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Recent Progress of Irreversible BTK Inhibitors

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Abstract. In recent years, Bruton tyrosine kinase (BTK) inhibitors that selectively inhibit B cell receptor (BCR) signaling have become a popular and effective treatment for lymphomas in the public. As the pivotal tyrosine kinase BTK regulates the BCR pathway, BTK inhibitors were developed to block the pathway by binding with BTK thereby relieving the B-cell lymphoma progression. Ibrutinib, the first-generation BTK inhibitor, can effectively inhibit BTK and alleviate various cancer diseases. However, ibrutinib's lack of selectivity has led to a series of side effects, having adverse effects on survival rates and tolerability. By altering the molecular structure, researchers have developed the next-generation irreversible BTK inhibitors aiming at increasing target specificity and decreasing off-target impacts, such as acalabrutinib, tirabrutinib, spebrutinib, branebrutinib, and zanubrutinib, who recently received approval by FDA. This article compares and analyzes the advantages and disadvantages of these irreversible BTK inhibitors, especially zanubrutinib, with ibrutinib and finally draws a conclusion.

Keywords: Bruton tyrosine kinase inhibitor; ibrutinib; zanubrutinib; safety; specificity.

1. Introduction

The BCR pathway facilitates the survival, differentiation, and clonal growth of cells by monitoring their activity and multiplication. Abnormal BTK activation is a significant oncogenic factor in a number of B-cell cancers [1]. BTK is required in the activation of myeloid cells and transduction of signals via the Fc and B cell receptors, which can monitor the physiological functions and development of B lymphocytes [2-4]. What's more, it has the properties of anti-apoptosis and anti-thrombosis in cancer cells, playing a key role in carcinogenic signaling [5]. Tyrosine kinase pathway dysregulation is the primary cause of leukemias in malignancy, including chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL), the two most prevalent hematological malignancies in the United States and Europe. The hyperactivated BTK signal pathway leads to abnormal reproduction of B cells, which causes a series of lymphoma diseases [6]. Nowadays, the promising treatment of these tumor diseases is BTK inhibitor therapy. This kind of therapy can prevent the growth and survival of target abnormal B cells by inhibiting BTK to alleviate the B-cell lymphoma progression. Ibrutinib, acalabrutinib, tirabrutinib, spebrutinib, branebrutinib, and zanubrutinib are covalent irreversible BTK inhibitors that bind with cysteine residue Cys-481 of BTK so that to exert a strong and sustained inhibitory effect on BTK enzyme activity [7]. These tyrosine kinase inhibitors have some manageably associated adverse events (AEs) and significantly improved prognosis of patients with hematologic malignancies. They have demonstrated promising benefits in several diseases including rheumatism, autoimmune diseases, inflammatory diseases, and B-cell lymphomas such as MCL, CLL, and Waldenstrom macroglobulinemia (WM) [8, 9]. In this article, I will focus on the description and comparison of some of the primary irreversible BTK inhibitors mentioned before, especially zanubrutinib, with ibrutinib in terms of pharmacological structure, design strategy, indications, clinical efficacy, and safety.

2. Ibrutinib

As the first-generation BTK inhibitor, ibrutinib was developed by Johnson and Alberta in 2007 and got approval in 2013 for the treatment of various B cell malignant tumors, which has shown

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significant benefits that changed the standard treatment and improved efficacy and safety versus traditional therapies [7, 10].

2.1. Design strategy

Ibrutinib downregulates NF-κB signaling and inhibits BCR signaling by covalently binding to Cys-481 with its acrylamide moiety (**Figure 1.**), significantly promoting cell apoptosis and reducing tumor growth through this process [11]. It also influences other TEC family kinases that regulate chemotaxis and intercellular signaling, enhance cell adhesion in the tumor microenvironment, and include interleukin-2 induced T cell kinase (ITK) [12]. Blocking ITK may improve Th1 differentiation and trigger anti-tumor responses since it promotes Th2 differentiation [10].

