectively. Relative risks (RRs) were estimated using random effects models and statistical heterogeneity was estimated with I^2 statistics. Of the 160 screened publications, 12 clinical trials were included in which enoxaparin was the active control. For knee arthroplasty, apixaban was associated with significantly fewer major bleeding events (6496 patients, RR 0.56, 95% confidence interval [CI] 0.32-0.96) and fewer total bleeding events (6496 patients, RR 0.81, 95% CI 0.67-0.97). There were no significant differences in the incidence of major bleeding events (5699 patients, RR 1.40, 95% CI 0.56-3.52) or in the incidence of total bleeding events for rivaroxaban (5699 patients, RR 1.09, 95% CI 0.91-1.30). No differences were found when thromboprophylaxis after hip replacement was the case. Apixaban seems to be associated with a lower risk of the incidence of hemorrhagic events after total knee arthroplasty. For hip arthroplasty, no differences were found between the studied drugs.

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A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer

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ABSTRACT

Aims: The association between GLP-1 agonists, acute pancreatitis (AP), any cancer and thyroid cancer is discussed. This meta-analysis was aimed at evaluating the risk of those serious adverse events associated with GLP-1 agonists in patients with type 2 diabetes.
Methods: Medline, EMBASE, Cochrane Library and clinicaltrials.gov were searched in order to identify longitudinal studies evaluating exenatide or liraglutide use and reporting data on AP or cancer. Odds ratios (ORs) were pooled using a random-effects model. I^2 statistics assessed heterogeneity.
Results: Twenty-five studies were included. Neither exenatide (OR 0.84 [95% CI 0.58–1.22], $I^2 = 30\%$) nor liraglutide (OR 0.97 [95% CI 0.21–4.39], $I^2 = 0\%$) were associated with an increased risk of AP, independent of baseline comparator. The pooled OR for cancer associated with exenatide was 0.86 (95% CI 0.29, 2.60, $I^2 = 0\%$) and for liraglutide was 1.35 (95% CI 0.70, 2.59, $I^2 = 0\%$). Liraglutide was not associated with an increased risk for thyroid cancer (OR 1.54 [95% CI 0.40–6.02], $I^2 = 0\%$). For exenatide, no thyroid malignancies were reported.
Conclusions: Current available published evidence is insufficient to support an increased risk of AP or cancer associated with GLP-1 agonists. These rare and long-term adverse events deserve properly monitoring in future studies evaluating GLP-1 agonists.

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug-safety alerts issued by regulatory authorities: usefulness of meta-analysis in predicting risks earlier

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Abstract
Purpose The purpose of this study was to evaluate how risk estimates generated from cumulative meta-analysis performs over time for drugs having their benefit/risk ratio re-evaluated due to safety issues and, additionally, assess whether results are consistent with regulatory authorities' conclusions.
Methods Four major regulatory authorities were searched for their issued safety alerts supported by longitudinal, comparative studies (experimentals and/or observationals). The random-effects model was used to pooled odds ratios (OR) over time by including studies according to the year they first became available.
Results Seventeen safety alerts were included in this study. In 2008, proton-pump inhibitors (PPIs) were associated with an increased risk for bone fractures [OR 1.25, 95 % confidence interval (CI) 1.00–1.55, P=0.049); the US Food and Drug Association (FDA) issued a safety alert in 2010 and added warnings to the label. An increased risk for *Clostridium-difficile*-associated diarrhea was pooled for PPIs in 2004 (OR 1.89, 1.19–3.02, P=0.007); US FDA issued a safety alert in 2012, adding warnings to the label. PPIs were associated with pneumonia in 2009 (OR 1.40, 1.06–1.85, P=0.017); US FDA issued an alert in 2012 but concluded that the benefit/risk (B/R) ratio remains positive. Statins were associated with an increased risk for diabetes (OR 1.07, 1.01–1.15, P=0.033) in 2008. The European Medicines Agency (EMA) issued an alert in 2012, including warnings to the label. The remaining cumulative meta-analyses did not estimate increased risks in advance of regulatory decisions.
Conclusion This study demonstrates that meta-analysis may help predict iatrogenic risks. However, between-study heterogeneity can considerably affect the estimated results, and therefore, this technique should not replace further assessments during BR ratio re-evaluations.

