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

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Case Report

Keywords: Bruton's Tyrosine Kinase, Zanubrutinib, Evans' syndrome, Immune thrombocytopenia, Splenectomy, Antiplatelet antibody, Refractory/relapse, Inhibitor of Bruton's Tyrosine Kinase

Posted Date: April 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1540326/v1

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Abstract

Methods

We report a case of a 15-year-old Chinese girl with Evans’ syndrome who presented with refractory/relapse thrombocytopenia successfully treated with zanubrutinib. There is no published cases of treating refractory/relapse thrombocytopenia with zanubrutinib, a second-generation selective covalent Inhibitor of Bruton's Tyrosine Kinase, in Evans’ syndrome.

Results

Despite the initial treatment with Dexamethasone, Recombinant human thrombopoietin, Thrombopoietin receptor agonist (Eltrombopag /Avatrobopa), immunoglobulin, Rituximab, immunosuppressants (Cyclosporine/Azathioprine /Sirolimus) and Splenectomy, our patient relapsed and finally applied zanubrutinib which resulted in successful remission. ES case treated on zanubrutinib without adverse effects. The patient had dramatic and long-lasting recovery that started following the drug. Clinical trials to assess the role of zanubrutinib in ES treatment are warranted.

Discussion

We conclude by reviewing the cases of refractory/relapse Evans’ syndrome and review the application of BTK Inhibitors for the treatment of autoimmune diseases in medical practice. Ours is the first published case of using covalent Inhibitor of BTK in refractory/relapse Evans’ syndrome and contributes to the literature on the successful use of zanubrutinib in clinical practice.

Conclusion

The zanubrutinib may be a feasible therapeutic option for patients with Evans’ syndrome who do not respond well to traditional therapies.

Background

Evans’ syndrome (ES) was first described by Evans in 1951 and is a rare autoimmune disorder that 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. ES represents primary in 30% of cases and its mortality rate is high. When AIHA and ITP occurred concomitantly or sequentially, the diagnosis procedure must rule out underlying pathological associations, such as systemic lupus erythematosus (SLE), infections, primary immune deficiencies, thrombotic microangiopathies (TMA), anemia complicating ITP, vitamin deficiencies, hematological malignancies, myelodysplastic syndromes (MDS),
paroxysmal nocturnal hemoglobinuria (PNH)[2]. Determination of the primary or secondary nature of ES can interfere with its management and alter its 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, supportive therapies and even hematopoietic stem cell transplantation. 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]. Here, we present a 15-year-old Chinese girl with ES who experienced several severe refractory/relapse thrombocytopenia successfully treated with zanubrutinib.

Case Presentation

A 15-year-old Chinese girl, with repeated skin petechiae and ecchymosis for more than one year and three months, was admitted to our hospital with symptoms worsen for one week in January 2021. On August 30, 2019, she presented to local hospital in view of petechiae seen on the trunk after upper respiratory tract infection. Blood routine showed purely severe thrombocytopenia (2×10⁹/L) and clinical biochemistry examinations were normal. Bone marrow smear and flow cytometry identified immune thrombocytopenia purpura (ITP). According to the latest diagnostic criteria and treatment strategy for ITP[4, 5]. She was treated with high-dose dexamethasone (40mg per day) for 4 days. Following this, she got a transient, slightly increase in platelet to 32×10⁹/L.

On September 14, 2019, she experienced a flare onset and went to a Hematology Specialist Hospital. Blood count manifested mild anemia (hemoglobin = 114g/L) and thrombocytopenia (7×10⁹/L). She underwent bone marrow biopsy, which showed megakaryocytic hyperplasia with immaturity with no significant dysplasia or increased blasts, with no evidence of metastatic carcinoma, lymphoma or granulomas. Myelodysplastic Syndrome-Associated exome sequencing analysis did not identify a pathogenic causative 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 investigations were consistent with a diagnosis of ITP. A platelet count showed no improvement after given high-dose dexamethasone (HD-DXM) again. Therapy with recombinant human thrombopoietin (rhTPO) of eleven days resulted in platelet count rapidly recovery (209×10⁹/L). She was discharged and 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 findings revealed very severe thrombocytopenia
(0×10^9/L) and moderate-to-severe anemia (53g/L ~ 90g/L) with normal white blood cell and coagulation. Coombs’ test was positive. A diagnosis of Evans’ syndrome was made. From then on, she had endured numerous flares, all of which required necessitated multiagent treatment. She experienced several severe flares over the next 5 months and failing to respond to multiagent therapy including Methylprednisolone 180mg twice daily for three days then 40mg per day, TPO 15000 unit per day, initially Eltrombopag 25mg per day for 8 days then 75mg per day over 2 months, 1 g/kg of intravenous immunoglobulin (IVIG) over 2 days, another round of HD-DXM, 2 doses of Rituximab (300mg/dose/week), Cyclosporine 125mg twice daily (4.0mg/kg) and azathioprine 50mg per day (Fig. 1).

