Clinical efficacy of high-dose dexamethasone with sequential prednisone maintenance therapy for newly diagnosed adult immune thrombocytopenia in a real-world setting

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Abstract

Objective: As first-line treatments for newly diagnosed adult immune thrombocytopenia (ITP), high-dose dexamethasone (HD-DXM) and conventional-dose prednisone achieve good initial responses, but their long-term efficacy is poor. To improve the long-term outcome of newly diagnosed ITP, we explored the efficacy and safety of HD-DXM with sequential prednisone maintenance therapy.

Methods: This retrospective study in a real-world setting assessed 72 consecutive newly diagnosed ITP patients administered first-line HD-DXM with sequential prednisone maintenance therapy from 1 June 2016 to 31 December 2019.

Results: Seventy patients obtained response (97.2%), and 55 achieved sustained response (SR) (76.4%). Fifty-three obtained complete remission (CR) (73.6%), and 39 achieved continuous CR at 6 months (54.2%). Among 36 anti-nuclear antibody-positive patients, 100% achieved response, and 28 achieved CR (77.8%). Among 24 antithyroid antibody-positive patients, 23 (95.8%) achieved response, and 20 achieved CR (83.3%). For patients with initial response, the

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12-month probability of SR was 78.6%. For patients with initial CR, the 12-month probability of continuous CR was 64.2%. At 12 months, 21.4% of patients with initial response and 11.3% of patients with initial CR showed loss of treatment response.

Conclusions: HD-DXM with sequential prednisone as the first-line treatment for newly diagnosed ITP patients may achieve good clinical efficacy.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia. The patient may be asymptomatic at the time of onset. Alternatively, they may present with mild skin and mucous membrane bleeding or severe and life-threatening hemorrhage.[1] At present, the first-line treatment of ITP recommended by international guidelines[2] is short-term high-dose dexamethasone (HD-DXM) (40 mg/day × 4 days) or long-term conventional-dose prednisone (1 mg/kg per day). A prospective clinical study indicated that the clinical efficacy of short-term HD-DXM is better than that of conventional-dose prednisone.[3] Although 60% to 80% of ITP patients responded to corticosteroid therapy, only 30% to 50% of adults with ITP achieved sustained response (SR) after the discontinuation of corticosteroids.[4,5] Given the relatively low chance of developing a cure for adult ITP, further expanding the first-line treatment options for ITP is necessary.

ITP is an autoimmune disease similar to systemic lupus erythematosus, rheumatoid arthritis and other connective tissue diseases involving abnormalities in B cells, T cells, macrophages and the bone marrow hematopoietic microenvironment. Therefore, completely suppressing this abnormal immunity using short-term HD-DXM alone is difficult. Inadequate immunosuppression may contribute to the delayed recovery of platelets and poor long-term outcomes of patients. Therefore, we speculate that prolonging the exposure time to corticosteroids may obtain sufficient immunosuppression for ITP patients. In this single-center study, we retrospectively analyzed the clinical efficacy and safety of HD-DXM with sequential prednisone maintenance therapy for 6 to 8 weeks in 72 patients with newly diagnosed ITP.

Methods

Patient selection

This is a retrospective study in a real-world setting. From 1 June 2016 to 31 December 2019, newly diagnosed ITP patients in our center were retrospectively studied. The inclusion criteria were newly diagnosed ITP patients, and the exclusion criteria included patients with secondary, relapsed or refractory ITP or those who had used corticosteroids for other diseases in the past 3 months. This study protocol was approved by the Ethics Committee of

Anhui Provincial Hospital (approval number: 2021-RE-013) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. All patient details have been de-identified to protect the privacy of the patients.

Treatment regimens

The diagnostic criteria for ITP were based on the international consensus of ITP.[2,6] The treatment regimen used was as follows: all patients were intravenously administered HD-DXM pulse therapy (40 mg/day × 4 days) immediately after the diagnosis of ITP, followed by oral prednisone (1 mg/kg daily) reduced by 0.2 mg/kg weekly over a 6- to 8-week period. Dexamethasone and prednisone were reduced by 50% of the original set dose for patients over 70 years old.

For severe ITP patients with clinically relevant bleeding, such as active central nervous system, gastrointestinal, or genitourinary bleeding in an emergency setting, high-dose intravenous immunoglobulin (IVIG) (0.4 g/kg/day × 3 to 5 days) was used.

Definitions and statistical analysis

Response was defined as platelet counts $\geq 30 \times 10^9$/L after treatment, complete remission (CR) was defined as platelet counts $\geq 100 \times 10^9$/L, and SR was defined as platelet counts $\geq 30 \times 10^9$/L for more than 6 months without bleeding symptoms. The follow-up time was defined as the time from diagnosis to the last follow-up evaluation. The analyzed data included age, gender, response, CR, time to reach response and CR, duration of response and CR, and the presence of other immune system abnormalities [anti-nuclear antibodies (ANAs) or antithyroid antibodies]. ANAs were detected by immunofluorescence assays, and antithyroid antibodies were detected by chemiluminescence assays.