Keywords Meta-analysis · Safety alerts · Data sources · Regulatory agencies

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Grading evidence on the safety arm

- Quantitative metrics:
  - NNTH
  - LHH

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015
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ORIGINAL REPORT

Number needed to harm in the post-marketing safety evaluation: results for rosiglitazone and pioglitazone

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ABSTRACT

Purpose Our aim is to investigate the usefulness of metric indices in post-marketing safety evaluations by estimating number needed to harm (NNH) values for cardiovascular (CV) adverse outcomes for rosiglitazone and pioglitazone.

Methods Reports from regulatory authorities (RAs) were consulted, and Medline searches were performed to identify studies assessing CV risks [all-cause death, CV death, myocardial infarction (MI), stroke, or congestive heart failure (CHF)] for thiazolidinediones. Meta-analyses were performed to pool evidence from randomized controlled trials (RCTs) and observational studies (OS). NNHs [with 95% confidence intervals (CI)] per year were estimated for CV adverse events.

Results Reports from RAs included two meta-analyses of short-term RCTs, two long-term RCTs (RECORD and PROACTIVE), and a systematic review of OS ($n = 29$). The Medline search identified six additional OS. Statistically significant NNH values were obtained for the following: (i) rosiglitazone versus control on MI and CHF in the meta-analysis of RCTs (NNH = 16; 95%CI = 10–255; and NNH = 7; 95%CI = 5–16, respectively) and meta-analysis of OS (NNH = 12; 95%CI = 9–20; and NNH = 5; 95%CI = 32–131, respectively) and on CHF in the RECORD (NNH = 6; 95%CI = 4–14); (ii) pioglitazone versus control on CHF (NNH = 11; 95%CI = 6, 403) in the meta-analysis of RCTs and PROACTIVE (NNH = 12; 95%CI = 8–43); and (iii) rosiglitazone versus pioglitazone on MI (NNH = 69; 95% CI = 32–379), stroke (NNH = 36; 95%CI = 20–225), CHF (NNH = 33; 95%CI = 19–47), and all-cause death (NNH = 63; 95%CI = 49–100) in the meta-analysis of OS.

Conclusion The NNH values suggested an increased CV risk with rosiglitazone versus pioglitazone across several sources of information. The inclusion of objective metrics in post-marketing drug's benefit–risk assessments could be of increased value and help RAs to make consistent decisions on drug safety.

KEY WORDS—benefit–risk assessment; safety-based drug withdrawals; NNH; rosiglitazone; pioglitazone; cardiovascular diseases; pharmacoepidemiology

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ORIGINAL RESEARCH

Testing the usefulness of the number needed to treat to be harmed (NNTH) in benefit-risk evaluations: case study with medicines withdrawn from the European market due to safety reasons

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ABSTRACT

Objective: To explore the usefulness of number needed to treat to be harmed (NNTH), in benefit-risk assessments, by studying the agreement between NNTH values and withdrawals of medicines from European market due to safety reasons.

Methods: Medicines with data from longitudinal studies were included. Studies were identified from European Medicines Agency's Reports. Meta-analyses were performed to pool odds ratios (OR) with 95% confidence-intervals (CI). Published control event rates were applied to ORs to calculate NNTHs (95%CI) for selected adverse events.

Results: NNTH (95%CI) decreased from pre- to post-marketing for the eight medicines included: peripheral neuropathy (∞ vs. 12[non-significant; NS] with almitrine; heart valve disease with benfluorex (∞ vs. NNTH ranging from 7[4–13] to 7[5–9]); myopathy (–4096[NS] vs. 797[421–1690]), new-onset diabetes (113[NS] vs. 390[425–778]), bleeding (∞ vs. 517[317–1153]), and infection (∞ vs. 253[164–463]) with niacin-laropiprant; psychiatric disorders (12[7–34] vs. 9[5–24]) with rimonabant; myocardial infarction (MI) [–1305 vs. 270[89–4362]) with rofecoxib; MI (–510 vs. NNTH ranging from 152[55–4003] to 568 [344–1350]) with rosiglitazone; cardiovascular events (∞ vs. 245[129–1318]) with sibutramine; and liver injury (∞ vs. 5957[NS]) with ximelagatran.

Conclusion: NNTH have potential of use as a supportive tool in benefit-risk re-evaluations of medicines and may help regulators to making decisions on drug safety.