2.2. Preclinical study

Research showed that ibrutinib not only induces the apoptosis of BTK, but also leads to increased apoptosis of breast cancer cells by inhibiting ErbB3, HER2, EGFR, and some other receptors [10]. Similarly, due to the inhibitions on stimulating myeloid-derived suppressor cells (MDSCs), the signaling pathway of mammalian rapamycin target (Akt/mTOR) and serine/threonine-specific protein kinase, and other intrinsic kinases, ibrutinib has shown to be a successful treatment with significant benefits on the diseases in cellular or murine models mentioned above [13, 14]. However, these characteristics reflect the lack of selectivity of ibrutinib [10]. Thus, as a cost of having multiple treatment targets, it is easier to develop drug resistance and leads to more off-target effects, or non-selective inhibition, resulting in toxic AEs and affecting overall survival and drug safety. Therefore, this has propelled the process of exploring combination therapies and more selective next-generation BTK inhibitors.

2.3. Clinical studies and results

A series of clinical trials of ibrutinib has been conducted, demonstrating significant therapeutic effects on tumor diseases such as CML, CLL, SLL, and WM via the BTK inhibition mechanism. However, a high dose of 560mg per day is required in ibrutinib treatment to effectively achieve BTK targeting occupancy, possibly due to its oral bioavailability is low [15]. In addition, 60% of patients treated with ibrutinib were found to have drug resistance during subsequent follow-up and AEs occur more commonly, as the proteins other than TEC, EGFR, and BTK were inhibited [16]. The insufficient safety of Ibrutinib makes improving selectivity one of the main goals when developing the next-generation BTK inhibitors.

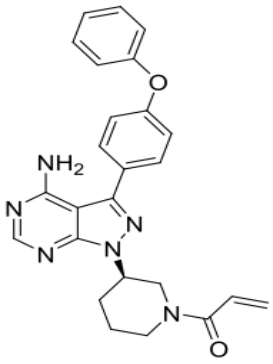

Figure 1. Structure of Ibrutinib. [7]

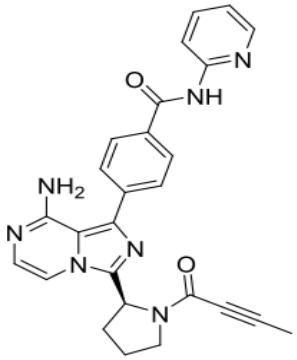

Figure 2. Structure of Acalabrutinib. [7]

3. Acalabrutinib

Acalabrutinib is a second-generation BTK inhibitor developed by AstraZeneca, which inhibits the BCR signaling pathway by reducing the PLCγ2 phosphorylation with a similar mechanism but higher selectivity, shorter plasma half-life, more favorable pharmacological properties, and lower off-target

effect versus ibrutinib. Acalabrutinib got its approval in 2017 for treating relapsed or refractory MCL and CLL [17-19].

3.1. Design strategy

The results of IC50 determinations on nine kinases showed that it is a cysteine residue situated similarly to BTK that brings acalabrutinib higher selectivity for BTK [20]. By optimizing its molecular structure (**Figure 2.**), acalabrutinib has higher selectivity for inhibiting BTK, BMX, and ErbB4 at clinical concentrations, demonstrating higher target specificity [21]. Compared with complete inhibition of TEC by ibrutinib, the selectivity for other TEC kinase family members of acalabrutinib is increased while it has no intervention on TEC, ITK, or EGFR, achieving less non-selective inhibition-related side effects caused and improved effectiveness [22]. The R&D team also improved the pharmacokinetic properties of acalabrutinib to ensure better stability and persistence in vivo. Furthermore, the selectivity for Src family kinases of acalabrutinib also contributes to better functional platelet thrombus formation over ibrutinib in non-Hodgkin lymphoma (NHL) patients [23, 24].

3.2. Preclinical study

Preclinical trials have studied the respective efficacy of acalabrutinib on primary cells and B cells with CLL via functional assays and signal transduction.

