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Pharmacovigilance Investigation of Tyrosine Kinase Inhibitors: Evaluation of Adverse Events

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ABSTRACT

This study aimed to examine adverse drug reaction (ADR) reports documented in the scientific literature that occurred during or after the administration of kinase inhibitors in patients treated for rheumatologic disorders, focusing on identifying their nature, prevalence, and severity. A systematic search was carried out in the MEDLINE and PubMed databases covering the period from January 2005 to May 2022. Out of 291 retrieved publications, only those meeting the inclusion criteria were selected for data extraction. Descriptive and variation analyses served as the primary statistical approaches, including the calculation of mean values, standard deviations, ranges, and 95% confidence intervals. The PICOS framework was applied to assess study outcomes. The investigated cohort comprised individuals diagnosed with rheumatologic as well as oncologic conditions. Growing attention has been directed toward the safety monitoring of kinase inhibitors, given their status as an emerging and dependable pharmacological category. Understanding the safety characteristics of these agents continues to hold clinical significance. A thorough evaluation of the full-text sources suggests that the notable number of reported serious ADRs likely reflects heightened awareness and publication activity rather than an actual increase in their occurrence.

Keywords: Systematic review, Kinase inhibitors, Rheumatologic diseases, Adverse drug reactions

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Introduction

Over the last two decades, kinase inhibitors have emerged as one of the most extensively developed classes of therapeutic agents, constituting more than 30% of all new drugs in development. This prominence stems from the fundamental role of kinases in maintaining cellular homeostasis and their involvement in the molecular mechanisms underlying numerous pathological conditions when dysregulated [1, 2]. Moreover, the structural characteristics of the kinase active site make it highly amenable to inhibition by small-molecule compounds [3]. The first FDA-approved small-molecule kinase inhibitor, imatinib, was introduced in 2001 for the treatment of Philadelphia chromosome-positive (bcr-abl) chronic myeloid leukemia, targeting the Bcr-Abl fusion protein. Since then, this pharmacological class has grown significantly, with more than 80 approved agents now available. Most kinase inhibitors are employed in oncology, where they have revolutionized therapeutic approaches for diseases such as non-small cell lung cancer, breast cancer, and renal cell carcinoma. In addition to oncology, their clinical use has expanded into rheumatology for managing conditions such as rheumatoid arthritis (RA), ulcerative colitis (UC), psoriatic arthritis (PA), and ankylosing spondylitis (AS).

As clinical experience accumulates across diverse patient populations, a clearer picture of the safety profiles of kinase inhibitors has emerged. Although extensive data confirm their therapeutic benefits, concerns about their safety persist [4–6]. Despite being designed for specific molecular targets, kinase inhibitor therapy is often associated with adverse drug reactions (ADRs), including diarrhea, fatigue, and skin rashes, which in some cases

can be severe. Given that preclinical and early clinical trials provide limited and often insufficiently predictive safety data, there is a pressing need for further assessment of their adverse effects in real-world clinical settings. Analyzing published scientific literature offers an effective approach to evaluating the post-marketing safety of medicinal products [7]. A systematic review allows for a structured and comprehensive assessment of existing research on a specific topic. The purpose of the present study is to systematically examine and analyze published reports of ADRs that occur during or after the administration of kinase inhibitors (KIs) in the treatment of rheumatologic diseases, with the aim of characterizing their nature, frequency, and severity.

Materials and Methods

This study employed a documentary research method, analyzing data derived from a systematic review of the scientific literature [8, 9]. The review was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The focus of the review was to assess the safety of kinase inhibitors used in rheumatological practice based on published evidence.
The search strategy involved identifying scientific publications in both English and Bulgarian using keywords such as kinase inhibitors, adverse drug reactions, toxicity, and cardiotoxicity. Searches were performed in PubMed, MEDLINE, the Central Medical Library, and peer-reviewed national journals in Bulgaria, covering the period from January 2005 to May 2022. A total of 291 relevant studies were initially retrieved.

