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Review Article

Pharmacovigilance study of tyrosine kinase inhibitors: Analysis of adverse reactions

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Abstract

The aim of the study is to analyze reports of adverse drug reactions published in the scientific literature occurring during and after the use of kinase inhibitors for the treatment of rheumatologic diseases to determine their type, frequency, and severity. The search was conducted in the MEDLINE and PubMed databases from January 2005 to May 2022. We found a total of 291 publications, from which we selected suitable ones for data extraction. We conducted descriptive and variation analyses as the main statistical analyses. We determined mean values, standard deviation, minimum, maximum, and 95% confidence intervals. The PICOS tool was used to evaluate the results. The analyzed population includes patients with rheumatologic and oncologic diseases. There is a significant interest in the drug safety of kinase inhibitors, as they represent a rapidly evolving and reliable pharmacological class. Clarifying the safety profile of their representatives remains important. In-depth review of full-text publications shows that the high frequency of reported serious ADRs is rather due to increased interest in reporting and publishing these cases than to their high frequency of occurrence.

Keywords

kinase inhibitors, adverse drug reactions, rheumatologic diseases, systematic review

Introduction

Over the past twenty years, kinase inhibitors have become one of the most widespread groups of medicinal products, accounting for over 30% of all medicines in development. This is due, on one hand, to the diverse role of kinases as regulators in most cellular homeostasis processes and the consequences of their dysregulation in the pathogenesis of various diseases (McGovern and Shoichet 2003; Kannaiyan and Mahadevan 2018). On the other hand, kinases possess an active center that is highly suitable for inhibition by small-molecule drugs (Liao 2007). The first small-molecule kinase inhibitor was approved by the FDA in 2001 with the INN Imatinib for the treatment of patients with Philadelphia chromosome-positive (bcr-abl) (Ph+) chronic myeloid leukemia, targeting the Bcr-Abl hybrid protein. In the following years, the group of kinase inhibitors has constantly expanded, and currently there are over 80 registered products. The majority of them are used in oncology, where they have revolutionized the treatment

of numerous diseases such as non-small cell lung cancer, breast cancer, renal cell carcinoma, and others. The other main area of application for kinase inhibitors is rheumatology, where they are used to treat rheumatoid arthritis (RA), ulcerative colitis (UC), psoriatic arthritis (PA), ankylosing spondylitis (AS), and others.

With the accumulation of data from real clinical practice, including an increasingly diverse patient population, a more comprehensive understanding of the safety profile of kinase inhibitors is achieved. The collected information, while strongly supporting their therapeutic effectiveness, raises several questions regarding their safety (Parvova et al. 2019, 2020; Lamore et al. 2020). Despite their targeted mechanism of action, therapy with kinase inhibitors is accompanied by the occurrence of adverse drug reactions, most commonly diarrhea, fatigue, and rashes, but they can also be significantly more severe. Considering that data from the preclinical trial phase are highly limited and do not show great predictive ability regarding the safety profile in real-world clinical practice, a more in-depth investigation of the adverse reactions of kinase inhibitors is of significant interest.

Analyzing data from the scientific literature is a very good approach to assessing the safety profile of medicinal products in the post-registration phase (Zhao 2024). A systematic review is a formal, systematic, and structured approach to reviewing all the scientific literature on a given topic. The aim of the study is to analyze published reports of adverse drug reactions (ADRs) occurring during and after the administration of kinase inhibitors (KIs) for the treatment of rheumatological diseases and to determine their type, frequency, and severity.

Materials and methods

The main method used in the present study is documentary—data analysis from a systematic review of scientific literature (Harris et al. 2014; Parvova et al. 2024). The systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Shamseer et al. 2015). The topic of the systematic review is the analysis of the safety of kinase inhibitors with application in rheumatology based on scientific literature. The search strategy includes actively searching for scientific publications using both Bulgarian and English keywords: kinase inhibitors, adverse drug reactions, toxicity, cardiotoxicity. The search was conducted in the PubMed, MEDLINE, Central Medical Library, and national peer-reviewed scientific journals in Bulgaria from January 2005 to May 2022. For this period, 291 scientific publications meeting the search criteria were identified. Evaluated results and inclusion criteria: only scientific publications containing reports of adverse reactions during kinase inhibitor therapy for diseases within the domain of the medical specialty "Rheumatology" were analyzed. The criteria for including scientific publications in the analyses are as follows: the scientific article must contain data on toxicity or ADR, patients must have a diagnosed disease according to applicable criteria, and patients must have undergone or are undergoing treatment with a kinase inhibitor. Data extraction: For the present study, the following data were extracted: names of authors, year of publication, country of origin, type of scientific communication, type of study or analysis, names of drugs used by INN, disease for which the investigated drugs were applied, types of reported ADRs by type, frequency, and severity, presented according to the MedDRA system organ class classification, version 25.1, general criteria for adverse events, number of patients included in the reported study/studies, and key findings. Statistical analyses: The open-source statistical software Jamovi and Microsoft Excel 2016 were used (Jamovi 2024; R Core Team 2024). Descriptive and variation analyses were conducted as basic statistical analyses.

