Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Mini Review

Highly Specific JAK3 Inhibitors and the Future of T cell Lymphoma Treatment

Wei Chen*

Department of Lymphoid Malignancies, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA

ABSTRACT

Janus kinse-3 (JAK3) exclusively associates with common gamma chain (γc) receptor of γc-cytokines. When γc cytokines, such as IL-2, IL-15, IL-21, IL-4, IL-7 and IL-9, bind their receptors, JAK3, in combination with JAK1 and downstream signal transducers and activators of transcription, STATs, initiate critical signaling cascades. These pathways underlie the hematopoiesis, proliferation and differentiation of normal hematopoietic cells. Conversely, the aberrant, constitutive activation of the JAK-STAT signaling pathways, including JAK3's, is associated with immune related disorders and cancers. Thus, inhibition of JAK-STAT signaling and their downstream tyrosine kinases have provided a therapeutic approach for treatment of several hemopoietic malignancies, especially T cell lymphomas. These cells typically harbor activating JAK mutations that lead to increased JAK-STAT signaling. In this review, we summarize the most recent developments of the JAK3 inhibitors on treatment of T cells lymphomas.

Keywords: JAK3 inhibitors; T cell lymphoma; Mutation; Pharmacological use; Clinical trials

INTRODUCTION

In the most recent years, progresses in the basic and translational researches have already identified more and more pathways and molecular targets that regulate host immune responses, leading to the development of new drugs with high specificities. Among them, targeting JAK-STAT pathways has been demonstrated great potential in the treatment of multiple malignancies.

This is enhanced by the fact that common JAK-STAT molecules initiate the signal transduction of many different cytokines and ligands [1].

In the past decades, JAK inhibitors, blocking one or more JAK molecules, have been developed and tested in clinical trials for many immune related disorders [2]. Herein, we describe JAK3 inhibitors that have been tested in basic experiments as well as preclinical trials on T-cell lymphoma, these include, Natural Killer Cell Lymphoma (NKTL), T-Acute Lymphoblastic Lymphoma/Leukemia (T-ALL), and ALK-Positive Anaplastic Large Cell Lymphoma (ALCL).

LITERATURE REVIEW

The JAK/STAT pathway

The Janus Kinase (JAK) family of tyrosine kinases is composed of four members: JAK1, JAK2, JAK3 and TYK2 [3]. JAK kinases, associated with specific receptors, are activated after ligands, such as cytokines, growth factors or interferons, bind to their cell-surface receptor resulting in receptor dimerization and JAKs being brought into proximity of one another. Activated JAKs then phosphorylate STAT binding sites on the receptor, allowing STATs to dock. STATS are subsequently phosphorylated and released, and form homo or hetero dimers with other pSTATs that move to the cell's nucleus. The pSTATs bind to specific DNA target sequences and finally activate gene transcription. The JAKs always function as pairs, such as JAK3 together with JAK1 are required for each other's phosphorylation. JAK3 is predominantly expressed in lymphoid tissues, although the JAK1, JAK2 and TYK2 are expressed universally. JAK3 selectively binds to the γc receptor, which is a receptor for the γc cytokines:

Correspondence to: Wei Chen, Department of Lymphoid Malignancies, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA, Tel: 240-858-3484; E-mail: wei.chen5@nih.gov

Received: 10-Aug-2022; Manuscript No. JLU-22-18779; **Editor assigned:** 12-Aug-2022; Pre-Qc No. JLU-22-18779 (PQ); **Reviewed:** 25-Aug-2022; Qc No. JLU-22-18779; **Revised:** 29-Aug-2022, Manuscript No. JLU-22-18779 (R); **Published:** 07-Sep-2022, DOI: 10.35248/2329-6917.22.10.311.

Citation: Chen W (2022) Highly Specific JAK3 Inhibitors and the Future of T cell Lymphoma Treatment. J Leuk.10:311.

IL-21, IL-4, IL-7 and IL-9 which are also paired with a signaling, cytokine-specific, alpha chain; IL-15, and IL-2, which are paired with a common beta chain (IL-2/IL-15Rß) and a specific non-signaling alpha chain [1]. JAK3 is an important regulator for development and function of lymphocytes, such as T cells, B cells and NK cells [4]. Loss-of-function mutations in JAK3 cause severe combined immunodeficiency (JAK3-SCID) in humans. Also, a similar phenotype has been described in JAK3 knockout mice. Deficiencies of γc also cause X-linked SCID (X-SCID) in humans and animal models [5]. Its specific expression pattern and functions make JAK3 as a potential target in the treatment of hematological cancers [6,7].

