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The Pharmacovigilance Landscape in China: Challenges and Strategies Exemplified by Zanubrutinib

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Abstract. Pharmacovigilance is a core component of risk management throughout a drug's lifecycle. It is essential because pharmaceutical products have an inherent benefit-risk balance. Zanubrutinib, a novel Bruton's tyrosine kinase (BTK) inhibitor originally developed in China, serves as an exemplary case for studying the safety management of innovative drugs in China across their entire lifecycle. This paper systematically analyzes the construction and operation of the pharmacovigilance system for zanubrutinib. Through a systematic review of its management strategies, the study explores the pharmacovigilance challenges faced by innovative drugs in China and corresponding countermeasures, providing references for their safety management. The research indicates that innovative drugs in China need to establish robust, internationally aligned pharmacovigilance systems from the outset to continuously monitor and manage adverse drug reactions, ensure patient medication safety, and provide a paradigm for the long-term safety monitoring of drugs included in the national reimbursement drug list.

Keywords: Zanubrutinib, BTK Inhibitor, Pharmacovigilance, China Innovation, Risk Management

1. Introduction

China's growing pharmaceutical innovation capabilities are driving domestically developed innovative drugs into the global market. In this context, establishing robust pharmacovigilance systems has become a core imperative. Since pre-marketing clinical trials have limited sample size, study duration, and homogeneous participants, they often misidentify rare, delayed, or adverse reactions in special populations. Therefore, post-approval, continuous monitoring and evaluation based on real-world data are crucial for ensuring public medication safety.

Zanubrutinib (brand name: Brukinsa) is a novel Bruton's tyrosine kinase (BTK) inhibitor independently developed by BeiGene. It was the first anticancer drug from China to receive a "Breakthrough Therapy" designation and approval from the U.S. Food and Drug Administration (FDA) [1]. Its key indications include mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), and chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) [2]. As a globally oriented innovative drug developed domestically in China, it possesses substantial high-quality international clinical research data and is subject to review and

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reporting requirements under multiple regulatory agencies such as the FDA and the European Medicines Agency (EMA), ensuring ample data sources.

Zanubrutinib has high selectivity for the BTK target and demonstrated a superior safety profile compared to ibrutinib in pivotal clinical trials [3]. However, significant research gaps remain. There is uncertainty about the long-term adverse reaction spectrum from clinical studies. Data on rare, delayed toxicities after very long-term use (>5 years) remain insufficient [4,5]. Rare adverse reactions such as neutropenia and thrombocytopenia are unknown. There is also a need to supplement safety data in complex populations, including those using combination therapies [6].

Therefore, this paper uses zanubrutinib as a case study to systematically dissect the pharmacovigilance system and risk management strategies it has constructed to address these challenges. Through this case, the paper explores the common pharmacovigilance challenges and solutions for Chinese innovative drugs in the global context, providing a theoretical reference for future domestic innovative drugs.

2. Literature review

2.1. Pharmacovigilance theory

Pharmacovigilance (PV) involves the monitoring of drug safety and risk management. Its core concept extends beyond just gathering traditional reports of adverse drug reaction (ADR) cases; it is an active, dynamic, and continuous process from start to finish of entire drug lifecycle. The goal of it is to identify, check, understand, and prevent side effects, mistakes in how drugs are used, drugs that do not work well, problems with drug quality, fake drugs, drug misuse, and other related issues [7].

Pharmacovigilance requires the implementation of multiple activities. First, systematic collection and monitoring of drug safety-related signals are conducted through spontaneous reporting systems, post-marketing studies, and other methods [8]. This is followed by assessing the nature, severity, frequency, and causal relationship of these risks to the drug. Based on the risk assessment results, a series of actions is taken, such as revising the product label, to minimize risks and maximize benefits. Effectively communicating drug safety information to healthcare professionals, patients, and the public is essential to promote rational drug use [9].

As a critical public health function and societal management tool, pharmacovigilance supports drug regulation, clinical practice, and public health decision-making. In this way, it maximizes the therapeutic benefits of drugs while minimizing their predictable and unpredictable risks, protecting patient and public interests. In China, innovative drug R&D is developing rapidly, and the accelerated market access is accelerating. Strengthening pharmacovigilance is increasingly imperative, representing a necessary requirement for ensuring the synergistic development of a sustainable pharmaceutical industry and public health security [7].