Tyrosine phosphorylation of downstream targets of ERK, IKB, and AKT was inhibited by acalabrutinib, as demonstrated by an in vitro signal transduction trial on primary human CLL cells [25]. Acalabrutinib also showed effects on inhibiting purified BTK in the activation of human CD69 B cells [26]. In a small animal model study, acalabrutinib reduced the self-phosphorylation of BTK to inhibit BCR signaling. Surface expression of CD69 and CD86, the markers of BCR activation, was also shown to be inhibited by acalabrutinib in the TCL1 adoption transfer. What's more, acalabrutinib could decrease the ERK and PLCγ2 phosphorylation to prevent the growth of human CLL cells in the murine spleen and reduce tumor burden with dose dependence [27, 28]. Another study on the B-cell NHL dog model showed that only half of the dogs had disease progression, indicating that acalabrutinib has monotherapy biological activity in large animals with NHL [29].

3.3. Clinical studies and results

According to the phase III study that compares acalabrutinib with ibrutinib, acalabrutinib has shown similar efficacy to Ibrutinib but fewer common clinical adverse reactions and cardiac events, achieving the primary endpoint of noninferiority. Among other selected secondary endpoints, both groups did not reach the median overall survival. What's more, other events that related to the natural course of CLL, mortality, Richter conversion, and level ≥ 3 infections were comparable. Acalabrutinib has much fewer treatment-related serious AEs and significantly lower discontinuation rates [17]. In general, acalabrutinib has non-inferior PFS with fewer cardiovascular AEs, demonstrating better safety and tolerability than ibrutinib [17].

4. Tirabrutinib

Being approved in 2020 by FDA for recurrent or refractory primary central nervous system lymphoma (PCNSL), and later approved by the JMPA for treating WM and lymphoplasmacytic lymphoma, tirabrutinib is made by Gilead and Ono Pharmaceutical, which has selectivity against important off-targets and shows clinical efficacy on several relapsed/refractory B-cell malignancies by suppressing aberrant B-cell receptor signaling in diseases [30,31].

4.1. Design strategy

Combined with the key fragments of ibrutinib as well as acalabrutinib, the parent nucleus of tirabrutinib changes to a structure with 6-aminopurine analog (**Figure 3.**), acilitating the formation of

hydrogen bonds, hydrophobic interactions, and Michael addition with Cys481 to help achieve efficient inhibition of BTK [30]. The value of IC50 is 2.2 nM, showing a comparable activity level to Ibrutinib. However, its IC50 values for other tyrosine kinases, such as Fyn, Lck, and Lyn, are all greater than 1 μM, demonstrating a higher selectivity [32].

4.2. Clinical studies and results

Patients who scored ≥ 70 in Karnofsky physical status with normal end-organ function were selected to respectively receive daily doses of 320 and 480 mg tirabrutinib treatment for recurrent or refractory PCNSL in the phase I study. The results showed no reached maximum dose at 480 milligrams and median overall survival at 2.9 months, no dose-limiting toxicity, and low rates of common AEs.

In the phase II study, tirabrutinib was used as a single agent at the dose of 480 mg once daily on an empty stomach and showed good stability and efficacy in both initial or relapsed WM patients [31]. After two years, the progression-free survival (PFS) and major response rate (MRR) of tirabrutinib were comparable with other existing BTK inhibitors at the time, indicating a favorable efficacy in patients with relapsed/refractory PCNSL [16, 33].

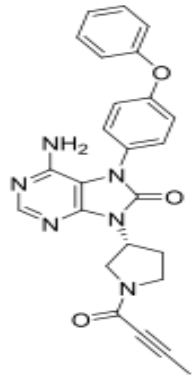

Figure 3. Structure of Tirabrutinib. [7]

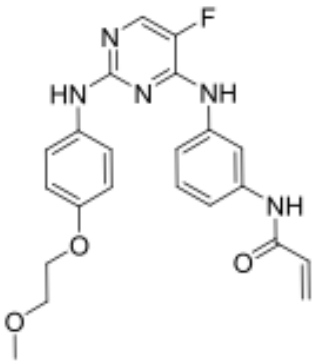

Figure 4. Structure of Spebrutinib. [7]

5. Spebrutinib

Spebrutinib, or AVL-292, in clinical trial still, has a selectivity of at least 1400 times for other tested kinases with IC50 value less than 0.5 nM. Same as other covalent BTK inhibitors, spebrutinib can effectively inhibit BTK kinase by binding stably with its cysteine residue, showing efficacy on treating CLL and RA [34].