Eligibility and inclusion criteria
Publications were included if they reported ADRs or toxicity events related to kinase inhibitor therapy in patients diagnosed with diseases within the field of rheumatology. Eligible studies had to provide specific information on adverse effects, patient diagnosis based on recognized criteria, and details of treatment involving kinase inhibitors.

Data extraction
From the selected studies, data were collected on the following parameters: author names, year of publication, country, publication type, study design, names of drugs (by INN), disease indications, types and frequencies of ADRs (classified by MedDRA version 25.1), severity of adverse events, total number of patients, and principal findings.

Statistical analysis
Descriptive and variation analyses were performed using open-source software Jamovi and Microsoft Excel 2016 [11, 12]. Key statistical indicators such as mean values, standard deviations, minimum and maximum values, and 95% confidence intervals were calculated.

Results and Discussion

The selection process for eligible studies was conducted according to the predefined search strategy and is summarized in the PRISMA flow diagram **(Figure 1)**. Both Bulgarian and English-language publications were reviewed. Initially, 291 records were identified, of which 8 duplicates were removed. Screening of 283 titles and abstracts resulted in the exclusion of 180 (62%) that did not meet the inclusion criteria. The full texts of 103 publications (35%) were further evaluated, and 80 (27%) were excluded due to insufficient data relevant to the study objectives. Ultimately, 23 studies (8%) were deemed eligible for data extraction and inclusion in the final systematic review.

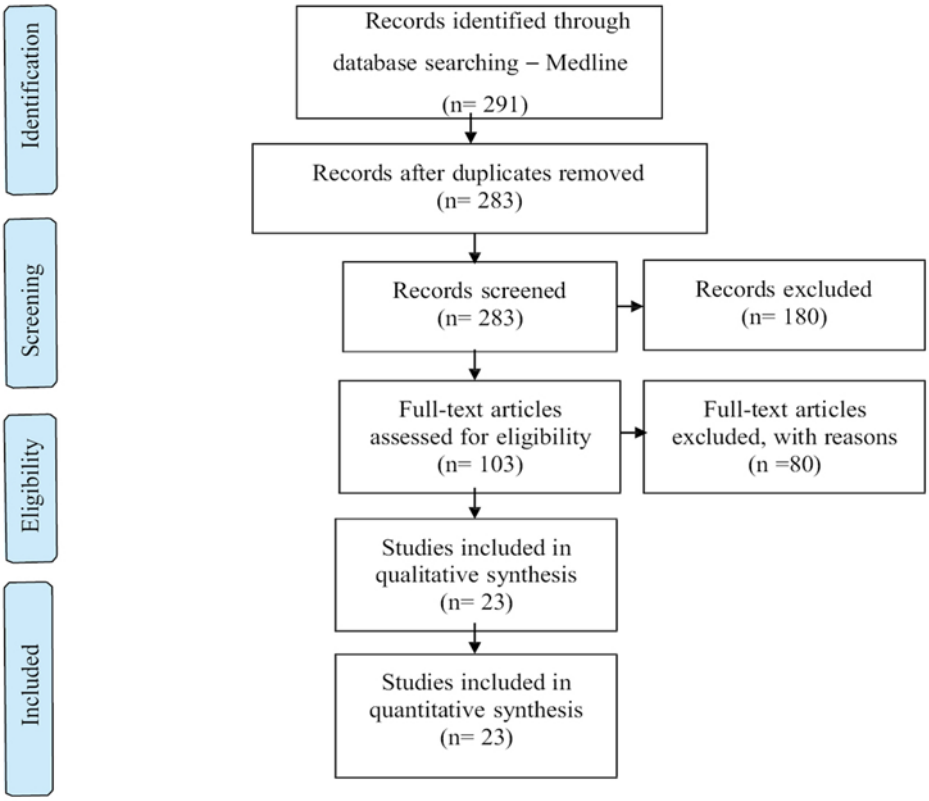

Figure 1. Overview of the search and selection process—PRISMA flow diagram.

