

# Refractory/relapse thrombocytopenia in a patient with Evans' syndrome successfully treated with zanubrutinib

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## Case Report

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# Abstract

## Background

Evans' syndrome (ES) is a rare autoimmune disorder and has high mortality rate. Due to the rarity of the disease, the treatments of ES are always empirical, including steroids, IVIG, rituximab, TPO-RAs, immunosuppressants, splenectomy and supportive therapies. However, many patients may become relapsed/refractory to a series of different interventions. Herein, we report a case that a ES patient with severe refractory/relapse thrombocytopenia was successfully treated with zanubrutinib.

## Case presentation

A 15-year-old Chinese girl, with repeated skin petechiae and ecchymosis, was diagnosed of Evans' syndrome finally. Despite the initial treatment with dexamethasone, recombinant human thrombopoietin receptor agonist (Eltrombopag /Avatrobopa), immunoglobulin, rituximab, immunosuppressants (Cyclosporine/Azathioprine /Sirolimus) and splenectomy, the patient relapsed and finally had a dramatic and lasting recovery after being treated with zanubrutinib, a second-generation selective covalent Inhibitor of Bruton's Tyrosine Kinase.

## Conclusion

We concluded by reviewing the cases of refractory/relapse Evans' syndrome and the application of BTK Inhibitors for the treatment of autoimmune diseases. Zanubrutinib may be a feasible therapeutic option for patients with Evans' syndrome who do not respond well to traditional therapies. Ours is the first published case of using covalent Inhibitor of BTK in refractory/relapse Evans' syndrome and contributes to the successful use of zanubrutinib in future clinical practice. However, the role of zanubrutinib in ES treatment requires more basic and clinical trials to test and evaluate.

## Background

Evans' syndrome (ES) was first described by Evans in 1951 and is a rare autoimmune disorder that is defined as the concomitant or sequential occurrence of coombs positive immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) [1]. The clinical manifestations of ES include anemia, bleeding, jaundice, hepatosplenomegaly, and hemoglobinuria. Primary ES represents in 30% of cases and its mortality rate is high. When AIHA and ITP occur concomitantly or sequentially, the diagnosis process must rule out underlying pathological conditions, such as systemic lupus erythematosus (SLE), infections, primary immune deficiencies, thrombotic microangiopathies (TMA), anemia complicating ITP, vitamin deficiencies, hematological malignancies, myelodysplastic syndromes (MDS), and paroxysmal nocturnal hemoglobinuria (PNH) [2]. Identification of the primary or secondary ES can influence its management and prognosis. Due to the rarity of the disease, the treatment of ES is mostly extrapolated from what is recommended for isolated-autoimmune-cytopenia (ITP and AIHA), mostly relying on corticosteroids, rituximab, splenectomy, thrombopoietin receptor agonists(TPO-RAs), erythropoietin,

immunosuppressants and supportive therapies. Despite recent therapeutic advances, responses to existing options are often temporary and durable remission remains elusive. Many patients experience a prolonged course and become relapsed/refractory to a series of different interventions [3]. In the present case, we describe the treatment of a 15-year-old Chinese girl with ES who suffered severe refractory/relapse thrombocytopenia and was treated with zanubrutinib.

## Case Presentation

A 15-year-old Chinese girl, with repeated skin petechiae and ecchymosis for more than 15 months, was admitted to our hospital with symptoms worsen for one week in January 2021. On August 30, 2019, she went to a local hospital with petechiae seen on the trunk after upper respiratory tract infection. Complete blood count showed purely severe thrombocytopenia ( $2 \times 10^9/L$ ) and Comprehensive metabolic panel were normal. Bone marrow smear and flow cytometry identified immune thrombocytopenia purpura (ITP). According to the latest diagnostic criteria and treatment guideline for ITP [4, 5], she was treated with high-dose dexamethasone (40 mg per day) for 4 days. Following this, she got a transient, slightly increase in platelet to  $32 \times 10^9/L$ .