Results

The selection of the analyzed scientific articles was conducted in accordance with the search strategy and presented as a PRISMA flow diagram (Fig. 1). The literature search covers articles published in Bulgarian and English. In the initial keyword search, 291 scientific publications were found, 8 of which were excluded due to duplication. 283 titles and abstracts were screened, of which 62% (n = 180) were excluded due to not meeting the inclusion criteria. 35% (n = 103) of full-text publications were evaluated against the inclusion criteria, of which 27% (n = 80) were excluded from subsequent analysis due to lack of necessary data for the study's purposes. In the final stage, 8% (n = 23) of the scientific publications were selected for data extraction and inclusion in the systematic review.

The results were evaluated using the population, intervention, comparison, outcomes, and study design (PICOS) criteria system (Methley et al. 2014). The PICO tool, adopted by the Cochrane Collaboration, is used to identify components of clinical evidence for evidence-based systematic reviews in medicine. The modified PICOS version also includes the study design, limiting the likelihood of inappropriate scientific publications being included in the analysis. The results are presented in Table 1.

The studies reported in the analyzed scientific publications are categorized by types: systematic reviews and meta-analyses, randomized controlled clinical trials, retrospective cohort studies, case-control studies, and single case reports. Systematic reviews and meta-analyses account for the largest share: 43% (n = 10), followed by publications based on randomized controlled clinical trials: 22% (n = 5), which gives greater significance to the data (Fig. 2).

The largest relative share of the analyzed scientific publications include patients treated with Tofacitinib: 70% (n = 16), followed by Baricitinib: 40% (n = 9), Upadacitinib: 22% (n = 5), and Filgotinib: 17% (n = 4), with the total exceeding the total number of accepted publications,

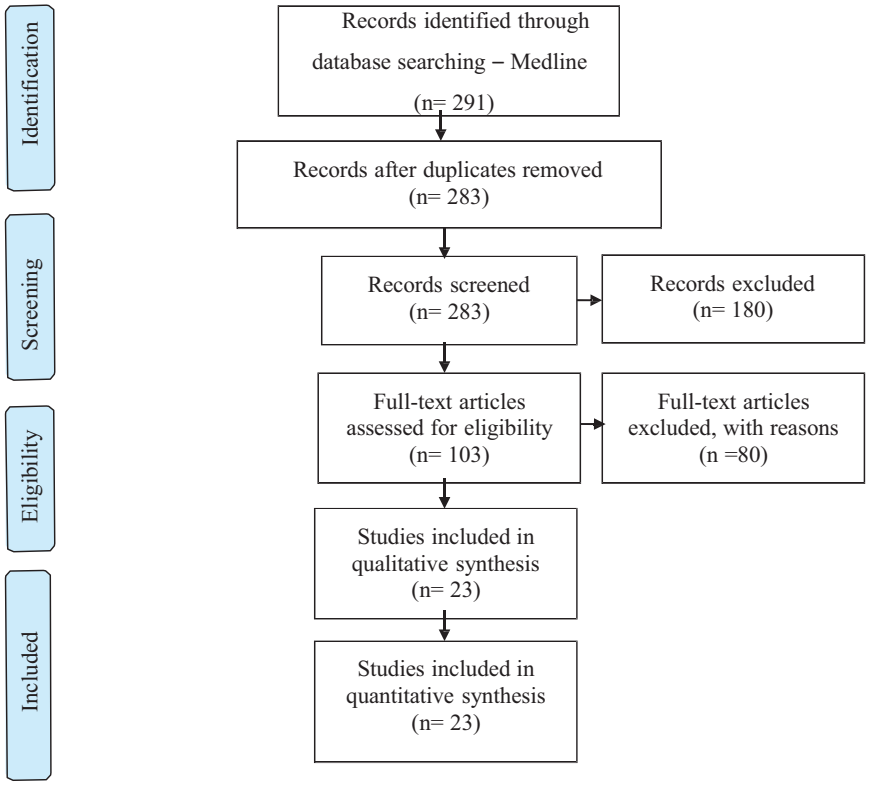

Figure 1. Overview of the search and selection process—PRISMA flow diagram.