The analysis of findings was guided by the PICOS framework, encompassing Population, Intervention, Comparison, Outcomes, and Study design [13]. Originally formulated by the Cochrane Collaboration as the PICO model to structure clinical evidence for evidence-based medical reviews, the adapted PICOS format introduces an additional parameter—study design—to enhance precision and prevent the inclusion of studies that do not meet methodological standards. The summarized results derived from this evaluation are displayed in **Table 1**.

Table 1. PICOS instrument.

Population	Intervention	Comparison	Outcomes	Study design
Individuals diagnosed with rheumatologic disorders.	Drug-based treatments administered following EULAR guideline recommendations.	Placebo	Adverse events	Systematic review and metaanalisys
The study population comprised a total of 348,549 patients.	Participants must have received treatment involving at least one kinase inhibitor (KI).	The most effective conventional therapy.		Retrospective observational study
		Any drug-based treatment administered following EULAR guideline recommendations.		Prospective observational study
				Open label study Cohort study Case series
				Case reports

The studies described in the reviewed scientific literature are classified into several types: systematic reviews and meta-analyses, randomized controlled trials, retrospective cohort studies, case-control studies, and individual case reports. Systematic reviews and meta-analyses represent the largest portion at 43 percent (n = 10), followed by randomized controlled trials at 22 percent (n = 5), which provides stronger evidence for the findings **(Figure 2)**.

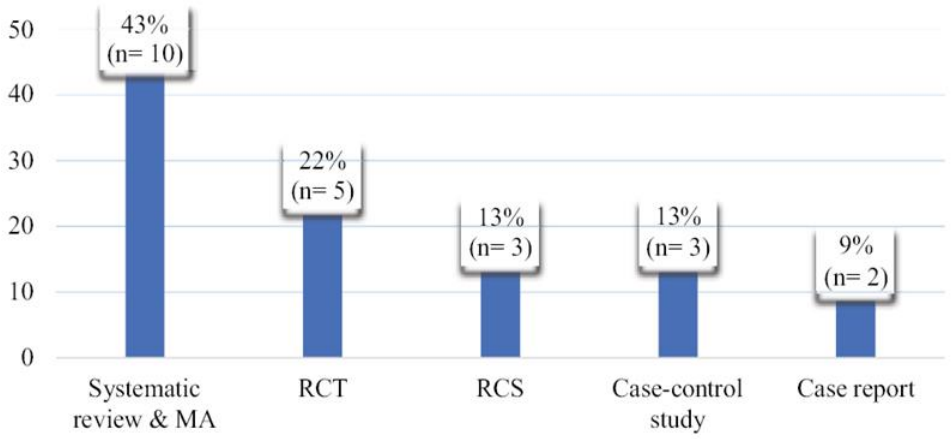

Figure 2. Publication by type of study.

The majority of the reviewed scientific publications involved patients treated with Tofacitinib, representing 70 percent (n = 16), followed by Baricitinib at 40% percent (n = 9), Upadacitinib at 22 percent (n = 5), and Filgotinib at 17 percent (n = 4); the total exceeds the number of included publications because some studies evaluated more than one drug. All four medications were approved via the European Medicines Agency's centralized procedure, with Tofacitinib [14] and Baricitinib [15] authorized in 2017, Upadacitinib [16] in 2019, and Filgotinib [17] in 2020. **Figure 3** summarizes the number of publications per drug.

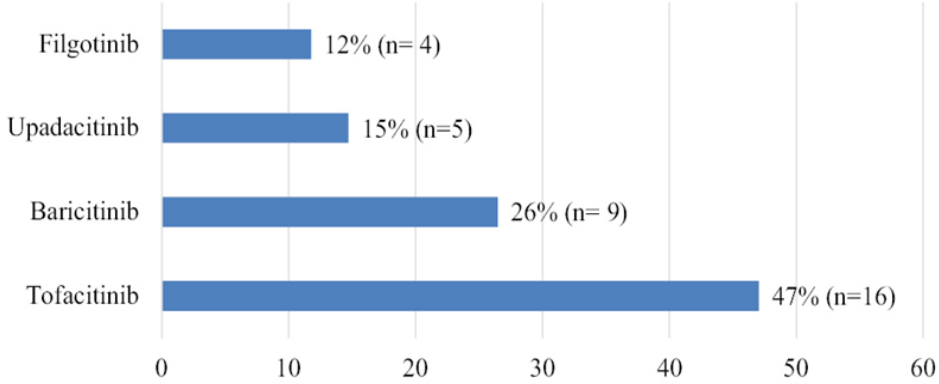

Figure 3. Publications categorized by the studied medications.

