



Mini Review

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# Immune Thrombocytopenia, Chronic Myeloid Leukemia, and Tyrosine Kinase Inhibitor Therapy

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## Article Info

### Article Notes

Received: December 23<sup>rd</sup>, 2025

Accepted: March 5<sup>th</sup>, 2026

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### Keywords

Immune Thrombocytopenia  
Chronic Myeloid Leukemia  
Tyrosine Kinase Inhibitor  
Imatinib  
Immunological Off-target Effects  
Bruton's tyrosine kinase

## ABSTRACT

Immune thrombocytopenia (ITP) and chronic myeloid leukemia (CML) are rarely observed concurrently. We recently reported a case of ITP in which CML developed over the course of the disease. Although the patient exhibited resistance and intolerance to corticosteroid therapy for ITP, thrombocytopenia improved following treatment with a tyrosine kinase inhibitor (TKI), imatinib, as a CML-directed therapy. We postulate that the off-target effects of TKI improve ITP by suppressing autoimmune responses. TKIs exert significant off-target multi-kinase inhibitory effects, including stimulatory and suppressive effects on the immune system. In addition to the immunomodulatory effects of T and natural killer cells, which elicit cytotoxicity against leukemic cells, TKIs also impair B cell-mediated humoral immunity. Notably, Bruton's tyrosine kinase, which has recently emerged as a therapeutic target in immunosuppressive treatment for ITP, has been demonstrated to be suppressed by the off-target effects of TKIs. Drawing on our clinical observations, this mini-review summarizes the association between ITP and CML, the immunological off-target effects of TKIs, and their potential therapeutic applications in autoimmune diseases, including ITP.

## Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder with a complex pathogenesis, characterized by peripheral destruction of platelets opsonized by antiplatelet autoantibodies, impaired thrombopoiesis, and T cell-mediated platelet destruction<sup>1</sup>

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia (Ph) chromosome, which is defined by the *BCR::ABL1* oncogene encoding a constitutively activated tyrosine kinase<sup>2</sup>.

Although ITP and CML are relatively common hematological diseases, they rarely occur concurrently. Recently, we reported a patient who developed CML after being diagnosed with ITP<sup>3</sup>. Corticosteroid therapy for ITP produced only a partial response and was maintained at the minimum effective dose due to exacerbation of concomitant diabetes mellitus. Subsequent tyrosine kinase inhibitor (TKI) therapy with imatinib for CML resulted in a deep molecular response. Interestingly, the thrombocytopenia improved, enabling corticosteroid discontinuation. Given the potential beneficial effects of TKI in ITP, we postulated that its off-target effects may suppress autoimmune response. Alternatively, immune reconstitution by non-leukemic cells or attenuation of the response to CML may have contributed to the observed improvement in ITP.

Based on our experience and observations, this mini-review

summarizes the association between ITP and CML, the immunological off-target effects of TKIs, and the potential application of TKIs in autoimmune diseases, including ITP.

## Methods

The literature search for this review formation was conducted in the PubMed database using combinations of the following keywords: “immune thrombocytopenia”, “chronic myeloid leukemia”, “imatinib”, “immunological off-target effect”, “immunomodulation”, “immunostimulation”, and/or “immunosuppression”. To describe immunological off-target effects, the author selected relevant preclinical studies reporting the effects of imatinib on immune cells.

## Association between ITP and CML

Autoimmune or chronic inflammatory diseases are known to be associated with the development of hematological malignancies, particularly malignant lymphomas, chronic lymphocytic leukemia, acute myeloid leukemia, and myelodysplastic syndrome<sup>4-6</sup>. A nationwide large-scale investigation of the Swedish population revealed that the prevalence of prior autoimmune diseases and malignancies was higher in patients with CML than in matched controls, suggesting that a hereditary or acquired predisposition to cancer and/or autoimmunity is involved in the pathogenesis of CML<sup>7</sup>. In this study, two cases of ITP diagnosed before CML are reported, although their clinical features are not described.