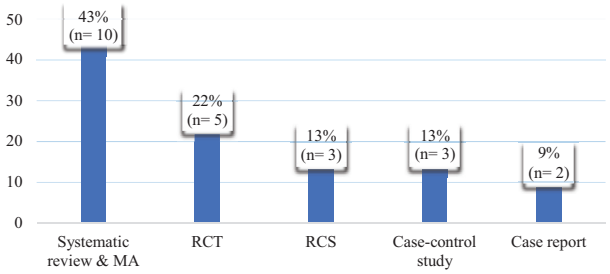

Figure 2. Publication by type of study.

as some of them consider more than one medicinal product. All four medicinal products have been authorized through a centralized procedure by the European Medicines Agency, with Tofacitinib (EMA 2017a) and Baricitinib (EMA 2017b) receiving marketing authorization in 2017, Upadacitinib (EMA 2019) in 2019, and Filgotinib (EMA 2020) in 2020. The data on the number of articles by medicinal product are summarized in Fig. 3.

Tofacitinib was initially approved for the therapeutic indication of rheumatoid arthritis, and subsequently new indications such as psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and juvenile idiopathic arthritis (JIA) were added. The first MA for Baricitinib is also only for RA, and then the indications atopic dermatitis, alopecia areata, and JIA were added. Upadacitinib, like the others, was initially approved only for the treatment of RA, but therapeutic indications were extended to include psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, ulcerative colitis, and Crohn's disease. Filgotinib is intended only for the treatment of RA, and subsequently indications were expanded to include ulcerative colitis. The different types and number of indications should be taken into account when drawing conclusions based on scientific publications for the various products.

We found that the largest share of the analyzed scientific publications are focused on rheumatoid arthritis: 62% (n = 18), followed by psoriasis: 14% (n = 4) and ankylosing spondylitis: 10% (n = 3). The majority of the articles included in the analysis are focused on single disease: 87% (n = 20), while only 13% (n = 3) cover two or more nosological units. The data on the number of articles per disease are summarized in Fig. 4.

Table 1. PICOS instrument.

Population	Intervention	Comparison	Outcomes	Study design
Patients with rheumatological diseases	Pharmacological interventions in accordance with EULAR criteria	Placebo	Adverse events	Systematic review and metaanalisys
The analyzed population includes 348 549 patients.	Patients should have been treated with at least one KI	The best standard treatment Any pharmacological intervention in accordance with EULAR criteria		Retrospective observational study Prospective observational study Open label study Cohort study Case series Case reports

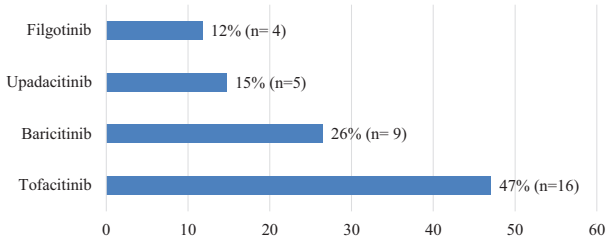

Figure 3. Scientific articles by investigated medicinal products.

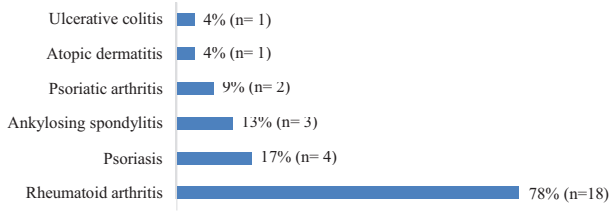

Figure 4. Diseases reported in scientific publications.

The systematic review showed that in 40% (n = 9) of the publications, authors actively investigate and report all adverse drug reactions; in 30% (n = 7) only ADRs from the "infections and infestations" group are reported; and in 17% (n = 4) the authors focused on cardiovascular disorders. The total patient population is 348 549, with the majority being on Tofacitinib therapy: 64% (n = 224 549), followed by treatment with an unspecified kinase inhibitor: 20% (n = 69 368), Baricitinib: 12% (n = 42 711), Upadacitinib: 3% (n = 10 359), and Filgotinib: 1% (n = 1 572). The reported ADRs in absolute number are 16 253, with the same trend observed, the majority reported in patients on Tofacitinib: 52% (n = 8 362), the unspecified kinase inhibitor group: 24% (n = 3 930), Baricitinib: 21% (n = 3 375), Upadacitinib (3%, n = 530), and lastly Filgotinib with less than 1% (n = 56) of the reported ADRs. The frequency of ADR is presented in Table 2.

Table 2. Frequency of ADR.