To date, gain-of-function mutations in JAK3 have been described in many hematological malignancies, especially all forms of T cell leukemia and lymphoma. For example, Some JAK3 mutations (L156P, E183G, R172Q) were found in adult T-cell leukemia/lymphoma(ATLL) and some (A572V, A573V) were found in Cutaneous T-cell Lymphoma(CTCL), and some (L857P, V674A, M511I, A573V) in T Acute Lymphoblastic Lymphoma/Leukemia(T-ALL), some (A572V,A573V,V722I) were found in Natural Killer Cell Lymphoma(NKTL). As well as the JAK3 mutation (Q501H, Q507P, R657Q/W, V674A, V678L, V722I) in the T Cell Prolymphocytic Leukemia (T-PLL) [8,9]. The importance of constitutive activation of JAK3 signaling in T cell lymphoma makes the development of specific immunosuppressive drugs targeting JAK3 more attractive. Considering JAK3 is restricted to the immune system and the others are expressed much more ubiquitously, a selective inhibitor only targeting JAK3 could reduce the off-target effects and improve the efficacy [10]. Therefore, JAK3 inhibitors have been used in basic and preclinical studies as potential therapeutic agents to treat T cell lymphoma.

Several JAK3 inhibitors have been studied in T cell lymphoma. The first drug approved by the FDA was to facitinib (known as CP-690,550 previously), a type I JAK inhibitor targeting JAK3. This drug is also being evaluated for the treatment of T cell-initiated autoimmune disorders, such as Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), psoriasis as well as Inflammatory Bowel Disease (IBD), and applications for organ transplantation. Although first tested as a selective JAK3 inhibitor, tofacitinib also inhibits JAK1, and its efficacy is mostly based on the combined inhibition of JAK1 and 3 kinases, it is now considered a pan-JAK inhibitor rather a specific JAK3 inhibitor [11]. There are also another five JAK inhibitors, ruxolitinib (JAK1/2 inhibitor), upadacitinib (selective JAK1 inhibitor), fedratinib (selective JAK2 inhibitor), abrocitinib (selective JAK1 inhibitor) and baricitinib (JAK1/2 inhibitor) approved by FDA for the treatment of immune disorders [2,12,13]. However, all of them are not JAK3 selective inhibitors. They inhibit JAK1/2 or TYK2 with selectivity over JAK3. Due to the pan expression of JAK1 amd 2 kinases, all these approved drugs have severe side effects, such as headache, diarrhea, serious infections and even heart attack [14].

JAK3 inhibitors in preclinical trials for T cell lymphoma

Recently, the major discovery of selective JAK3 inhibitors have increasingly focused on targeting the cysteine residue (Cys909), which located in the ATP binding site and is the key figure for the development of the JAK3 inhibit selectivity over the other JAK family members [15]. The academic and industrial research groups embarked on drug discovery projects aimed to achieve high selectivity for JAK3 over other JAK kinases [16]. The majority of them are at the very early stage of development, however, ritlecitinib (PF06651600), has been tested in both mouse models and in clinical trial for RA [17]. Only few of them focused on the treatment of T cell lymphoma by JAK3 inhibitors, such as PRN371, EP009 and NIBR3049 [18-20].

The new JAK3 inhibitor, PRN371 is developed to improve the therapeutic effects through the JAK3 inhibition in Natural Killer/T-Cell Lymphoma (NKTL). It is a small molecule with high selectivity and durability, which potently inhibits the activity of JAK3 kinase over the other JAK kinases, JAK1, JAK2 and TYK2. PRN371 is shown to specifically bind to cysteine 909 pocket binding site of JAK3 kinase and effectively suppress the proliferation of the NKTL cells as well as induce apoptosis of NKTL cells through abrogation of the JAK3-STAT signaling pathway. Also, because of covalent and irreversible engagement of the target cysteine, the activity of PRN371 has a more durable inhibition on JAK3 compared to facitinib, *in vitro*, on cell lines harboring JAK3 activating mutations. Moreover, PRN371 is found to increase the phosphorylation of JAK3 through activation of an auto-feedback loop. These data suggest that PRN371 may have a higher anti-tumor activity and fewer side effects than to facitinib. Also, they demonstrate that PRN371 induces significant inhibition of tumor growth in NKTL subcutaneous xenograft model with JAK3 constitutively activated *in vivo*. These findings of the new JAK3 inhibitor PRN371 provide a novel approach of JAK3 targeted therapy for the treatment of NKTL.

