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Original Research Article

Therapeutic effect of the combination of eltrombopag and low-dose hormone in patients with primary immune thrombocytopenia

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Abstract

Purpose: *To investigate the clinical effect and side effects of early addition of small-dose eltrombopag in initial treatment of primary immune thrombocytopenia (ITP) patients with decreased platelet count and hormone reduction, and patients with persistent ITP.*
Methods: *Thirty ITP patients newly diagnosed with poor hormonal levels were recruited, along with 36 patients with persistent ITP. The ITP patients were given prednisone in combination with eltrombopag. Blood routine tests, blood pressure, blood sugar, liver and kidney function, and serum ion levels were monitored every two weeks. Adverse events were recorded at 2, 4, and 8 weeks after eltrombopag treatment.*
Results: *After treatment for 2, 4, and 8 weeks, there was obvious effectiveness in 45.0, 39.4, and 40.9 % of patients, respectively, while effectiveness was good in 22.7, 37.9, and 50 % of patients, respectively. Treatment was ineffective in 31.8, 22.7, and 9.1 % of patients, respectively. In the 8th week, 15 patients (22.7 %) had to use prednisone at a dose of more than 20 mg/day to keep their platelet level above 30 x 109/L, while 7 patients (10.6 %) stopped using prednisone completely. Moreover, 4 patients (6.1 %) had their platelet counts maintained above 30 x 109/L after stopping the use of eltrombopag for more than 2 weeks.*
Conclusion: *The combined use of eltrombopag and low-dose hormone is an effective treatment for ITP patients. It produces only a slight side effect, and it is affordable. A larger population study will be required to validate these findings of this new therapeutic option.*

Keywords: *Eltrombopag, Primary immune thrombocytopenia, Therapeutic effect, Drug toxicity*

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INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by increased destruction of platelets and platelet clearance. The IgG anto-antibodies mediate platelet destruction. These antibodies bind to surface antigens in the platelets and megakaryocytes (MKs) such as glycoprotein (GP) αIIbβ3 (GPIIbIIIA) and GPIb-IX-V, leading to platelet clearance primarily in the liver and spleen [1]. Autoreactive CD4+T cell subsets

induce and accelerate platelet destruction through recognition of epitopes on GPIIbIIIa. Although the triggers for this autoreactive have not yet been identified, autoreactive Th cells that interact with antibody-producing B cells are important in this reaction [2]. The binding of anto-antibodies to MKs inhibits platelet maturation and accelerates platelet destruction. Moreover, about 60 % of patients with ITP have normal or decreased plasma TPO levels, indicating that functional deficits in TPO may cause ITP [3].

In vitro and clinical studies have shown that TPO-RAs form platelets by enhancing MKs and proliferation of MKs from bone marrow, thereby presenting effective and well-tolerated treatment for ITP patients [4]. Eltrombopag is a small, oral, and non-peptide TPO-RA which has been proven to be effective and safe for patients with refractory ITP [5]. Although most patients need long-term Eltrombopag therapy, approximately one-third of patients maintain safe platelet counts after stopping this treatment [6]. In this study, Eltrombopag was used in combination with low-dose hormone to treat newly-diagnosed refractory and persistent ITP patients, and the efficacy and safety of the combined treatment on the patients were evaluated so as to provide a new therapeutic option for ITP.

EXPERIMENTAL

Patients

A total of 30 newly diagnosed ITP patients with poor hormone levels and 36 patients with persistent ITP were enrolled in this study. The patients were on admission to Anshan Central Hospital of Anshan City from June 2018 to December 2020. Informed consent was obtained from all patients.

Inclusion criteria

Patients in the following categories were included in the study: newly-diagnosed ITP patients in whom the efficacy of first-line standard hormone treatment was good or very good, with platelet count less than 30 x10^9/L; those with persistent ITP and platelet counts less than 30 × 10^9 /L, and patients with ECOG score > 3.

Exclusion criteria

Hypertensive and diabetic patients with uncontrollable blood sugar, and patients with amino aminotransferase and bilirubin levels greater than 3 times the upper limit of normal, were excluded from the study.

Treatment

Eltrombopag was purchased from GlaxoSmithKline. The newly-diagnosed ITP patients were given prednisone at a dose of 1 mg/kg/day. If the resultant efficacy was good, the prednisone dose was reduced. In patients with platelet levels less than 30 x 10^9 /L, oral administration of eltrombopag was added at a dose of 25 mg/kg. When the efficacy of the treatment was good or very good, the dose of hormone was slowly reduced and eventually stopped. When the platelet count became stable, the frequency of administration of eltrombopag was slowly reduced to 25 mg, 1 - 3 times/week, and eventually stopped. Patients with persistent ITP were given prednisone at a dose of 0.5 mg/kg/day, in combination with oral eltrombopag at a dose of 25 mg/day. Again, if the efficacy of the treatment was good, the hormone dose was slowly reduced, and the drug was eventually withdrawn.