Medicinal product	Number of patients N = 348 549	ADR frequency (%/n)
Tofacitinib	64% (n = 224 549)	3.72% (n = 8 362)
Baricitinib	12% (n = 42 711)	7.90% (n = 3 375)
Upadacitinib	3% (n = 10 359)	5.12% (n = 530)
Filgotinib	1% (n = 1 572)	3.56% (n = 56)
Unspecified KI	20% (n = 69 358)	5.67% (n = 3 930)

The heterogeneity of the data presented in scientific publications represents a significant challenge in extracting and systematizing information. The main shortcomings include presenting adverse drug reactions (ADR) as a total number without being classified by type and severity, as well as the use of different classifications in different articles. In data extraction, it was found that in 26% (n = 6) of the publications, ADRs were only presented as a total number and the number of serious ADRs; in 22% (n = 5) only the total number of ADRs was presented; and in the remaining 52% (n = 12), the MedDRA classification was used. Additionally, only 40% (n = 9) of the publications performed an analysis of all types of ADRs, 13% (n = 3) of the reports do not specify whether they consider safety data, although such data are presented, and the rest focus on one or more types of ADRs, which should be taken into account when interpreting the results. We found that nearly 50% (n = 3 374) of the reported ADRs are related to cardiovascular disorders, 31% (n = 2 121) of the reported ADRs are classified as serious adverse reactions, and 19% (n = 1 297) fall into the category of infections and infestations. Data on the five most reported ADRs in the analyzed scientific publications are presented in Fig. 5.

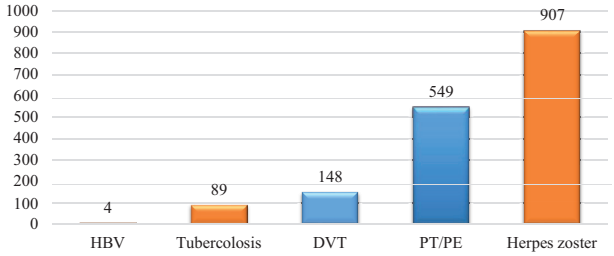

Figure 5. ADR types.

Discussion

When conducting the systematic review of scientific publications, we identified a high interest in the drug safety of kinase inhibitors and significant publication activity, which is consistent with the rapid expansion of therapeutic indications and the number of representatives of this class of drugs. The largest share of the articles examines rheumatoid arthritis alone or in conjunction with other diseases, which is expected given that this is the initial approved therapeutic indication for all drugs under consideration. There is also a heightened interest in specific ADR groups; more than half of the publications focus solely on the "infections and infestations" and "cardiovascular disorders" groups. Upon closer examination, it is established that pre-registration trials of the studied kinase inhibitors do not show trends that predict such a result and distribution. However, data from real clinical practice show that these ADR groups, especially cardiovascular disorders, pose a significant risk and burden to patients, their families, healthcare systems, paying institutions, and society. Furthermore, although consensus precise data are lacking, it is well known that in patients with rheumatoid arthritis, cardiovascular comorbidities occur at a higher frequency compared to the general population and are among the most significant factors for increased mortality in this group (Taylor et al. 2021).

Our analysis also shows that the largest share, 50% (n = 3 374) of the total number of ADRs, which have been identified by type in the publications, specifically affect the cardiovascular system.

The lack of consistency in the data and non-compliance with ADR reporting standards create significant difficulties and impose limitations on the usability of information for subsequent analyses.

Half of the publications (n = 10) present as a main conclusion that there is an increased risk of ADRs in studies with MP and ADR type; 6 report a risk considered similar to the selected comparative alternative in the publication; 2 report a likely increased risk; and 2 state that more information is necessary. Staging the frequency of ADRs according to MeDRA as: very common (≥ 1/10); common (≥ 1/100 – < 1/10); uncommon (≥ 1/1,000 – < 1/100); rare (≥ 1/10,000 – < 1/1,000); very rare (<1/10,000), and with unknown frequency (not known), cannot be fully done from the available data. The calculated frequencies for the occurrence of ADRs with the studied kinase inhibitors obviously relate to all types of ADRs, and a more detailed analysis with the available data is impossible. Also, in the group of unspecified kinase inhibitors, the relative weight of different products is not known, and the result should be considered as an average value of occurrence for the entire group. In-depth review of full-text publications shows that the high frequency of reported serious adverse events is more likely due to increased reporting and publication interest in these cases rather than their high occurrence rate.

Conclusion

We have observed a high publication activity and scientific interest in the safety of kinase inhibitors, especially publications containing information on cardiovascular toxicity. Understanding and applying standards for analysis and reporting of adverse drug reactions are crucial for the correct interpretation of results and subsequent use of data for additional analytical and review works. Targeted research and publication in a specific domain of safety profile, such as cardiovascular toxicity, are useful for a deeper understanding of the frequency and mechanisms of adverse drug reactions, with emphasis on post-marketing behavior of kinase inhibitors and real-world clinical practice data.

Additional information

Conflict of interest

The authors declare that the research conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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