DISCUSSION

In another study, Elisabeth Losdyck and her colleagues investigated the effects of another JAK3-specific inhibitor, NIBR3409, in a mouse model of T Acute Lymphoblastic Lymphoma/Leukemia (T-ALL) containing JAK3 mutants in the FERM domain, JAK3L857P and JAK3L857P/Y100A [21]. Since the residue L857P is the key domain inducing constitutive activation of JAK3 kinase, they first transformed JAK3L857P and JAK3L857P/Y100A JAK3 mutants into Ba/F3 cells to activate of JAK3 kinase and intriguingly, these transformed cells are more sensitive to NIBR3049. The calculated IC50 values are similar to ruxolitinib (JAK1/2 inhibitor) but higher than to facitinib (JAK1/3 inhibitor). Also, NIBR3049 is found to block STAT5 and JAK3 phosphorylation completely in the Ba/F3 cells with the JAKL857P/Y100A mutant, confirming their sensitivity to this molecule. However, in similar studies, NIBR3049 barely interfered with the phosphorylation of STAT5 and JAK1 with the classic JAK3 mutant, JAK3V674A. Thus, in this case, by inducing increases in JAK3 phosphorylation, NIBR3049, as a type I inhibitor, blocked JAK3 in the active conformation without affecting the kinase activity of the JAK1 partner. Nevertheless, these results show that JAK3 can serve as a potent scaffold in the receptor complex to enable JAK1 constitutive kinase activity. Therefore, it is also important to the select different JAK inhibitors in the treatment of the T-ALL based upon specific mutations. Depending on the specific mechanisms

of signal transduction inhibition, different JAK inhibitors have distinct efficacy on blocking different JAK3 mutants.

In a recent report, Ross JA, et al identified a novel selective inhibitor of JAK3 kinase, named EP009, which is further developed from the JAK3 inhibitor, NC1153 [22]. They first tested the anti-tumor efficacy of EP009 with the JAK3 dependent tumor cell line as well as the leukemia patients' PBMCs. SU-DHL-1 is ALK-positive anaplastic large cell lymphoma (ALCL) cell line.

Tumor growth is inhibited by the EP009 through inhibition of JAK3 kinase and induction of apoptosis. Further, they set up a SCID/NOD murine xenograft model with this human T-NHL ALCL to evaluate therapeutic efficacy of EP009 *in vivo*. Tumor growth is inhibited only after greater tissue accumulation through oral administration. However, once tumor responses are established, the inhibition is maintained for the duration of the treatment. In conclusion, the effects of the EP009 on JAK3 could serve as a potent therapeutic strategy for intervention in hematopoietic malignancies with constitutive activated JAK3 mutants as an oncogenic driver, such as ALK-positive T-NHL ALCL. Thus, EP009 causes a viable therapeutic efficacy for the treatment of JAK3-dependent T-cell malignancies [23,24].

CONCLUSION

Aberrant JAK/STAT signaling is associated with hematopoietic malignancies which mainly harbor somatic JAK mutations that constitutively activate JAK/STAT signaling. JAK inhibitors have been demonstrated their potential on the therapy of immune disorders, such as Rheumatoid Arthritis, and some of them have already been tested in clinical trials for the hematopoietic malignancies, such as AZD4205 (selective JAK1i) on PTCL(NCT04105010). However, since many of JAK inhibitors are pan-inhibitor or will inhibit other JAKs at high concentrations *in vivo*, there have been abundant off-target effects and diverse side effects correlated with the administration of the JAK inhibitors.

Thus, the highly selective inhibitor of JAK3 has been recognized as an alternative, attractive candidate since expression of JAK3 is restricted to the hematopoietic lineage cells and JAK3 is associated exclusively with the common gamma chain.

The most recent approach to discover the highly selective JAK3 inhibitors has primarily focused on targeting the cysteine residue, Cys909, to generate selectivity over the other JAK family members, and the enzymatic outcomes have successfully translated into *in vitro* and *in vivo* potency selectively, such as NIBR3409, EP009 and PRN371. The future work will be testing these potent inhibitors to further reveal its efficacy on hematopoietic malignancies in human patients.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENT

Thanks to Richard N. Bamford (Transponics, Essex Junction, and Vermont 05452) and Tony Hsiao (National Cancer Institute), for helping me a lot on the manuscript editing.