5.1. Design strategy

The innovation in molecular structure is a highlight of spebrutinib (**Figure 4.**). In recent research, spebrutinib has been used as a starting point for designing BTK-targeted protein degrading agents called PROTACs, a new mechanism of action [35]. PROTACs show higher degradation efficiency and in vitro activity than the original spebrutinib, aiming to improve the degradation efficiency of BTK and expand its indications [35].

5.2. Preclinical study

Spebrutinib was tested with CIA murine models in the preclinical trial showed that the inhibition of arthritis progression is significantly dose-dependent, similar to dexamethasone [36]. Only half of BTK proteins existed within 1-2 days after receiving spebrutinib once, demonstrating great efficiency on BTK inhibition, though undetectable plasma levels and a long recovery time. The amount of BTK bound to spebrutinib is correlated with its efficacy in vitro and collagen-induced arthritis models of autoimmune diseases [37, 38].

5.3. Clinical studies and results

The first clinical trial conducted in a healthy population showed that spebrutinib has a good tolerance to sustain the participation of BTK protein in all cycles as monotherapy at the dose of 2mg/kg up to 1000 mg/kg orally at once or at twice [37]. In patients taking twice a day, the rate of BTK receptor occupancy was observed over 90% during the 4-hour and 24-hour periods [10]. However, its clinical activity, like the duration of remission, is relatively low versus ibrutinib [39]. Another clinical study evaluated spebrutinib with RA patients. Due to the inhibition of lymphokines and the formation of some cells by spebrutinib, the serum levels of some factors related to inflammation are reduced. [40]. Further more, spebrutinib has good performance in almost all the laboratory conditions in stability testing without noticeable degradation of analytes. However, the disadvantages of low extraction rate and slow metabolism in the body of spebrutinib may lead to its accumulation in the body but can be slowly cleared by the liver, which requires more monitoring in more experiments [34].

6. Branebrutinib

Branebrutinib is an effective BTK inhibitor belonging to the Tec family developed by Bristol Myers Squibb, who received accelerated approval by FDA in 2019 but still in the process [41].

6.1. Design strategy

The original intention of Branebrutinib's development was to provide both low expected human doses and rapid enzymatic inactivation in vivo. Branebrutinib optimized the geometry of the receptor and linker aiming to explore the low intrinsic reactivity of Cys481 to bond with electrophilic receptors thereby alleviating off-target interactions (**Figure 5.**), whose selectivity of branebrutinib towards BTK is >5000-fold that of more than 240 kinases, significantly reducing the selective inhibition of kinases and making branebrutinib excellent in tolerability [41]. Currently undergoing clinical studies, brentebrutinib is anticipated to have its application in treating immune-mediated illnesses such as arthritis in the future.

6.2. Preclinical study

The preclinical trials of branebrutinib were conducted on mouse models with lupus nephritis, or rheumatoid arthritis (RA) induced by collagen and collagen antibody. In the first group of mouse models, a strong inhibitory effect on BTK activity was observed at the dose of 0.2 mg/kg. In the second group of mouse models, strong in vivo therapeutic effects were also demonstrated, which can prevent some clinically significant diseases. In both models, oral administration once daily at a ≥ 0.5 mg/kg dose has achieved maximum efficacy of $\geq$ 90% BTK inactivation in vivo [41]. In addition, therapeutic efficacy has been observed in both animal models of rheumatism and immune-mediated diseases. Based on the observed therapeutic effects in animal models, the first human study was conducted [41, 42]. Its stability was also tested in cynomolgus monkeys and dogs. Finally, the researchers identified its 5a type, which has relatively higher bioavailability, higher dose stability, and better BTK inactivation, to accept clinical trials [41].