However, documented cases of CML occurring after diagnosis of ITP remain limited, and only five such cases, including ours, have been found in the literature<sup>3,8-11</sup>. Two of these were pediatric ITP cases that later became refractory to corticosteroids and splenectomy and subsequently developed CML 7.5 or 29 years after the initial ITP diagnosis<sup>8,9</sup>. The remaining cases involved adult patients who developed CML 5 or 15 years after initial ITP diagnosis<sup>3,10,11</sup>. Notably, two of the three adult cases were managed with eltrombopag, a thrombopoietin (TPO) receptor agonist, after ITP became refractory to corticosteroids<sup>10,11</sup>. In these reports, long-term use of a TPO receptor agonist was proposed to increase the risk of CML onset.

A previous study revealed that Ph chromosomes are present in myeloid cells and most B cells, but not in mature T cells or natural killer (NK) cells in CML, despite the involvement of multipotent hematopoietic stem cells<sup>12</sup>. In the present case, ITP preceded the CML. The subsequent coexistence of ITP and CML suggested that autoreactive B cells persisted even after the replacement of the hematopoietic and immune systems by the CML clone. Whether CML cells exhibit enhanced pathological immune activity driven by the BCR::ABL1 tyrosine kinase remains unclear.

The causal relationship between the TKI therapy and the improvement of ITP in our case remains undetermined. However, if imatinib exerts favorable effects on ITP, immunosuppression, especially the reduction of autoantibody production by B cells, through off-target effects appears to play a key role. Alternatively, the reconstitution of the immune systems by Ph-negative hematopoietic cells and changes in the immunological environment after TKI therapy may have exerted favorable effects on ITP, in addition to the immunological off-target effects of TKIs.

## TKI therapy for CML

The BCR::ABL1 fusion protein, which is exclusively expressed in CML cells, plays a key role in leukemogenesis, and has been investigated as a therapeutic target for TKIs for decades<sup>2</sup>. Based on their mechanism of action, BCR::ABL1 inhibitors can be classified into two types: ATP-competitive inhibitors (imatinib, nilotinib, dasatinib, bosutinib, and ponatinib) and allosteric inhibitors (asciminib). TKIs have markedly reduced CML-related mortality, with patients exhibiting survival rates comparable to those of the age-matched general population<sup>2</sup>

TKIs are known to cause a variety of agent-specific or non-specific toxicities, including myelosuppression (all TKIs), edema and skin rash (imatinib), pleural effusion (dasatinib), arterio-occlusive events such as myocardial infarction, stroke, peripheral artery disease (nilotinib and ponatinib), gastrointestinal disturbance (bosutinib), and hyperamylasemia/hyperlipasemia or pancreatitis (nilotinib, ponatinib, and asciminib)<sup>2,13</sup>. Although inhibition of BCR::ABL1 kinase activity represents the primary mechanism of action of TKIs, they do negatively regulate various kinases beyond ABL1 and extensive research has been conducted to identify additional targets. For instance, imatinib inhibits KIT, PDGFRA/B, LCK, DDR1/2, and NQO2 in addition to ABL1/2<sup>13</sup>. Thus, imatinib is also used to treat chronic eosinophilic leukemia, atypical myelodysplastic/myeloproliferative neoplasms, and gastrointestinal stromal tumors, by targeting PDGFRA/B or KIT. Knowledge of the differential mechanisms of action and target profiles of individual drug across available TKIs should be considered when managing patients with CML. This may guide the selection of optimal TKI to achieve better clinical outcomes and tolerability related to the on- and off-target effects of the drugs.

## Immunological off-target effects of imatinib

TKIs have been shown to affect T cells, NK cells, dendritic cells, monocytes/macrophages, and B cells, thereby modulating kinase activity in these cells via off-target mechanisms<sup>14</sup>. KIT, FLT3, LCK, macrophage colony-stimulating factor receptor (FMS), and Bruton's tyrosine kinase (BTK) are direct targets of kinase inhibition

by imatinib<sup>14</sup>. Many previous studies have focused on immunomodulatory activity to elicit cytotoxicity against CML cells. Because TKIs do not affect stem cells in CML, efficient immunosurveillance by both effector and regulatory immune cells has been suggested to eradicate tumor cells<sup>14</sup>.