When the platelet count was stable, the dose of eltrombopag was slowly reduced to 25 mg given 1 - 3 times/week, prior to withdrawal of the drug. Hospital admission and symptomatic treatments such as intravenous immunoglobulin and platelet transfusions were used when bleeding occurred in skin, gastrointestinal tract or other important organs during treatment.

Parameters evaluated

Blood parameters

Routine blood test, blood pressure, blood sugar, liver and kidney functions, and gastrointestinal function were monitored every 2 to 4 weeks after eltrombopag treatment.

Clinical symptoms

Clinical treatment was categorized as “obviously effective”, “good” or “ineffective”. “Obviously effective” referred to normal platelet count without bleeding for more than 3 months, while “good effectiveness” was defined as platelet count ≥ 50 x 10^9/L, or platelet count which was higher than baseline platelet count by 30 x 10^9/L, without bleeding for more than 2 months. On the other hand, treatment was ineffective for platelet counts < 50 × 10^9/L, or less than 30 x 10^9/L higher than baseline platelet counts [7].

Adverse events

Dizziness, vomiting, thrombosis, infection, and hepatic dysfunction were taken into account in the evaluation of adverse events.

Statistical analysis

The R3.4.3 software was used for data analysis. Continuous variables were analyzed using Student's *t*-test, while categorical variables were analyzed using the chi-square test. Values of $p < 0.05$ were assumed as indicative of statistically significant differences.

RESULTS

The ITP patients comprised 16 males and 50 females with a median age of 54.2 years (IOR = 32-87 years). The median course of disease was 9 months (IOR = 1-25 months), and the median baseline platelet count before treatment was 9×10^9/L (IOR = $0 – 29 \times 10^9$/L). Bleeding occurred in all patients. A breakdown showed that 42 patients had skin bleeding and petechia, 6 patients had menorrhagia, 14 patients experienced gingival bleeding, and 6 subjects had epistaxis.

Table 1: Incidence of AEs due to administration of low-dose eltrombopag plus low-dose hormone to ITP patients

Adverse event	Patients (n (%))
Increased serum liver enzyme level	7 (10.6)
Thrombosis	0 (0)
Dizziness	4 (6.1)
Vomiting	5 (7.6)
Infection	11(16.7)

Treatment efficacy

After treatment for 2, 4, and 8 weeks, there was obvious effectiveness in 45.0, 39.4, and 40.9 % of patients, respectively, while effectiveness was good in 22.7, 37.9 and 50 % of patients, respectively. Treatment was ineffective in 31.8, 22.7, and 9.1% of patients, respectively. In the 8^{th} week, 15 patients (22.7 %) had to use prednisone at a dose of more than 20 mg/day to keep platelet levels above 30 x 10^9/L, while 7 patients (10.6 %) stopped using prednisone completely. Moreover, 4 patients (6.1 %) had their platelet counts maintained above 30 x 10^9/L after stopping the use of eltrombopag for more than 2 weeks.

Adverse events (AEs)

No patients withdrew due to drug-related AEs. There was a total of 27 AEs, all of which were grade I or II. However, all the AEs were self-relieved or relieved after symptomatic treatment. No serious bleeding occurred during treatment in all patients.

DISCUSSION

Studies on the pathogenesis of ITP have shown that ITP patients have immunity-related platelet dysfunction and destruction of MKs, as well as abnormal TPO levels. It is known that TPO is the primary regulator of platelet production, and it affects the survival, proliferation, and differentiation of MKs [8-10]. A recent study has shown that platelets are removed by the hepatic AMR when they age and become de-sialylated, resulting in increased feedback for hepatic TPO production [10].

In mice, platelets bound to antibodies are rapidly cleared by the reticuloendothelial cells in liver and spleen. This cuts off AMR from platelet recognition, resulting in blockage of the feedback-induced increase in TPO production [10]. Abnormal TPO levels in the peripheral blood induce deficit in platelet production as well as decreased platelet count in ITP patients. Thus, it may be hypothesized that the efficacy of treatment for ITP patients would be significantly improved using a combination of hormones and TPO-Ras. The present study has confirmed this hypothesis.

In recent years, the therapy for chronic refractory ITP has focused on TPO-RAs. Eltrombopag, a small, orally-administered non-peptide TPO-RA, has been used for the management of adult chronic ITP, based on approval by FDA. Eltrombopag binds to the transmembrane domain of TPO receptor and stimulates platelet production by activating the JAK2/STAT signal pathway [11]. A previous study has shown that eltrombopag increased platelet count in peripheral blood and reduced bleeding events for adult and child patients with chronic ITP [12].