In November 2020, the patient developed hemolysis and persistent hematuria and uterine bleeding with headache, and performed a cerebral computed tomography (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 finally. 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 was severe anemia, moderate scleral jaundice, systemic edema and bleeding. She was repeatedly conducted flowcytometric surveillance for malignancy, autoimmune lymphoproliferative syndrome and PNH, as well as repeated 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/IIa, GPIb/IX, and GPIa/IIa showed positive GPIIb/IIa 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, and it improved after active blood transfusion, anti-infection and anti-hemolysis treatment, and the platelets did not rebound significantly. She had poor responses to above different therapeutic interventions(Fig. 2). On March 15, 2021, she was administered orally Zanubrutinib 160 mg twice a day. After 8 weeks, she experienced a dramatic clinical response with immediate improvement of platelet (48×10^9/L), and hemoglobin returned to normal. After 6 months, she achieved platelet count greater than 100×10^9/L. Then zanubrutinib was gradually tapered and discontinued due to hair loss and economic factors, but still providing an ongoing remission of 8 months so far. There were no obvious adverse events during the application.

**Discussion**

The pathophysiology of Evans’ syndrome remains unknown, but it is recognized as a condition of immune dysregulation[6]. ES is often more challenging to treat than isolated-autoimmune-cytopenia and...
has a higher mortality rate. Many cases are idiopathic, as was the case with this patient. Although there is no standard diagnostic approach of laboratory tests for Evans syndrome, a systematic approach should be taken to screen patients for underlying or associated diseases. The treatment of ES is mostly empirical with a low level of evidence with differences strategies between different centers. The management of ES-ITP 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.

Recent advances in the understanding of ITP pathogenesis break new ground of therapeutic interventions, which give the opportunity to target different pathways involved in ITP pathogenesis, either on the peripheral destruction of platelets or the inappropriate bone marrow production[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 plasma 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 expressed in B and innate immune cells, participating in both adaptive and 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 found ibrutinib showed benefits in AIC related to chronic lymphocytic leukemia (CLL). In the study, 29/193 patients treated with ibrutinib for CLL had an AIC before the initiation of therapy. Eight patients had ITP and five had Evans’ syndrome. Overall, no worsening of AIC was observed. On the contrary, treatments dedicated to AIC were reduced in 42% and discontinued in 25% of the cases[11]. 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 has the potential to target multiple immune-mediated disease[9, 15-18]. Rilzabrutinib, an oral, reversible, covalent molecule highly selective inhibitor of BTK, can diminish platelet loss and shown 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[19, 20]. The preliminary results of a phase 1/2 study 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 irrespective of splenectomy or lack of response to prior ITP interventions, could receive clinically significant platelet responses with Rilzabrutinib treatment and maintained responses for long periods of time. It was well tolerated, whether given as a monotherapy or with allowed concomitant ITP therapy[21-23]. A phase 3 study assessing the efficacy and tolerance of rilzabrutinib in ITP is ongoing (NCT04562766).

We couldn’t achieve this BTKi in China. So we attempt application of approved BTKi, zanubrutinib, a second-generation selective covalent inhibitor of BTK. Zanubrutinib was approved in 2019 by the US Food & Drug Administration for the treatment of adult patients with mantle cell lymphoma (MCL) who
have received at least one prior therapy[24]. We refer to the dose used in lymphoma 160mg twice daily.
Our patient who was irrespective of splenectomy or lack of response to other ITP therapies finally
responded to zanubrutinib which resulted in dramatic and long-lasting recovery without severe adverse
effects. Ours is the first published case of using covalent inhibitor of BTK in refractory/relapse Evans’
syndrome and contributes to the literature on the successful use of zanubrutinib in clinical practice.
Zanubrutinib targeted underlying disease mechanisms of platelet destruction might be regarded as
effective for a patho-physiology-guided compassionate off-label use in cases of ES-ITP. Although the
database is yet limited, this might represent a reasonable paradigm for emergency repurposing of this
approved drugs in ES. But the role of zanubrutinib in ES treatment needs to be further confirmed in
clinical trials.

Conclusion

The zanubrutinib, a second-generation selective covalent Inhibitor of Bruton's Tyrosine Kinase, may be a
feasible therapeutic option for patients with EVANs’ syndrome who do not respond well to traditional
therapies.

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

Acknowledgments

The authors would like to thank all members of the study team, the patient and their family.

Funding

This paper is supported by grants from the National Science Foundation of China (Grant Nos. 82070120[24],

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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**Figures**

<table>
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<th>Medication</th>
<th>Dosage</th>
<th>Duration</th>
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<th>Time (Months)</th>
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<td>rhTPO</td>
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**Figure 1**

Schematic illustration of response to various treatments in the patient presented. Therapeutic interventions used in the case before and after hospitalization for more than two years prior to final using zanubrutinib.
Abbreviations: IVIG: intravenous immunoglobulin, rhTPO: Recombinant human thrombopoietin, Hb: hemoglobin, Plt: platelets, ANC: absolute neutrophil count

Figure 2

See image above for figure legend