Tofacitinib was originally approved for treating rheumatoid arthritis, with later expansions to include psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and juvenile idiopathic arthritis (JIA). Similarly, Baricitinib initially received marketing authorization solely for RA, with subsequent approvals for atopic dermatitis, alopecia areata, and JIA. Upadacitinib began as a treatment exclusively for RA, later extending to psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, ulcerative colitis, and Crohn's disease. Filgotinib was first indicated for RA, with later expansion to ulcerative colitis. These variations in the number and type of approved indications should be considered when interpreting data from scientific publications on each drug. Among the reviewed studies, the majority focused on rheumatoid arthritis at 62 percent (n = 18), followed by psoriasis at 14 percent (n = 4) and ankylosing spondylitis at 10 percent (n = 3). Most publications addressed a single disease (87 percent, n = 20), whereas only 13 percent (n = 3) covered two or more conditions. **Figure 4** summarizes the number of articles by disease.

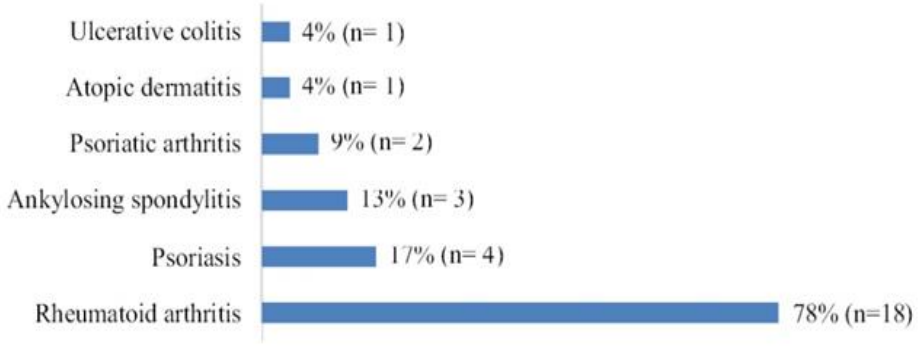

Figure 4. Diseases reported in scientific publications.

The systematic review revealed that 40 percent (n = 9) of the studies comprehensively examined and reported all adverse drug reactions (ADRs); 30 percent (n = 7) reported only ADRs related to "infections and infestations," and 17 percent (n = 4) focused specifically on cardiovascular disorders. The total patient population across these studies was 348,549, with most receiving Tofacitinib therapy (64 percent, n = 224,549), followed by an unspecified kinase inhibitor (20 percent, n = 69,368), Baricitinib (12 percent, n = 42,711), Upadacitinib (3 percent, n = 10,359), and Filgotinib (1 percent, n = 1,572). A total of 16,253 ADRs were reported, showing a similar distribution: Tofacitinib accounted for 52% (n = 8,362), the unspecified kinase inhibitor group 24 percent (n = 3,930), Baricitinib 21 percent (n = 3,375), Upadacitinib 3 percent (n = 530), and Filgotinib less than 1 percent (n = 56). **Table 2** presents the frequency of reported ADRs.

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 variability in data reported across scientific publications poses a major challenge for extracting and organizing information. Key limitations include reporting adverse drug reactions (ADRs) only as total counts without detailing type or severity, and the inconsistent use of classification systems across studies. During data extraction, it was observed that 26 percent (n = 6) of publications reported ADRs solely as total numbers and serious ADRs, 22 percent (n = 5) presented only total ADR counts, and 52 percent (n = 12) employed the MedDRA classification. Furthermore, only 40 percent (n = 9) of studies analyzed all ADR types, 13 percent (n = 3) did not explicitly indicate whether safety data were considered despite including them, and the remaining studies focused on one or more specific ADR categories, which should be considered when interpreting results. Among reported ADRs, nearly 50 percent (n = 3,374) involved cardiovascular disorders, 31 percent (n = 2,121) were classified as serious, and 19 percent (n = 1,297) fell under infections and infestations. **Figure 5** presents data on the five most frequently reported ADRs in the analyzed publications.