2.2. BTK inhibitors in China

Bruton's tyrosine kinase (BTK) inhibitors are a major breakthrough in targeted therapy for B-cell malignancies and have experienced rapid development in China in recent years. With the successive approvals of ibrutinib, zanubrutinib, orelabrutinib, and the non-covalent BTK inhibitor which were introduced by 2024, a multi-generational landscape will be created. In 2023, the domestic innovative drug zanubrutinib showed a significant increase, particularly in cardiovascular effects [10].

However, the clinical use of this drug class is consistently accompanied by specific safety challenges, including bleeding tendencies, susceptibility to infections, and cardiotoxicity, which

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constitute core issues for pharmacovigilance [11]. Although second-generation drugs have somewhat reduced the incidence of off-target related adverse events through improved target selectivity, the use of non-covalent inhibitors, while overcoming resistance mechanisms, also introduces new safety uncertainties [12,13]. Particularly noteworthy is that factors such as the genetic background, spectrum of comorbidities, and medication habits of Chinese patients may lead to a unique drug safety profile. Currently, large-scale, long-term, real-world study evidence based on the Chinese population remains relatively scarce. With regard to the drug. Based on the risk assessment results, a series of actions is taken, such as revising the product label, to minimize risks and maximize benefits. Effectively communicating drug safety information to healthcare professionals, patients, and the public is essential to promote rational drug use [9].

China's pharmacovigilance system faces several challenges. The inclusion of BTK inhibitors in the National Reimbursement Drug List (NRDL) through national price negotiations has improved accessibility, resulting in widespread use from top-tier medical centers to primary healthcare institutions. However, there are significant disparities exist in ADR monitoring, diagnosis, and reporting capabilities among different institutions, which may delay safety signal identification or uneven data quality [11]. Furthermore, the coexistence of multiple drug generations makes comparing the risk-benefit profiles of different BTK inhibitors a challenge in clinical decision-making, placing higher demands on pharmacovigilance activities [14].

3. Core pharmacovigilance activities for zanubrutinib

3.1. Identification and collection of adverse events

The identification and collection of adverse events form the foundation of pharmacovigilance, with data mainly drawn from clinical trials and diverse real-world settings.

3.1.1. Clinical trial safety profile

Pivotal registration clinical trials initially established the safety profile of zanubrutinib. To comply with the stringent post-marketing safety data requirements of various regulatory agencies, its developer, BeiGene, established a globally unified, real-time safety database [4]. This system integrates massive data from global clinical trials, spontaneous reports, and active monitoring studies [15]. By recognizing potential regional and population differences, the drug has been involved in large-scale international multi-center real-world studies and specialized pharmacoepidemiological investigations designed for long-term tracking of specific adverse events [2]. These trials identified common adverse reactions associated with zanubrutinib, mainly hematological and non-hematological toxicities, providing a basis for identifying and controlling risks early after market launch.

3.1.2. Post-marketing real-world data

Clinical trial participants are relatively homogeneous and limited in number, making it difficult to detect rare, delayed, or long-term adverse reactions [9]. Therefore, collecting post-marketing data through global spontaneous reporting systems is vital. Healthcare professionals and patients can report any suspected adverse reactions encountered during zanubrutinib use through these channels. Aggregating and analyzing these case reports effectively addresses the limitations of clinical trials. This process helps uncover new safety signals within specific subpopulations.

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3.2. ICSR management process compliant with international standards

As a drug approved in multiple global markets, the management of Individual Case Safety Reports (ICSRs) for zanubrutinib must comply with the E2B(R3) standard established by the International Council for Harmonisation (ICH). This standard specifies the data structure and format for the electronic transmission of ICSRs. It ensures that safety information from different sources (e.g., pharmaceutical companies, hospitals, regulatory agencies) can be interpreted and exchanged efficiently, accurately, and unambiguously.

Zanubrutinib's global pharmacovigilance system strictly adheres to the ICH E2B(R3) international standard. Its ICSR management process begins with the unified receipt of cases and assignment of unique identifiers. During data processing, a core step involves using the MedDRA terminology set to accurately encode adverse events. This ensures unambiguous information exchange. After medical review, cases meeting expedited reporting criteria are converted into standard-compliant electronic files and submitted via validated electronic channels to relevant global regulatory agencies within the statutory 15-calendar-day timeframe from the date of awareness, thereby achieving efficient and compliant global synchronization of safety data.