On September 14, 2019, she experienced a flare and went to a hematological hospital. Complete blood count manifested mild anemia (hemoglobin = 114g/L) and thrombocytopenia ( $7 \times 10^9/L$ ). Bone marrow biopsy showed megakaryocytic hyperplasia with immaturity, no significant dysplasia or increased blasts and no evidence of metastatic carcinoma, lymphoma or granulomas. Myelodysplastic Syndrome-Associated exome sequencing analysis did not identify a pathogenic causative gene mutation. Flow cytometry showed no evidence of lymphoproliferative disorder or myeloid neoplasm. The patient also underwent tests for secondary thrombocytopenia and was found to have negative results for antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigen, anticardiolipin antibody and lupus anticoagulant. Viral infections known to trigger ITP (Epstein–Barr virus [EBV], seasonal influenza, adenovirus, hepatitis C, hepatitis B, human immunodeficiency virus, Varicella Zoster virus, and cytomegalovirus [CMV]) were excluded with serologic tests. The history and tests were consistent with a diagnosis of ITP. Platelet count showed no improvement after given high-dose dexamethasone (HD-DXM) again. The treatment with recombinant human thrombopoietin (rhTPO) of eleven days resulted in platelet count rapidly recovering ( $209 \times 10^9/L$ ). She was discharged and received maintenance therapy with Chinese herbal medicine, providing an ongoing remission of 9 months.

On July 10, 2020, she presented with epistaxis, melena, petechiae, bruises, hematuria and uterine bleeding again after urinary tract infection. Laboratory studies revealed very severe thrombocytopenia ( $0 \times 10^9/L$ ) and moderate-to-severe anemia (53g/L ~ 90g/L) with normal white blood cell and coagulation. Coombs' test was positive. Therefore, a diagnosis of Evans' syndrome was made. Since then, she endured numerous flares, all of which required multiagent treatment. She experienced several severe flares over the next 5 months and failed to respond to multiagent therapy including Methylprednisolone 180 mg twice daily for three days then 40 mg per day, TPO 15000 unit per day, initially Eltrombopag 25 mg per

day for 8 days then 75 mg per day over 2 months, 1 g/kg of intravenous immunoglobulin (IVIG) over 2 days, another round of HD-DXM, 2 doses of Rituximab (300 mg/dose/week), Cyclosporine 125 mg twice daily (4.0 mg/kg) and azathioprine 50 mg per day (Fig. 1).

In November 2020, the patient developed hemolysis and persistent hematuria and uterine bleeding with headache, and a brain CT scan showing a little subarachnoid hemorrhage. Fundoscopy exhibited mottled hemorrhage around the optic disc of the left eye and massive hemorrhage under the internal limiting membrane in the macular region. Symptoms continued to worsen and Doppler ultrasound of left eye showed vitreous hemorrhage resulting in left eye blindness. Multiagent therapy and platelets and erythrocytes transfusion were given. She had a transient improvement in bleeding tendency but persistent thrombocytopenia.

On January 2, 2021, the patient's bleeding and hemolytic symptoms further aggravated, so she was transferred to our hospital. On admission, physical examination showed that she had severe anemia, moderate scleral jaundice, systemic edema and bleeding. Flowcytometric surveillance was repeated for malignancy, autoimmune lymphoproliferative syndrome and PNH, as well as bone marrow testing still manifesting megakaryocytic hyperplasia with immaturity. Genetic testing for inherited blood disorders was negative. Hematology investigations showed a positive Coombs' test for AIHA with C3d antibodies (direct antiglobulin testing positive and indirect antiglobulin testing weakly positive). Antiplatelet antibodies to glycoproteins GPIIb/IIIa, GPIb/IX, and GPIa/IIa showed positive GPIIb/IIIa in circulating plasma. Her symptoms and examinations were still consistent with a diagnosis of ES. She was given multiagent therapy including HD-DXM, rhTPO, Avatrombopag, Eltrombopag, 0.4g/kg of IVIG over 5 days, Splenectomy and Sirolimus. During this period, the patient suffered from severe bleeding with aggravation of hemolysis for many times, which improved after active blood transfusion, anti-infection and anti-hemolysis treatment, but the platelets did not recover significantly. She had poor responses to the above various therapeutic interventions (Fig. 2). On March 15, 2021, she was administered orally Zanubrutinib 160 mg twice a day. After 2 months, she experienced a dramatic clinical response with immediate improvement of platelet ( $48 \times 10^9/L$ ), and hemoglobin returned to normal. After 6 months, she achieved platelet count greater than  $100 \times 10^9/L$ . Then zanubrutinib was gradually tapered and discontinued due to hair loss and economic reasons, but she still experiencing an ongoing remission of 8 months so far. There were no obvious adverse events during the application.