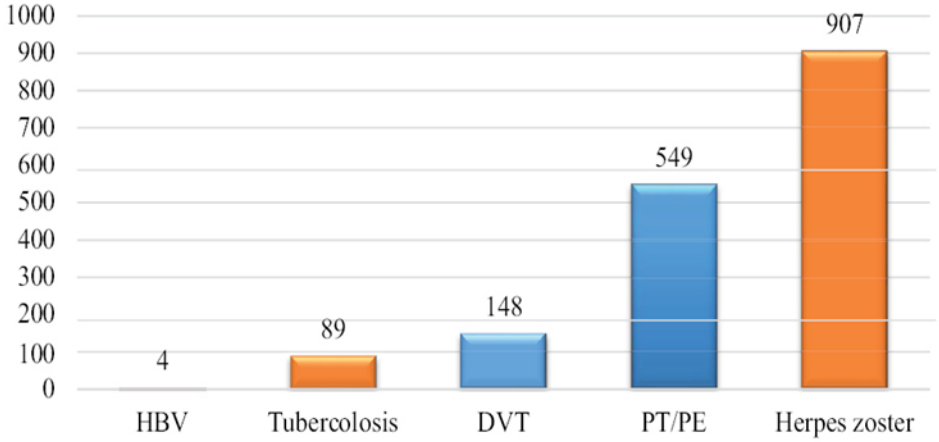

Figure 5. ADR types.

The systematic review of scientific publications revealed substantial interest in the safety of kinase inhibitors and notable publication activity, reflecting the rapid expansion of therapeutic indications and the growing number of drugs in this class. Most studies focus on rheumatoid arthritis, either alone or alongside other conditions, which aligns with the fact that RA was the initial approved indication for all the analyzed drugs. There is also a pronounced focus on specific ADR categories, with more than half of the publications concentrating on "infections and infestations" or "cardiovascular disorders." Interestingly, pre-registration trials of these kinase inhibitors do not predict this distribution of ADRs; however, real-world clinical data indicate that these ADR groups, particularly cardiovascular disorders, represent significant risks and burdens for patients, families, healthcare systems, payers, and society. Moreover, it is well established that patients with rheumatoid arthritis experience cardiovascular comorbidities more frequently than the general population, contributing substantially to mortality in this group [18].

Our analysis indicates that 50% (n = 3,374) of ADRs reported by type specifically involve the cardiovascular system. The inconsistencies in data reporting and lack of adherence to ADR reporting standards pose challenges and limit the utility of this information for further analyses. Half of the reviewed publications (n = 10) conclude that kinase inhibitors are associated with an increased risk of ADRs; six report a risk comparable to alternative treatments, two suggest a likely increased risk, and two highlight the need for more information. Applying the MedDRA frequency categories—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 unknown—cannot be fully accomplished with the available data. The calculated ADR frequencies pertain to all ADR types collectively, making a more detailed analysis impossible. For unspecified kinase inhibitors, the relative contribution of individual drugs is unknown, so reported frequencies reflect average values for the group. Detailed review of full-text articles suggests that the high number of serious ADRs reported is likely due to heightened reporting and publication interest rather than an actual high occurrence rate.

Conclusion

There is considerable publication activity and scientific interest in the safety of kinase inhibitors, particularly regarding cardiovascular toxicity. Adhering to standardized methods for ADR analysis and reporting is essential for accurate interpretation and for the effective use of data in further analyses and reviews. Focused research and publications on specific safety domains, such as cardiovascular toxicity, are valuable for improving understanding of ADR frequency and mechanisms, especially in the context of post-marketing surveillance and real-world clinical practice.

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Ethics Statement: None

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