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SYSTEMATIC REVIEW

Benefit–Risk of Therapies for Relapsing–Remitting Multiple Sclerosis: Testing the Number Needed to Treat to Benefit (NNTB), Number Needed to Treat to Harm (NNTH) and the Likelihood to be Helped or Harmed (LHH): A Systematic Review and Meta-Analysis

Diogo Mendes[1,2] · Carlos Alves[1,2] · Francisco Batel-Marques[1,2]

Abstract

Objective This study aimed to test the number needed to treat to benefit (NNTB) and to harm (NNTH), and the likelihood to be helped or harmed (LHH) when assessing benefits, risks, and benefit–risk ratios of disease-modifying treatments (DMTs) approved for relapsing–remitting multiple sclerosis (RRMS).

Methods In May 2016, we conducted a systematic review using the PubMed and Cochrane Central Register of Controlled Trials databases to identify phase III, randomized controlled trials with a duration of ≥2 years that assessed first-line (dimethyl fumarate [DMF], glatiramer acetate [GA], β-interferons [IFN], and teriflunomide) or second-line (alemtuzumab, fingolimod, and natalizumab) DMTs in patients with RRMS. Meta-analyses were performed to estimate relative risks (RRs) on annualized relapse rate (ARR), proportion of relapse-free patients (PPR-F), disability progression (PP-F-CDPS3M), and safety outcomes. NNTB and NNTH values were calculated applying RRs to control event rates. LHH was calculated as NNTH/NNTB ratio.

Results The lowest NNTBs on ARR, PPR-F, and PP-F-CDPS3M were found with IFN-β-1a-SC (NNTB 3, 95 % CI 2–4; NNTB 7, 95 % CI 4–18; NNTB 4, 95 % CI 3–7, respectively) and natalizumab (NNTB 2, 95 % CI 2–3; NNTB 4, 95 % CI 3–6; NNTB 9, 95 % CI 6–19, respectively). The lowest NNTH on adverse events leading to treatment discontinuation was found with IFN-β-1b (NNTH 14, 95 % 2–426) versus placebo; a protective effect was noted with alemtuzumab versus IFN-β-1a-SC (NNTB 22, 95 % 17–41). LHHs >1 were more frequent with IFN-β-1a-SC and natalizumab.

Conclusions These metrics may be valuable for benefit–risk assessments, as they reflect baseline risks and are easily interpreted. Before making treatment decisions, clinicians must acknowledge that a higher RR reduction with drug A as compared with drug B (versus a common comparator in trial A and trial B, respectively) does not necessarily mean that the number of patients needed to be treated for one patient to encounter one aditional outcome of interest over a defined period of time is lower with drug A than with drug B. Overall, IFN-β-1a-SC and natalizumab seem to have the most favorable benefit–risk ratios among first- and second-line DMTs, respectively.

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BMC Medicine

RESEARCH ARTICLE Open Access

Number needed to treat (NNT) in clinical literature: an appraisal

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Abstract

Background: The number needed to treat (NNT) is an absolute effect measure that has been used to assess beneficial and harmful effects of medical interventions. Several methods can be used to calculate NNTs, and they should be applied depending on the different study characteristics, such as the design and type of variable used to measure outcomes. Whether or not the most recommended methods have been applied to calculate NNTs in studies published in the medical literature is yet to be determined. The aim of this study is to assess whether the methods used to calculate NNTs in studies published in medical journals are in line with basic methodological recommendations.

Methods: The top 25 high-impact factor journals in the "General and/or Internal Medicine" category were screened to identify studies assessing pharmacological interventions and reporting NNTs. Studies were categorized according to their design and the type of variables. NNTs were assessed for completeness (baseline risk, time horizon, and confidence intervals [CIs]). The methods used for calculating NNTs in selected studies were compared to basic methodological recommendations published in the literature. Data were analyzed using descriptive statistics.

Results: The search returned 138 citations, of which 51 were selected. Most were meta-analyses ($n = 23$, 45.1%), followed by clinical trials ($n = 17$, 33.3%), cohort ($n = 9$, 17.6%), and case–control studies ($n = 2$, 3.9%). Binary variables were more common ($n = 41$, 80.4%) than time-to-event ($n = 10$, 19.6%) outcomes. Twenty-six studies (51.0%) reported only NNT to benefit (NNTB), 14 (27.5%) reported both NNTB and NNT to harm (NNTH), and 11 (21.6%) reported only NNTH. Baseline risk ($n = 37$, 72.5%), time horizon ($n = 38$, 74.5%), and CI ($n = 32$, 62.7%) for NNTs were not always reported. Basic methodological recommendations to calculate NNTs were not followed in 15 studies (29.4%). The proportion of studies applying non-recommended methods was particularly high for meta-analyses ($n = 13$, 56.5%).