## Conclusion

The pathophysiology of Evans' syndrome remains unknown, but it is recognized as a condition of immune dysregulation [6]. ES is usually more challenging than isolated-autoimmune-cytopenia and has a higher mortality rate. Many cases are idiopathic, as was the case presented here. Although there is no standard method to diagnose Evans syndrome with laboratory tests, patients should be screened for underlying or associated diseases using a systematic approach. Most ES treatments are empirical, without adequate evidence, and with varying strategies among different centers. The management of ES-I TP is based on the utilization of steroids, IVIG, rituximab, TPO-RAs, immunosuppressants and

splenectomy. Despite significantly therapeutic advances in ITP, a subset of patients is refractory to existing options and durable remission remains elusive.

In recent years, advances in understanding the pathogenesis of ITP have opened up the possibility of therapeutic intervention targeting different pathways involving peripheral destruction of platelets or inappropriate myelopoiesis [7]. It is well known that the B cell receptor (BCR) plays an essential role in B cell development and function, controlling the activation of B lymphocytes and their subsequent differentiation into antibody secreting plasm cell and memory B cells [8]. Bruton tyrosine kinase is a critical immune signaling element downstream of BCR and is an essential intracellular signaling enzyme expressing in B and innate immune cells and participating in both adaptive and innate immune responses. The treatment regimens targeting BCR pathways are based on the close association and the several common pathogenetic mechanisms in autoimmune diseases [9, 10]. Thus BTK inhibitors (BTKis) become interesting target interventions in autoimmune cytopenias (AIC) , inhibiting the phagocytosis of platelets and erythrocytes by splenic macrophages. Hampel[11] found that ibrutinib had a beneficial effect in AICs related to chronic lymphocytic leukemia (CLL). In his study, 29/193 patients treated with ibrutinib for CLL had an AIC before starting treatment, including 8 patients with ITP and 5 with Evans' syndrome. As a result, there was no worsening of AIC. In fact, 42% of treatments for AIC were cut back, while 25% were discontinued. So BTKis may provide a new approach for treating patients with autoimmune cytopenias, including immune thrombocytopenia and autoimmune hemolytic anemia. Currently approved BTKis are irreversible covalent inhibitors and limited to oncology indications [12-14]. But more and more reports showed that selective BTK inhibition had the potential to target multiple immune-mediated diseases [9, 15-18]. Rilzabrutinib, an oral, reversible, covalent molecule highly selective inhibitor of BTK, could diminish platelet loss and showed a good safety profile in ITP. It works via inhibition of autoantibody/Fc-gamma receptor signaling in splenic macrophages and affecting autoantibody generation through effects on B-cell activation in the data of preclinical and clinical studies [19-21]. The preliminary results of a phase 1/2 study [22] conducted in 32 chronic ITP patients treated with rilzabrutinib 400 mg twice daily showed promising results. In the study, heavily pretreated ITP patients, who were lack of response to prior ITP interventions, showed significant platelet responses with Rilzabrutinib and maintained responses for a long period of time. It was well tolerated, whether given as a monotherapy or with allowed concomitant ITP therapy [23]. A phase 3 study assessing the efficacy and tolerance of rilzabrutinib in ITP is still ongoing (NCT04562766).

We could not get this BTKi in China. So we attempted another approved BTKi, zanubrutinib, which is a second-generation selective covalent inhibitor of BTK. Zanubrutinib was approved in 2019 by the US Food & Drug Administration for the treatment of adults with mantle cell lymphoma (MCL) who have received at least one prior therapy[24]. We referred to the dose of 160mg twice daily used in lymphoma. Our patient who was lack of response to splenectomy and other ITP therapies finally responded to zanubrutinib which produced a dramatic and lasting recovery without severe adverse effects. It might be possible to consider zanubrutinib for ES-ITP as a patho-physiology-guided compassionate off-label treatment targeting underlying disease mechanisms of platelet destruction. The use of zanubrutinib may be an option for treating ES patients who don't respond well to traditional therapies. This is the first case

of using a covalent inhibitor of BTK in refractory/relapse Evans' syndrome and will thus contribute to the wide utilisation of zanubrutinib in the future. Although the database is still limited, this might represent a reasonable paradigm for emergency repurposing of this approved drugs in ES. However, zanubrutinib needs to be further investigated in clinical trials with regard to its role in ES treatment.