Mild side effects due to use of eltrombopag have been reported. These AEs comprise headache, nasopharyngitis, upper respiratory tract infection, and fatigue. Moreover, AEs such as visual impairment, arthritis, hepatotoxicity, and fatigue occur during or after administration of eltrombopag [13].

In this study, 1 to 2 weeks after treatment with eltrombopag, platelet count was significantly increased, and skin bleeding or gingival bleeding was significantly reduced. Eltrombopag-related AEs such as increased liver enzymes, dizziness, infection, and fatigue were mild, and they were relieved after symptomatic treatment. These results are consistent with results published earlier. This is an indication that eltrombopag has good tolerability.

Study limitations

There are some limitations in this study. The sample size used was small. Moreover, there was a lack of randomization. Therefore, further studies are required to confirm the therapeutic efficacy of this treatment for refractory and chronic ITP.

CONCLUSION

This study has demonstrated obvious curative effect of oral administration of eltrombopag on ITP. It was observed that small-dose eltrombopag was effective in the treatment of ITP patients and chronic ITP patients with poor levels of hormone. However, most patients needed continued eltrombopag treatment to avoid platelet destruction. A larger population, multicentered randomized study will be required to validate these findings of a new therapeutic option for ITP.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Chaoqi Yan conceived and designed the study, and drafted the manuscript. Qing Len, and Zhen Ji collected, analyzed, and interpreted the experimental data. Yin Wu, Daohua Ning, and Lijun Zhang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. *Kapur R, Zufferey A, Boilard E, Semple JW. Nouvelle cuisine: platelets served with inflammation. J Immunol 2015; 194: 5579-5587.*
2. *Iraqi M, Perdomo J, Yan F, Choi PY, Chong BH. Immune thrombocytopenia: antiplatelet autoantibodies inhibit proplatelet formation by megakaryocytes and impair platelet production in vitro. Haematologica 2015; 100: 623-632.*
3. *Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med 2017; 6: 16.*
4. *Di Buduo CA, Currao M, Pecci A, Kaplan DL, Balduini CL, Balduini A. Revealing eltrombopag's promotion of human megakaryopoiesis through AKT/ERK-dependent pathway activation. Haematologica 2016; 101: 1479-1488.*
5. *Bussel J, Mahmud S, Brigstocke S, Torneten SM. Tapering eltrombopag in patients with chronic ITP: how successful is this and in whom does it work? Blood 2015; 126: 1054-1054.*
6. *Wong RSM, Saleh MN, Khelif A, Salama A, Portella MSO, Burgess P, Bussel JB. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood 2017; 130: 2527-2536.*
7. *Zhang Z, Shen T. Diagnostic and therapeutic criteria of hematological diseases, 3rd Edition. Beijing: Science Press 2007: 131-134*
8. *Aledort LM, Hayward CP, Chen MG, Nichol JL, Bussel J, ITP Study Group. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. Am J Hematol 2004; 76: 205-213.*
9. *Chang M, Qian JX, Lee SM, Joubran J, Fernandez G, Nichols J, Knoppel A, Buzby JS. Tissue uptake of circulating thrombopoietin is increased in immune-mediated compared with irradiated thrombocytopenic mice. Blood 1999; 93: 2515-2524.*

10. Grozovsky R, Begonja AJ, Liu K. The Ashwell-Morell receptor regulates hepatic thrombopoietin production via JAK2-STAT3 signaling. Nat Med 2015; 21: 47-54.
11. Miyamoto T, Kikushige Y, Yoshimoto AG. Frontline treatment of AML in adults. Rinsho Ketsueki 2017; 58: 1884-1894.
12. Elgebaly AS, Ashal GE, Elfil M, Menshawy A. Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia: meta-analysis of randomized controlled trials. Clin Appl Thromb Hemost 2017; 23: 928-937.
13. Depré F, Aboud N, Ringel F, Salama A. Thrombopoietin Receptor Agonists Are Often Ineffective in Immune Thrombocytopenia and/or Cause Adverse Reactions: Results from One Hand. Transfus Med Hemother 2016; 43: 375-379.
14. Hammond WA, Vishnu P, Rodriguez EM, Li Z, Dholaria B, Shreders AJ, Rivera CE. Sequence of splenectomy and rituximab for the treatment of steroid-refractory immune thrombocytopenia: does it matter? Mayo Clin Proc 2019; 94: 2199-2208.
15. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017; 129: 2829-2835.