Reports on the immunostimulatory effects of imatinib in preclinical models are presented in Table 1. Imatinib has been demonstrated to enhance antigen-presenting cell function<sup>15,16</sup>, activate NK cells<sup>17,18</sup>, impair immunosuppressive function and FoxP3 function of regulatory T cells, probably by inhibiting the phosphorylation of ZAP70 and the linker of activated T cells (LAT) and subsequently reducing the activation of STAT3 and STAT5<sup>19</sup>. Imatinib is also shown to revert immunosuppressive polarization of M2 macrophage and provide M1-polarized M2 macrophage with the capability of activating NK cells<sup>18</sup>.

In contrast, as shown in Table 2, preclinical studies revealed that imatinib treatment is associated with various types of immunosuppression. For instance, imatinib has been demonstrated to inhibit the differentiation of dendritic cells and the induction of primary cytotoxic T-lymphocyte response through reduced phosphorylation of AKT and down regulation of nuclear-localized NF- $\kappa$ B<sup>20,21</sup>. Another study reported the impairment of FLT3L-mediated dendritic cell expansion by imatinib<sup>22</sup>. Furthermore, studies have reported that imatinib inhibits T-cell proliferation by inhibiting the phosphorylation of LCK<sup>23,24</sup>, ERK1/2<sup>23</sup>, ZAP70<sup>24,25</sup>, and LAT<sup>24</sup>. Imatinib was also shown to reduce secondary expansion of antigen-experienced memory CTLs and delay the onset of autoimmune diabetes in a murine model<sup>26</sup>, inhibit antigen-specific memory CD8+ T cell responses by reduction of IL7 receptor  $\alpha$ <sup>27</sup>, and induces T-cell lymphopenia through the inhibition of STAT5 phosphorylation in response to IL-7 signaling<sup>28</sup>.

TKIs have also been shown to inhibit the growth and development of monocytes and/or macrophages by inhibiting FMS phosphorylation<sup>29</sup>, impairing class switch recombination of the immunoglobulin heavy chain gene through the down-regulation of activation-induced cytidine deaminase<sup>30</sup>, and impairing cell signaling and survival by inhibiting BTK phosphorylation, resulting in reduced numbers of IgM-producing memory B cells and humoral responses to influenza and pneumococcal vaccination<sup>31</sup>.

Some studies have reported controversial results regarding the influences of imatinib on immune function. Experimental variations under different *in vitro* conditions may explain the conflicting data. The immunostimulatory off-target actions of imatinib may contribute to its anti-tumor effects. In contrast, despite the immunosuppressive *in vitro* data, patients treated with imatinib did not present an apparent susceptibility to opportunistic infections.

### Imatinib as a targeted therapy for autoimmune diseases

Autoimmune disease is a condition in which the immune system mistakenly attacks healthy tissues or cells. The treatment of many autoimmune disorders is limited by drug efficacy, and long-term use is associated with severe side effects. Imatinib exerts various immunomodulatory effects by abrogating multiple signal transduction pathways involved in the pathogenesis of autoimmune diseases. Therapeutic efficacy of imatinib has been demonstrated in numerous animal models of inflammatory or autoimmune diseases<sup>32</sup>. Subsequent clinical trials have offered an increasing opportunity to use imatinib for the treatment of autoimmune or inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, autoimmune diabetes, glomerulonephritis, systemic autoimmune diseases, systemic scleroderma, chronic graft versus host

**Table 1.** Previous reports demonstrating immunostimulatory effects by imatinib

Model and Targeted Cells	Immunological Effects	Proposed Molecular Mechanisms	References
Leukemia-derived DCs from CML patients	Increased expression of CD1a, CD80, CD83, CD86; Increased ability of antigen expression	NA	15
BM-derived DCs from BALB/C mice	Enhancement of antigen-presentation and antigen-specific CD4 <sup>+</sup> T cell response	Inhibition of phosphorylation of KIT	16
BM-derived DCs from C57BL/6 mice or W/Wv mice	DC-mediated NK cell activation; NK cell-dependent antitumor effect	Inhibition of phosphorylation of KIT	17
Monocytes/macrophages and NK cells from human healthy donors	Increased expression of CXCR4 in NK cells and monocytes; Reduction of CXCR3 in NK cells and CCR1 in monocytes; Reversion of immunosuppressive polarization of M2 macrophages; Activation of NK cells by M1-oriented macrophages	NA	18
Treg cells from BALB/C mice	Reduction of the number and impairment of immunosuppressive activity of Treg cells; Restraint of FoxP3 expression in Treg cells	Inhibition of phosphorylation of ZAP70 and LAT; Reduction of downstream STAT3 and STAT5	19