Conclusions: A considerable proportion of studies, particularly meta-analyses, applied methods that are not in line with basic methodological recommendations. Despite their usefulness in assisting clinical decisions, NNTs are uninterpretable if incompletely reported, and they may be misleading if calculating methods are inadequate to study designs and variables under evaluation. Further research is needed to confirm the present findings.

Keywords: Numbers needed to treat, Evidence-based medicine, Epidemiologic methods, Data interpretation, Statistical, Meta-analysis, Randomized controlled trial, Cohort studies, Case–control studies

Second generation pharmacovigilance

- Populational safety
  - Quinolones and catharats
  - Statins and diabetes

- How to deal with such results ?

Acta Ophthalmologica

Acta Ophthalmologica 2016

A systematic review and meta-analysis of the association between systemic fluoroquinolones and retinal detachment

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[2]School of Pharmacy, University of Coimbra, Coimbra, Portugal

ABSTRACT.

Purpose: **Several pharmacoepidemiologic studies have been carried out evaluating the risk of retinal detachment associated with systemic fluoroquinolones. This meta-analysis aims to investigate such association, in the light of the best scientific evidence available.**

Methods: **A literature search was conducted to identify relevant studies evaluating the risk for retinal detachment associated with systemic fluoroquinolones. A meta-analysis was performed to pool rate ratios (RRs). Meta-regressions were conducted aiming to evaluate the influence of time interval between fluoroquinolones use and retinal detachment diagnosis or treatment risk estimates.**

Results: **Ten observational studies from seven publications were included. Overall, fluoroquinolones were not associated with an increased risk for retinal detachment [RR 1.47 (95% CI 0.95–2.27): p = 0.09; I^2 = 92.8%]. When the analysis was stratified according to different study designs, the result was statistically significant for retrospective cohort studies [RR 1.87 (95% CI 1.36–2.58); p < 0.001; I^2 = 0.0%] and for past users of fluoroquinolones, based on data from case–control studies [RR 1.07 (95% CI 1.01–1.12); p = 0.01; I^2 = 0.0%]. According to meta-regressions, the risk for retinal detachment did not vary due to different time intervals between fluoroquinolones prescription and retinal detachment occurrence. No statistically significant results were identified among studies evaluating only rhegmatogenous retinal detachments, as well as among studies that evaluated patients not requiring a prior ophthalmologist visit to be included.**

Conclusions: **In light of the current available evidence, systemic fluoroquinolones do not seem to be associated with retinal detachment.**

Key words: drug safety – fluoroquinolones – meta-analysis – pharmacovigilance – post-marketing drug surveillance – retinal detachment

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cataract surgery, myopia and trauma are the most common risk factors for retinal detachment (Gariano & Kim 2004). The annual incidence of this condition is approximately 12 cases per 100 000 people in the general population, and 18 per 100 000 in patients previously submitted to cataract surgery (D'Amico 2008). Although retinal detachments may require urgent surgical intervention, they are often repaired with little or no vision loss, being a less significant cause of irreversible blindness than other retinal diseases, such as diabetic retinopathy or macular degeneration (Gariano & Kim 2004; D'Amico 2008; Cunha Vaz et al. 2014).

Two observational pharmacoepidemiologic studies have recently identified a statistically significant increased risk for retinal detachment in patients treated with systemic fluoroquinolones (Etminan et al. 2012; Kuo et al. 2014). However, the results from other sources of evidence are contradictory with such findings (Pasternak et al. 2013; Chui et al. 2014, 2015; Eftekhari et al. 2014; Fife et al. 2014; Kapoor et al. 2014). Regulatory authorities considered that most of these observational studies have limitations, such as lacking of ability to deal with ophthalmological confounding factors, retinal detachment risk factors and heteroge-

Genetics/genomics of drug safety

- Risk stratification (population/regulatory)
- Risk stratification (clinical/regulatory)

Challenges (Old and New)

- Underreporting
- Assessing causality
- Safety signal generation methodologies
- Measuring exposure
- Grading evidence on the safety arm
- Second generation pharmacovigilance
- Genetics/genomics of drug safety

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