6.3. Clinical studies and results

The clinical trial evaluating branebrutinib in a healthy population has shown that branebrutinib therapy has rapid oral absorption and diffusion in plasma, a short half-life, no typical EGFR inhibition rash occupancy, and no delayed pharmacological dynamic effects [41, 42]. Oral administration of $\leq$ 30 mg branebrutinib had no significant safety findings, supporting its further exploration for immune-mediated diseases [42].

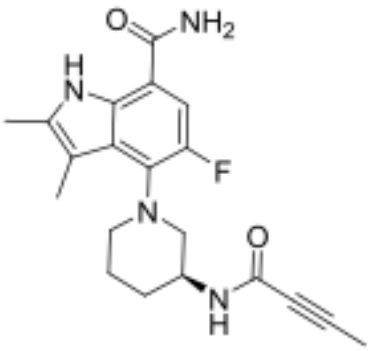

Figure 5. Structure of Branebrutinib. [7]

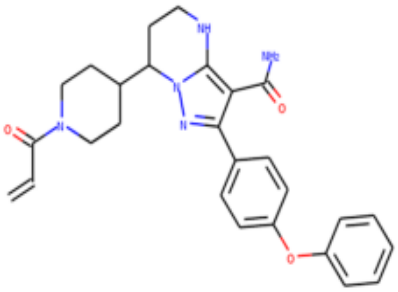

Figure 6. Structure of Zanubrutinib. [43]

7. Zanubrutinib

Zanubrutinib is the first Chinese independently researched and produced with independent intellectual property rights BTK inhibitor developed by Baiji Shenzhou and got its FDA approval in 2019 for advanced treated MCL [44]. And then being additionally approved around the country in 2020 and 2021.

7.1. Design strategy

Versus ibrutinib, zanubrutinib is an ATP structural analog that retains the diphenyl ether groups and electrophilic groups acrylamide without a pyrimidine ring (**Figure 6.**). The change in this structure reduces the appetency of zanubrutinib with other kinases, aiming to maximize BTK occupancy and reduce off-target effects towards kinases as much as possible, leading to better BTK inhibition rate and much lower toxicity than traditional BTK inhibitors [5, 10, 45]. Zanubrutinib does not inhibit ERBB2/HER2, which improves the phenomenon of myocardial cell dysfunction and decreased cardiac contractile efficiency observed in ibrutinib treatment [45]. In addition, other chemical modifications of zanubrutinib can improve its bioavailability and metabolic stability in vivo [45]. The high plasma level of zanubrutinib has the potential to penetrate bone marrow and lymph nodes. In addition, its steady exposure results in persistent inhibition of BTK of lymph nodes and peripheral blood monocytes, leading to a high peripheral blood BTK blockade/occupancy rate and the ability to achieve continuous therapeutic exposure and better bioavailability [46].

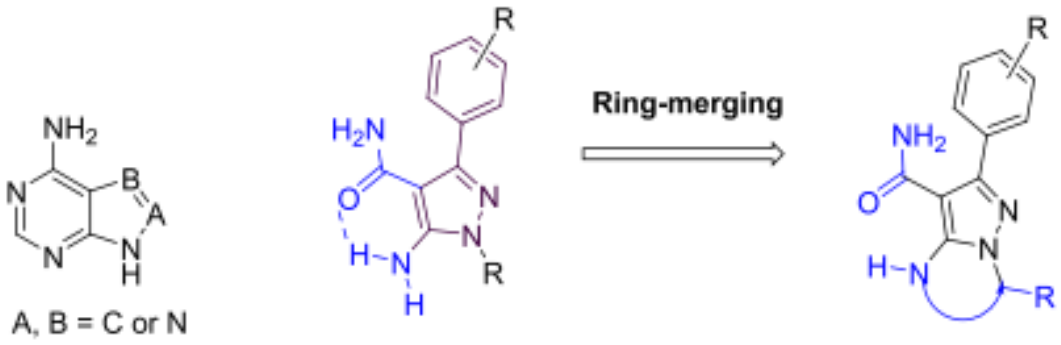

Figure 7. Structural Evolution of Zanubrutinib. [7]