BM; bone marrow, CML; chronic myelogenous leukemia, DC; dendritic cell, LAT; Linker of activated T cells, NA; not assessed, NK; natural killer, Treg; regulatory T

**Table 2.** Previous reports demonstrating immunosuppressive effects by imatinib

Model and targeted cells	Immunological effects	Proposed molecular mechanisms	References
PB CD34+ cells, monocytes, and differentiated DCs from human healthy donors	Inhibition of mobilization of DCs (evaluated by expression of CD1a, CD86, CD80, CD40); Reduction of the capacity to induce primary CTL responses chemokine/ cytokine secretion of DCs	Inhibition of AKT phosphorylation; Down regulation of nuclear-localized NF-κB family members	20, 21
Splenic DCs from C57BL/6 and SWISS <sup>nu/nu</sup> mice	Impairment of FLT3L-mediated DC expansion and antitumor effect	NA	22
T cells from human healthy donors and T cell lines; B6AF1 mice	Inhibition of T cell proliferation and cell cycle progression; Inhibition of delayed-type hypersensitivity in murine model	Inhibition of LCK tyrosine phosphorylation Inhibition of ERK1/2 and RB phosphorylation; Reduction of cyclin D3 protein level	23
T cells from human healthy donors and T cell lines; In vitro tyrosine kinase assay	Inhibition of T-cell receptor-mediated T-cell proliferation and activation; Reduction of antigen-triggered expansion of CD8 <sup>+</sup> T cells	Inhibition of ZAP70 and LAT tyrosine phosphorylation; Direct inhibition of LCK tyrosine phosphorylation	24
T cells from CML patients	Inhibition of cytokine synthesis by activated CD4 <sup>+</sup> T cells	Inhibition of ZAP70 tyrosine phosphorylation	25
T cells from C57BL/6 mice: Diabetic model (RIP-GP) mice	Reduction of secondary expansion of antigen-experienced memory CTLs: Delay of the onset of autoimmune diabetes	NA	26
T cells from C57BL/6 mice and OT-1 mice	Inhibition of antigen-specific memory CD8 <sup>+</sup> T cell responses	Reduction of IL7R α expression	27
T cells from human healthy donors, CML patients, and mice	Reduction of number of T cells	Inhibition of STAT5 phosphorylation and IL7 signaling	28
BM hematopoietic stem cells and PB monocytes human healthy donors: Murine FDC-P1 cell line	Inhibition of growth and development of monocyte and/or macrophage	Inhibition of M-CSF receptor (FMS) tyrosine phosphorylation	19, 29
Murine splenic B cells	Impairment of class switch recombination of the immunoglobulin gene	Down regulation of AID	30
T and B cells from human healthy donors, CML patients	Reduction of number of IgM memory B cells and impairment of humoral response against infection	Inhibition of BTK phosphorylation	31

AID; activation-induced cytidine deaminase, BM; bone marrow, BTK; Bruton's tyrosine kinase, CML; chronic myelogenous leukemia, CTL; cytotoxic T lymphocyte, DC; dendritic cell, FLT3; FMS-like tyrosine kinase-3, FLT3L; FLT3-ligand, LAT; Linker of activated T cells, LCK; LSTRA cell kinase, M-CSF; macrophage colony stimulating factor, NA; not assessed, PB; peripheral blood

disease, and viral liver diseases<sup>32</sup>. However, definitive data from further clinical trials are required to define the role of imatinib in the treatment of autoimmune diseases.