In addition, steroid-related side effects, such as hypertension, hyperglycemia, femoral head necrosis, Cushing face, infection and edema, were recorded. Categorical variables were assessed using the chi-square test or Fisher's exact test, and continuous variables were assessed using the Mann–Whitney U test. Time-to-event outcomes for the loss of therapeutic response were estimated using cumulative incidence curves. The probabilities of the estimated 12-month SR or CR were calculated using the Kaplan–Meier method. Statistical analyses were conducted using R (www.r-project.org). Differences with $p < 0.05$ were considered significant.

Results

Patient characteristics

Seventy-two consecutive newly diagnosed ITP patients were retrospectively studied (Table 1). The median age was 53 years (ranged 15–90 years). There were 23 men (32%) and 49 women (68%). ANA testing was performed in all patients, among which 36 (50%) were positive. Forty-one patients received thyroid antibody testing, and 24 (58.5%) were positive. Forty-five patients received antiphospholipid antibody testing, and only 2 (4.4%) were positive. Comorbidities included hypertension (n = 11, 15.3%), cerebral infarction (n = 6, 8.3%), tumor (n = 6, 8.3%), arrhythmia (n = 5, 6.9%), coronary atherosclerotic heart disease (n = 3, 4.2%) and diabetes mellitus (n = 3, 4.2%).

Response and CR

The overall responses of the patients in this study are summarized in Table 2. Of the 72 patients who received HD-DXM with sequential prednisone maintenance therapy, 44 patients (61.1%) also received high-dose IVIG. Seventy patients obtained response

Table 1. Clinical characteristics.

Clinical characteristics	Results
Total patients, n	72
Median age, years (range)	53 (15–90)
Women, n (%)	49 (68)
ANA-positive, n (%)	36 (50)
Anti-thyroid antibody-positive, n (%)	24/41 (58.5)
Antiphospholipid antibody-positive, n (%)	2/45 (4.4)
Comorbidities at first diagnosis, n (%)	
Hypertension	11 (15.3)
Cerebral infarction	6 (8.3)
Tumor	6 (8.3)
Arrhythmia	5 (6.9)
Coronary heart disease	3 (4.2)
Diabetes	3 (4.2)
Combined with high-dose IVIG, n (%)	44 (61.1)
Overall response, n (%)	70 (97.2)
Time to response, (days)	3 (1–17)
SR, n (%)	55 (76.4)
CR, n (%)	53 (73.6)
Time to CR, (days)	9 (2–87)
Sustained CR, n (%)	39 (54.2)
Adverse events, n (%)	
Hypertension	10 (13.9)
Hyperglycemia	11 (15.3)
Severe intracranial infection	1 (1.4)
Intracranial hemorrhage	1 (1.4)

ANA, anti-nuclear antibody; IVIG, intravenous immuno-globulin; SR, sustained response; CR, complete remission.

(97.2%), and 53 patients obtained CR (73.6%); the average time of obtaining response and CR was 3 days (range 1–17 days) and 9 days (range 2–87 days), respectively. During the follow-up of 6 months, 55 patients (76.4%) achieved SR (Figure 1a), and 39 patients (54.2%) achieved continuous CR (Figure 1b).

Thirty-six patients with positive ANAs achieved response (100%) after treatment, and 28 patients achieved CR (77.8%). At the sixth month of follow-up, 28 ANA-positive patients achieved SR (77.8%),

Table 2. Comparison of the results between this study and previous studies in newly diagnosed adult ITP.

	Our study	Wei[3]		Cheng[5]	Sakamoto[7]		Sadeghi[14]		Takase[15]	Yu[16]	
Number of patients	72	95	97	125	31	69	40	40	23	100	96
Treatment regimens	HD-DXM+PDN	HD-DXM	PDN	HD-DXM	HD-DXM	PDN	HD-DXM	PDN	HD-DXM	HD-DXM+rhTPO	HD-DXM
Response (%)	97.2%	82.1%	69.1%	85%	100%	95.7%	69.4%	30.6%	82.2%	89%	66.7%
CR (%)	73.6%	50.5%	26.8%	ND	90.3%	91.3%	22.2%	8.3%	ND	75%	42.7%
SR (%)	76.4%	40%	41.2%	53%	42.7% (1 year)	28.4% (1 year)	88.9%	66.7%	60.9%	51%	36.5%
Sustained CR (%)	54.2%	27.4%	17.5%	ND	32.3%	25.1%	ND	ND	52.2%	46%	32.3%