3.3. Signal detection and evaluation

After accumulating substantial safety data, scientific methods should be employed proactively identify potential safety signals.

3.3.1. Ongoing monitoring of "class-effect" risks

As part of the BTK inhibitor class, zanubrutinib requires continuous monitoring of "class-effect" risks, such as bleeding. Pharmacovigilance activities need to utilize accumulating post-marketing data to quantify the incidence of these events in broader, more complex real-world populations, explore associated risk factors, and provide management guidance for clinical practice, which is an essential pharmacovigilance function [16,17].

3.3.2. Identification of new signals

Beyond monitoring known risks, the company proactively investigates potential unique safety signals associated with zanubrutinib that differ from those of ibrutinib. This is achieved utilizing data mining techniques, such as disproportionality analysis. Specifically, by calculating metrics like the Reporting Odds Ratio for specific drug-event combinations, it probes for combinations reported significantly more frequently than expected within large global spontaneous reporting databases [10]. The company continuously monitors for potential adverse reactions related to zanubrutinib's molecular structure or selectivity, prompting further investigation.

3.4. Risk assessment and minimization

The ultimate goal of identifying and assessing risks is to take effective measures to manage them, minimizing potential harm to patients. The application logic begins with a comprehensive risk assessment, aggregating preclinical, clinical trial, and post-marketing data to structurally categorize drug risks into "Important Identified Risks," "Important Potential Risks," and "Missing Information," thereby precisely defining targets for intervention.

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3.4.1. Product labeling

Within the drug lifecycle management framework, the Risk Management Plan (RMP) systematically establishes a complete framework from risk identification to control implementation. Based on this, the RMP deploys tiered risk minimization measures. The primary tool is the product label (medication guide) serving as a routine risk communication tool. In the "Adverse Reactions" section, the global and Chinese labels for zanubrutinib detail adverse reactions and their incidence rates obtained from clinical trials and post-marketing surveillance [12]. The "Warnings and Precautions" and "Drug Interactions" sections explicitly warn of key risks such as bleeding, infections, and cytopenias, and provide guidance on interactions with anticoagulants, antiplatelet agents, etc.

3.4.2. Medication education

Effective risk management requires the joint participation of physicians and patients. By developing detailed patient leaflets and implementing physician education programs, patients are educated on self-monitoring for signs of bleeding, symptoms of infection, etc., and the importance of timely reporting [8]. This translates key information from the label into easily understandable and actionable guidelines. Engaging patients in their own safety monitoring constitutes the last line of defense in the pharmacovigilance system [8].

4. Risk management from global and Chinese regulatory perspectives

Pharmacovigilance, as a scientific practice throughout the drug lifecycle, evolves with its focus and challenges depending on the drug's stage. For innovative drugs approved via accelerated pathways and subsequently included in the National Reimbursement Drug List (NRDL), the pharmacovigilance system faces a complex transition from integrating global evidence to localized risk management. Therefore, the core value of pharmacovigilance in addressing regulatory harmonization and differentiation, as well as new challenges post-NRDL inclusion, deserves attention.

4.1. Harmonization and differentiation among global regulatory agencies

Against the backdrop of global drug development integration, the regulatory review and post-marketing surveillance of innovative drugs increasingly reflect both harmonization and regional differentiation.

4.1.1. Approvals and requirements from global regulatory agencies

Regulatory agencies such as the FDA and EMA often grant conditional approval for innovative drugs targeting serious or life-threatening diseases based on limited clinical trial data. Consequently, these agencies commonly mandate Post-Authorisation Safety Studies (PASS) and Risk Management Plans (RMP) as prerequisites or post-approval commitments. This signifies that drug approval is not the endpoint of safety monitoring but rather the beginning of a new phase of continuous risk-benefit evaluation in broader, more heterogeneous populations [17].

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4.1.2. Regulatory requirements and local development of China's NMPA

The National Medical Products Administration (NMPA), as the regulatory agency in the country of origin, imposes comprehensive regulatory requirements. The Pharmacovigilance System Master File (PSMF) requirement is one of the core regulatory frameworks used to oversee the pharmacovigilance system [7].