Imatinib can be administered orally to patients without increasing the rate of infectious complications or notable side effects following long-term use. Generally, the most frequent side effects of imatinib, including nausea, edema, and muscle cramps, are mild. Although the incidence of serious side effects seems to be low, they may occur preferentially in patients with pre-existing diseases. Therefore, careful monitoring of side effects and dose adjustment according to renal and hepatic functions is required when using imatinib.

### TKI or BTK inhibitor therapy for ITP

ITP is an acquired autoimmune disorder characterized by immune-mediated platelet destruction and impaired platelet

production<sup>1</sup>. Standard first-line therapies for adult ITP include corticosteroids, intravenous immunoglobulin, and anti-D immunoglobulin. Although these therapies typically result in an initial response, long-term durable remission is uncommon and patients frequently relapse, requiring the consideration of alternative treatment options, such as thrombopoietin receptor agonists, rituximab, and/or splenectomy<sup>1,33</sup>. Relapsed/refractory cases of ITP have prompted identification of new drugs that target various pathways involved in ITP pathogenesis. Inhibition of platelet phagocytosis by splenic macrophage targeting Fcγ receptor (FcγR) signaling (spleen tyrosine kinase (SYK) and BTK), neonatal Fc receptor inhibition (efgartigimab), inhibition of the classical complement pathway (sitimlimab), and inhibition of platelet desialylation (neuramidase-1 inhibitor) are novel strategies to limit peripheral platelet destruction<sup>1,33</sup>.

Platelets opsonized with IgG autoantibodies undergo rapid destruction via phagocytosis. IgG-coated platelets are recognized by splenic macrophages via their FcγR<sup>1,33</sup>. Upon cross-linking of immune complexes to FcγR, immunoreceptor tyrosine-based activation motifs (ITAMs) located on the cytoplasmic tail are activated, with tyrosine residues phosphorylated by SRC family kinases. This step leads to the recruitment of SYK, an enzyme that propagates a signaling cascade that promotes phagocytosis and cytokine production. Among the various recruited molecules, BTK, which activates RAC and RHO, leading to reorganization of the cytoskeleton, is also required for phagocytosis. SYK is widely expressed in hematopoietic cells, immune cells (B cells, T cells, and macrophages), and platelets. Moreover, SYK is expressed in B cells, and plays a crucial role in antibody formation.

SYK and BTK target platelet phagocytosis by splenic macrophages. Fostamatinib is an SYK inhibitor approved for the treatment of refractory/relapsed chronic ITP<sup>33</sup>.

BTK is critical for signal transduction of the B cell antigen receptor, leading to the development and maturation of B cells. The development of BTK inhibitors has revolutionized the treatment of chronic lymphocytic leukemia and other B cell neoplasms. Rilzabrutinib, is a reversible, covalent, highly selective, and potent inhibitor of BTK that, unlike ibrutinib, does not affect platelet functions<sup>34</sup>. A clinical trial demonstrated that BTK inhibition with rilzabrutinib effectively suppress immune-mediated platelet destruction in patients with ITP, providing evidence for a new mechanism for targeting the underlying pathological characteristics of the disease<sup>34</sup>. The rationale for using rilzabrutinib is based on its ability to inhibit the maturation of autoreactive B cells and auto-antibody production, as well as decrease platelet destruction by impairing macrophage FcγR-mediated signaling.

With BTK inhibition being established as a therapeutic approach for ITP, TKIs against ABL1, which have been demonstrated to possess off-target BTK-inhibitory effects, may constitute a potential treatment strategy.

## Conclusion

The coexistence of CML and autoimmune diseases, such as ITP, may be rare but recurrent. Based on our report, we propose the potential application of ABL1-targeted TKI as immunosuppressive therapies for autoimmune diseases owing to their off-target effects. However, the experience and observational data regarding this approach remain limited. Further investigations are required, and the accumulation of such cases could be useful for developing novel treatments for refractory ITP.

## Declarations

### Conflict of interest

The author declares no conflicts of interest associated with this manuscript.

### Data availability statement

The data supporting the findings of this study are not publicly available because they contain information that compromise the privacy of the research participants. The data are available from the corresponding author (Yuichi Nakamura), upon reasonable request

### Acknowledgments

We thank Editage for English language editing.

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