## Abbreviations

BTK: Bruton's Tyrosine Kinase, BTKis: Inhibitors of Bruton's Tyrosine Kinase, ES: Evans' syndrome, ITP: Immune thrombocytopenia, AIHA: autoimmune hemolytic anemia, EBV: Epstein–Barr virus, CMV: cytomegalovirus, SLE: Systemic lupus erythematosus, TMA: thrombotic microangiopathies, MDS: myelodysplastic syndromes, PNH: paroxysmal nocturnal hemoglobinuria, TPO-RA: Thrombopoietin receptor agonist, IVIG: intravenous immunoglobulin, CT: computed tomography, rhTPO: Recombinant human thrombopoietin, DXM:Dexamethasone, HD-DXM: high-dose dexamethasone, PDN: Prednisolone, Hb: Hemoglobin, PLT: Platelets, ANC: Absolute neutrophil count. BCR:B cell receptor, AIC: autoimmune cytopenias, CLL:chronic lymphocyticleukemia, MCL: mantle cell lymphoma.

## Declarations

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### Availability of data and materials

The data supporting the conclusion of this article is included within the article.

### Authors' contributions

ML and ZH conceived and designed the study. ZH, ML, YS and LL analyzed and interpreted the data. ZH, ML, and LL wrote the manuscript. BD, AX, YH, XS, XW and YS provided the study materials or patients. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable

### Consent for publication

The authors have obtained consent to publish from the participants to report individual patient data.

## Competing interests

The authors declare that they have no competing interests.

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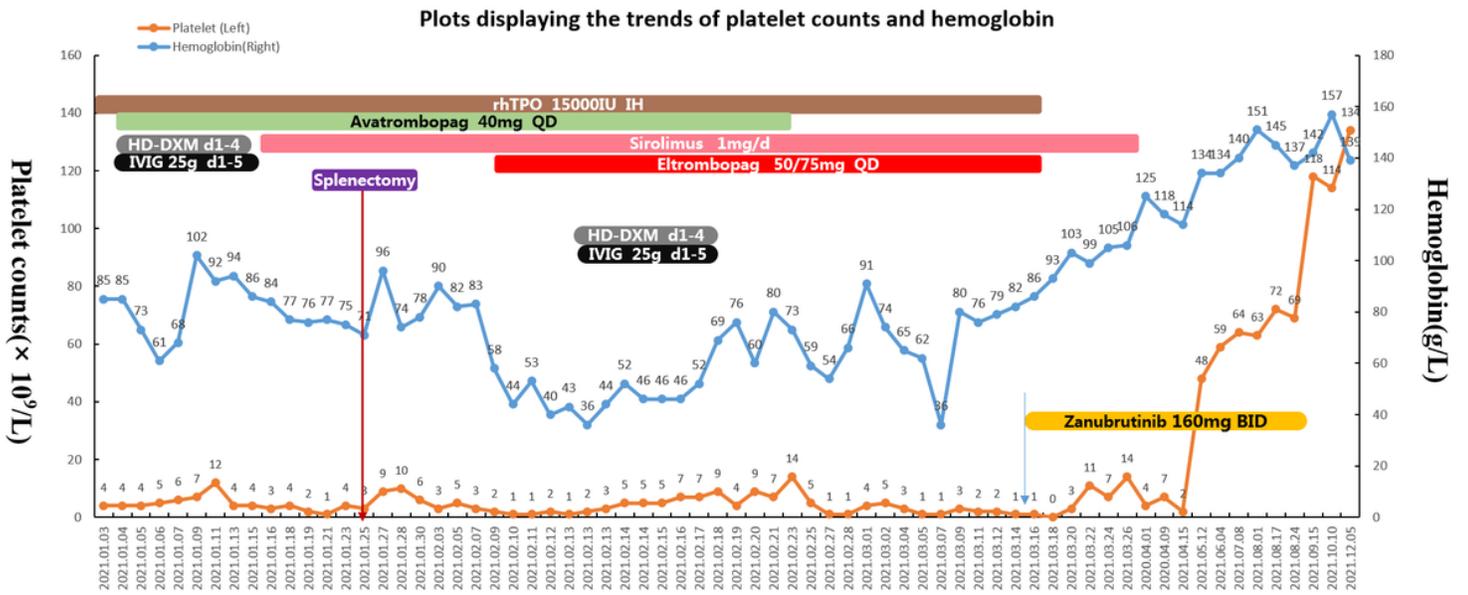
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**Figure 2**

Patient's treatment timeline after hospitalization.

Abbreviations: IVIG:intravenous immunoglobulin, rhTPO: Recombinant human thrombopoietin, HD-DXM: high-dose dexamethasone,IH: hypodermic injection, BID: bis in die/twice day, QD: quaque die/every day.