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MINIREVIEWS

Ibrutinib and atrial fibrillation: An in-depth review of clinical implications and management strategies

Moiud Mohyeldin, Shitij Shrivastava, Sai Vishnu Vardhan Allu

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Abstract

Ibrutinib, a targeted therapy for B-cell malignancies, has shown remarkable efficacy in treating various hematologic cancers. However, its clinical use has raised concerns regarding cardiovascular complications, notably atrial fibrillation (AF). This comprehensive review critically evaluates the association between ibrutinib and AF by examining incidence, risk factors, mechanistic links, and management strategies. Through an extensive analysis of original research articles, this review elucidates the complex interplay between ibrutinib's therapeutic benefits and cardiovascular risks. Moreover, it highlights the need for personalized treatment approaches, vigilant monitoring, and interdisciplinary collaboration to optimize patient outcomes and safety in the context of ibrutinib therapy. The review provides a valuable resource for healthcare professionals aiming to navigate the intricacies of ibrutinib's therapeutic landscape while prioritizing patient well-being.

Key Words: Ibrutinib; Bruton's tyrosine kinase inhibitor; Atrial fibrillation; Cardiovascular risk; Management strategies

Core Tip: This review examines the association between ibrutinib, a Bruton's tyrosine kinase inhibitor, and atrial fibrillation (AF). It explores the underlying mechanisms, clinical implications, and management strategies for AF in patients treated with ibrutinib. The article emphasizes the need for cardiovascular monitoring and alternative treatments to balance therapeutic efficacy and safety.

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INTRODUCTION

Ibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, has emerged as a pivotal therapeutic agent for B-cell malignancies, particularly chronic lymphocytic leukemia and mantle cell lymphoma[1,2]. While ibrutinib has demonstrated remarkable efficacy in improving progression-free survival and quality of life, concerns have arisen regarding its association with atrial fibrillation (AF)[3-6]. This comprehensive review aims to dissect the intricate relationship between ibrutinib and AF, encompassing incidence, risk factors, mechanistic underpinnings, clinical implications, and evolving management strategies. By providing valuable insights for informed decision-making, this review seeks to guide healthcare professionals in optimizing therapeutic outcomes while ensuring the cardiovascular well-being of patients receiving ibrutinib.

INCIDENCE AND RISK FACTORS OF ATRIAL FIBRILLATION WITH IBRUTINIB

Several studies have reported an increased incidence of AF in patients treated with ibrutinib[3-5,7,8]. In a pooled analysis of four randomized controlled trials, the incidence of AF was 6.5% in the ibrutinib group, whereas it was 1.6% in the comparator group (relative risk: 4.1; 95%CI: 2.2-7.5)[3]. The median time to AF onset was 2.8 months (range: 0.3-26.6 months)[3]. Risk factors associated with ibrutinib-related AF include older age, hypertension, prior history of AF, and the concomitant use of anticoagulants or antiplatelet agents[3,7]. Recent findings by Tang *et al*[9] further support the association between ibrutinib and cardiac side effects, including AF.

MECHANISTIC LINKS BETWEEN IBRUTINIB AND ATRIAL FIBRILLATION

The mechanisms linking ibrutinib to AF are multifaceted and involve various pathways[5,10-12] (Figure 1). Ibrutinib has been shown to inhibit PI3K-Akt signaling, leading to reduced phosphorylation of the protein kinase Ca^{2+}/calmodulin-dependent protein kinase II, which plays a crucial role in calcium handling and atrial electrophysiology[10-13]. The dysregulation of calcium homeostasis can trigger AF by promoting delayed afterdepolarizations and increasing atrial ectopy[11,12]. Additionally, ibrutinib inhibits the tyrosine kinase CSK, resulting in enhanced activity of Src kinases, which can modulate ion channel function and contribute to atrial remodeling[11,12,14]. Furthermore, ibrutinib has been associated with the inhibition of AMP-activated protein kinase, a key regulator of cellular energy homeostasis, potentially exacerbating oxidative stress and inflammation in the atrial myocardium[11,12]. McMullen *et al*[15] and Xiao *et al*[16] have provided evidence supporting the role of ibrutinib in increasing the risk of AF through inhibition of cardiac PI3K-Akt signaling and C-terminal Src kinase, respectively. Jiang *et al*[17] also highlighted ibrutinib's promotion of AF *via* structural remodeling and calcium dysregulation in the atrium.

CLINICAL IMPLICATIONS AND MANAGEMENT STRATEGIES

The association between ibrutinib and AF necessitates a multidisciplinary approach to patient care involving close collaboration among oncologists, cardiologists, and hematologists[10]. Baseline cardiovascular risk assessment, including electrocardiogram (ECG) and echocardiography, should be performed before initiating ibrutinib therapy[7]. Regular monitoring for signs and symptoms of AF, along with periodic ECG evaluations, is crucial for early detection and intervention[7].

Strategies for managing ibrutinib-associated AF involve a personalized approach tailored to individual patient characteristics and risk profiles[11,18]. In patients with a high risk of thromboembolism (CHA2DS2-VASc score ≥ 2), anticoagulation should be considered while weighing the benefits against the bleeding risk[12]. Novel oral anticoagulants have emerged as a promising option since their safety profile is more favorable than that of warfarin[12,19]. Rhythm control strategies, including pharmacological cardioversion and catheter ablation, may be considered in symptomatic patients or those with persistent AF[5].