Once a drug enters the Chinese market and is included in the NRDL, the NMPA's regulatory concerns exhibit distinct local characteristics. The surge in patient numbers and increased population diversity following NRDL inclusion create an urgent need for safety data derived from the Chinese real-world setting. Given potential differences in genetic background, epidemiological characteristics, medical practices, and concomitant medication patterns, the extrapolability of international clinical trial data may be limited [7]. Therefore, the NMPA increasingly emphasizes the generation and submission of real-world evidence based on the Chinese population to accurately identify and manage potential risks specific to the Chinese healthcare environment.

4.2. Special challenges after NRDL inclusion and strategies

The inclusion of a drug in the NRDL significantly improves patient access, but the consequent shifts in the clinical setting also introduce a series of new challenges that the pharmacovigilance system must address.

4.2.1. Expansion and diversity of the user population

Post-NRDL inclusion, the user population expands rapidly, encompassing more elderly patients, those with multiple comorbidities, polypharmacy, and hepatic or renal impairment. This sharp increase in population heterogeneity may lead to new drug-disease or drug-drug interactions and alter the incidence and severity of known adverse reactions. The core strategy to address this challenge involves strengthening the sensitivity and coverage of the ADR monitoring and reporting system within medical institutions [18]. Particularly, it is crucial to enhance the ability and awareness of healthcare professionals in primary care and non-specialist institutions to identify and report ADRs, ensuring the spontaneous reporting system effectively captures potential safety signals arising from real-world clinical practice.

4.2.2. Data gaps in long-term safety

Due to the limited follow-up duration inherent in clinical trials, it is difficult to fully assess potential delayed toxicities or long-term cumulative risks. As patients use the drug long-term under reimbursement coverage, the uncertainties associated with these data gaps are amplified [14]. Establishing hospital-based patient registries, which collect long-term clinical outcomes and safety events from large-scale user populations, is a key initiative. This approach is crucial for generating robust, long-term, real-world safety data specific to the Chinese population, directly addressing the limitations of trial data regarding rare or delayed events.

Furthermore, innovative applications of Artificial Intelligence (AI) in pharmacovigilance promise to enhance the precision and proactivity of drug safety monitoring [19]. To tackle challenges in pharmacovigilance, China's NMPA issued relevant documents in 2020 encouraging the use of big data and AI technologies to achieve intelligent functions such as data sharing and feedback, risk warning, and signal identification [7]. Leveraging big data and sophisticated algorithms, AI has the

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potential to mine more signals from complex unstructured data, providing the necessary data foundation to help fill these gaps [19].

4.2.3. Communication of drug safety information

As the prescribing physician base rapidly expands from core specialists to a vast number of primary care physicians, awareness of the drug's specific risks, necessary baseline assessments, monitoring parameters during treatment, and risk minimization measures is crucial. Therefore, establishing efficient, accurate, and continuous safety information communication channels is key to ensuring safe use post-NRDL inclusion.

Currently, many Marketing Authorization Holders (MAHs) assign low priority to pharmacovigilance and are insufficiently proactive in ADR collection and analysis [8]. MAHs need to collaborate with regulatory agencies to ensure critical safety information reaches all prescribers accurately and in a timely manner [20]. This can be achieved through measures such as promptly updating the product label, developing and distributing clinical practice guidelines, conducting systematic training for healthcare professionals, and utilizing digital information platforms to push safety alerts.

5. Conclusion

This paper used zanubrutinib as a case study to explore its pharmacovigilance system. The case demonstrates that innovative drugs in China should establish high-standard, internationalized pharmacovigilance systems from the R&D stage to meet global regulatory requirements and market expansion. Inclusion in the NRDL is not the finish line but rather the starting point for more intensive pharmacovigilance efforts. It is necessary to leverage the advantages of local data to continuously monitor, evaluate, and manage safety risks during widespread real-world use, ultimately safeguarding patients' long-term medication safety and contributing to the global safety database.

This study has several limitations. It primarily relies on available literature, regulatory documents, and corporate disclosures, without access to BeiGene's internal primary pharmacovigilance data or detailed operational procedures, which may limit the depth of analysis in certain areas. As the research focuses on a single prominent drug, the generalizability of the conclusions requires validation through more studies on similar products. Future studies should continuously track, evaluate, and acquire more granular operational data; conduct comparative multi-case studies; and perform long-term dynamic observations.

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