7.2. Preclinical study

Preclinical studies have confirmed that zanubrutinib has greater specificity and bioavailability. Its activity and safety in treating B-cell malignancies agree with the results of AEs in preclinical studies. The following clinical projects then significantly expanded with ongoing studies in combination therapies and hemato-oncological diseases [46].

7.3. Clinical studies and results

One of the phase I studies of zanubrutinib indicated that zanubrutinib has achieved the expected therapeutic efficacy and has promissing tolerability, even at higher doses [46-48]. Another phase one study observed the response of patients with WM receiving continuously increasing doses of zanubrutinib exceeding 80mg per day. It was found that the immunoglobulin M response gradually improved, and the incidence of one of the AEs, atrial fibrillation, was lower than expected. It seems that the inhibition of BTK by zanubrutinib can be further optimized in WM [47]. Subsequently, an ASPEN study, published in 2024, showed that WM patients with CXCR4 or TP53 mutations treated with zanubrutinib showed more significant survival benefits than those treated with ibrutinib. Then based on its results of long-term follow-up, it can be confirmed that zanubrutinib has better long-term safety and tolerability, and can bring deeper, earlier, and more lasting relief to WM patients, further confirming zanubrutinib's leading position in BTKi [16]. What's more, in a recent phase I study, zanubrutinib showed good tolerability as monotherapy at the dose of 160mg twice or 320mg once daily, showing more safety than ibrutinib [49]. The SEQUOIA study and the ALPINE study have been the basis for zanubrutinib's approval by the FDA in 2023, whose results show that zanubrutinib has significantly higher ORR and PFS, even evident in subgroups and mutation groups, and lower AEs and cardiac events including those lead to drug withdrawal or death [50]. In addition, in the ASPEN study on Fahrenheit macroglobulinemia, patients in the zanubrutinib group had significantly less diarrhea at all levels, more stable hypertension tendency, lower incidence of adverse cardiac events, and lower incidence of discontinuation or death-related AEs [50, 51]. All of these demonstrate that zanubrutinib has significant advantages over ibrutinib in all aspects and is an advanced BTK inhibitor. Additionally, Zanubrutinib shows better economic benefits compared to ibrutinib among the statistics of the comparisons of cost-effectiveness from both the American ASPEN trial and cost-effectiveness analyses (CEAs) [52, 53].

8. Conlcusion

BTK inhibitors are developed for cancer treatment based on human understanding of the BCR signaling pathway that differs from traditional therapies. Since the emergence of ibrutinib, hundreds of new-generations BTK inhibitors are still in trials to further understand the effectiveness of BTK inhibitors on more target cells and the overall internal environment of tumors. Some novel inhibitors with significantly effective and safe against a range of malignant tumors have not been confirmed a stable long-term efficacy yet. More long-term clinical researches are needed. All types of identified protein kinases require ATP as a cofactor, leading to some AEs because of non-selective inhibitions. Moreover, the mutagenicity of malignant tumor cells can lead to possibly drug resistance. Thus, the updated iteration of BTK inhibitors seems to be an eternal battle. Along the history of BTK inhibitors, their specificity was continuely increased as the off-target side effects significantly reduced. As the latest effectively selective inhibitor of BTK, zanubrutinib is a representative of continuously developing anti-cancer strategies. Future studies on combination therapy, mutation screening, and the development of next-generation BTK inhibitors will be conducted, aiming to alleviate adverse reactions caused by non-selective inhibition and the impact of drug resistance [10]. Zanubrutinib is a breakthrough and a more cost-effective choice to achieve more significant OR and PFS and bring a better outcome as well as a bright future for patients who suffer from tumor diseases [52].

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