Dose reduction or temporary interruption of ibrutinib may be necessary in cases of recurrent or symptomatic AF[7]. Alternative BTK inhibitors with potentially lower AF risk, such as acalabrutinib or zanubrutinib, can be considered in select patients[20,21]. Ongoing research aims to develop risk stratification tools and predictive models to identify patients with a higher risk of developing ibrutinib-related AF, enabling proactive management and personalized treatment decisions[7].

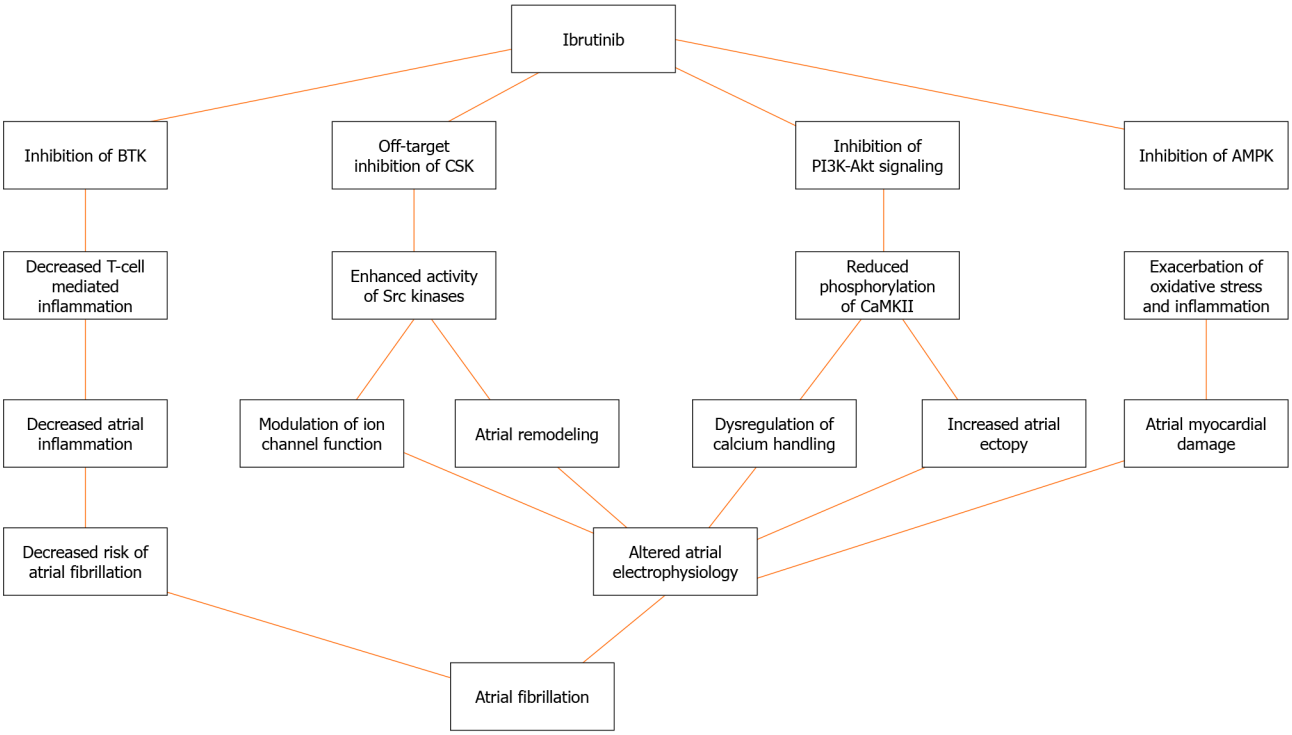

Figure 1 Mechanistic links between ibrutinib and atrial fibrillation. Ibrutinib inhibits various signaling pathways, including PI3K-Akt, CSK, and AMP-activated protein kinase, leading to the dysregulation of calcium handling, atrial remodeling, oxidative stress, and inflammation, ultimately contributing to the development of atrial fibrillation. BTK: Bruton's tyrosine kinase; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; CSK: C-terminal src kinase; AMPK: AMP-activated protein kinase.

CONCLUSION

The association between ibrutinib and AF represents a significant challenge in the management of patients with B-cell malignancies. This comprehensive review highlights the incidence, risk factors, mechanistic links, clinical implications, and evolving management strategies related to this complex relationship. By integrating insights from original research articles, this review provides a robust evidence base to guide healthcare professionals in navigating the intricacies of ibrutinib therapy while prioritizing patient safety and cardiovascular well-being. Multidisciplinary collaboration, personalized risk assessment, and tailored management approaches are paramount in optimizing outcomes for patients receiving ibrutinib. Ongoing research efforts aimed at unraveling the underlying mechanisms, developing risk stratification tools, and exploring alternative therapeutic options could refine the approach to managing ibrutinib-associated AF. As the therapeutic landscape continues to evolve, this review serves as a valuable resource for healthcare professionals seeking to balance the remarkable efficacy of ibrutinib with the need for vigilant cardiovascular monitoring and proactive management strategies. By staying abreast of the latest evidence and adopting a patient-centric approach, clinicians can harness the transformative potential of ibrutinib while minimizing cardiovascular risks and ensuring the best possible outcomes for patients with B-cell malignancies.

FOOTNOTES

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