REFERENCES

1. Waldmann TA. JAK/STAT pathway directed therapy of T-cell leukemia/lymphoma: Inspired by functional and structural genomics. Mol Cell Endocrinol. 2017;451:66-70.
2. Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A Comprehensive overview of globally approved jak inhibitors. Pharmaceutics. 2022;14(5):1001.
3. Hu X, li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduction and Targeted Therapy. 2021;6(1):402.
4. Liao W, Lin J-X, Leonard WJ. IL-2 family cytokines: New insights into the complex roles of IL-2 as a broad regulator of T helper cell differentiation. Current Opinion in Immunology. 2011;23(5): 598-604.
5. Shuai K, Liu B. Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol. 2003;3(11):900-911.
6. Li B, Wan Q, Li Z, Chng WJ. Janus kinase signaling: Oncogenic criminal of lymphoid cancers. Cancers (Basel). 2021;13(20):5147.
7. Vainchenker W, Constantinescu SN. JAK/STAT signaling in hematological malignancies. Oncogene. 2013;32(21):2601-2613.
8. Simpson HM. Investigating the role of common gamma chain signaling in peripheral T-cell lymphoma. University of Maryland Dissertation or Thesis. 2017.
9. Waldmann TA, Chen J. Disorders of the JAK/STAT pathway in T cell lymphoma pathogenesis: Implications for immunotherapy. Annu Rev Immunol. 2017;35:533-550.
10. Thoma G, Drückes P, Zerwes HG. Selective inhibitors of the Janus kinase Jak3: Are they effective? Bioorg Med Chem Lett. 2014;24(19): 4617-4621.
11. Dhillon S. Tofacitinib: A Review in rheumatoid arthritis. Drugs. 2017;77(18):1987-2001.
12. Giollo A, Fuzzi E, Doria A. Methotrexate in early rheumatoid arthritis: Is the anchor drug still holding? Autoimmunity Reviews. 2022;21(4):103031.
13. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: A systematic review and Meta-Analysis. Gastroenterology. 2020;158(6):1554-1573.
14. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. US FDA. 2021.
15. Forster M, Gehringer M, Laufer SA. Recent advances in JAK3 inhibition: Isoform selectivity by covalent cysteine targeting. Bioorg Med Chem Lett. 2017;27(18):4229-4237.
16. Dai J, Yang L, Addison G. Current Status in the Discovery of covalent Janus Kinase 3 (JAK3) inhibitors. Mini Rev Med Chem. 2019;19(18):1531-1543.
17. Robinson MF, Damjanov N, Stamenkovic B, Radunovic G, Kivitz A, Cox L, et al. Efficacy and safety of PF-06651600 (ritlecitinib), a novel JAK3/TEC inhibitor, in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate. Arthritis & Rheumatology. 2020;72(10):1621-1631.
18. Losdyck E, Hornakova T, Springuel L, Degryse S, Gielen O, Cools J, et al. Distinct Acute Lymphoblastic Leukemia (ALL)-associated Janus Kinase 3 (JAK3) Mutants Exhibit Different Cytokine-Receptor

Requirements and JAK Inhibitor Specificities. J Biol Chem. 2015;290(48):29022-29034.

19. Nairismagi M, Gerritsen ME, Li ZM, Wijaya GC, Chia BKH, Laurensia Y, et al. Oncogenic activation of JAK3-STAT signaling confers clinical sensitivity to PRN371, a novel selective and potent JAK3 inhibitor, in natural killer/T-cell lymphoma. Leukemia. 2018;32(5):1147-1156.
20. Ross JA, Spadaro M, Rosado DC, Cavallo F, Kirken RA, Pericle F. Inhibition of JAK3 with a novel, selective and orally active small molecule induces therapeutic response in T-cell malignancies. Leukemia. 2014;28(4):941-944.
21. Thoma G, Nuninger F, Falchetto R, Hermes E, Tavares GA, Vangrevelinghe E, et al. Identification of a potent Janus kinase 3 inhibitor with high selectivity within the Janus kinase family. J Med Chem. 2011;54(1):284-288.
22. Stepkowski SM, Kao J, Wang ME, Tejpal N, Podder H, Furian L, et al. The Mannich base NC1153 promotes long-term allograft survival and spares the recipient from multiple toxicities. J Immunol. 2005;175(7):4236-4246.
23. Su Q, Banks E, Bebernitz G, Bell K, Borenstein CF, Chen H, et al. Discovery of (2 R)-N-(3-(2-((3-Methoxy-1-methyl-pyrazol-4-yl) amino) pyrimidin-4-yl)-1H-indol-7-yl)-2-(4-methylpiperazin-1-yl) propenamide (AZD4205) as a Potent and Selective Janus Kinase 1 Inhibitor. J Med Chem. 2020;63(9):4517-4527.
24. Lv K, Li X, Yu H, Chen X, Zhang M, Wu X. Selection of new immunotherapy targets for NK/T cell lymphoma. Am J Transl Res. 2020;12(11):7034-7047.