ITP, immune thrombocytopenia; HD-DXM, high-dose dexamethasone; PDN, prednisone; rhTPO, recombinant human thrombopoietin; CR, complete response; SR, sustained response; ND, no data.
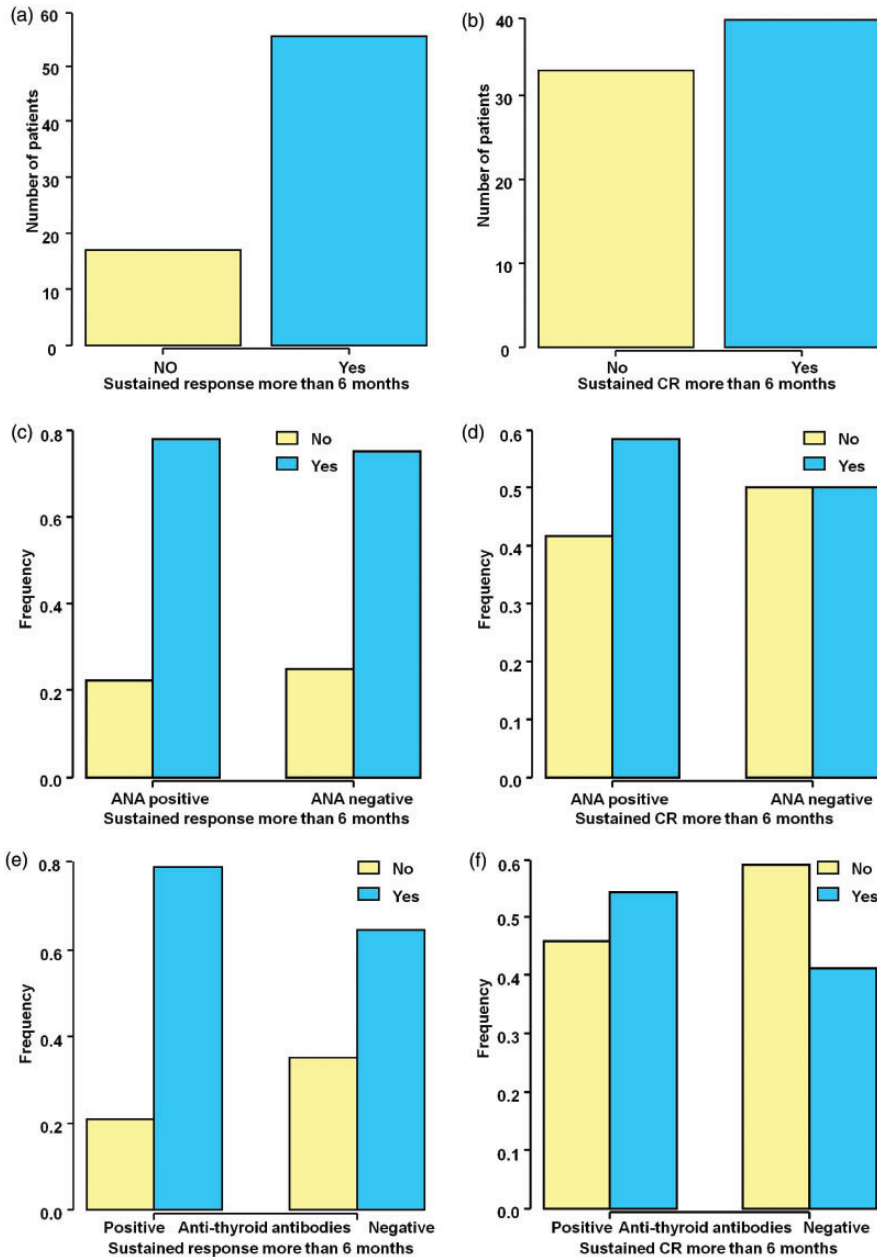
Figure 1. Sustained response (SR) and complete remission (CR) in 72 newly diagnosed immune thrombocytopenia adult patients administered intravenous high-dose dexamethasone (40 mg/day × 4 days) with sequential oral prednisone maintenance therapy (1 mg/kg daily). During the 6-month follow-up, 55 patients (76.4%) achieved SR (a), and 39 patients (54.2%) achieved continuous CR (b). Twenty-eight anti-nuclear antibody (ANA)-positive patients achieved SR (77.8%), and 21 achieved continuous CR (58.3%). Compared with ANA-negative patients, there were no significant differences in SR and CR between the two groups at 6 months (p = 0.96, 0.64) (c and d). Nineteen patients with positive antithyroid antibodies achieved SR (79.2%), and 13 achieved continuous CR (54.2%). There were no statistical differences in SR and CR between patients with positive or negative antithyroid antibodies at 6 months (p = 0.50, 0.62) (e and f).

and 21 ANA-positive patients achieved continuous CR (58.3%). Compared with ANA-negative patients, there were no significant differences in SR and CR between the two groups at 6 months (Figure 1c and 1d).

Twenty-three patients with positive antithyroid antibodies (95.8%) achieved response after treatment, and 20 patients (83.3%) achieved CR. Nineteen patients achieved SR (79.2%), and 13 patients achieved continuous CR (54.2%) during the 6-month follow-up period. There were no statistical differences in SR and CR between patients with positive or negative antithyroid antibodies at 6 months (Figure 1e and 1f).

Twelve-month SR and CR

For patients who obtained initial response (n = 70), the 12-month probability of SR was 78.6% (range 67.0%–86.5%) (Figure 2a). For patients who obtained initial CR (n = 53), the 12-month probability of continuous CR was 64.2% (49.7%–75.4%) (Figure 2b).

For ANA-positive patients, the 12-month probability of SR was 77.8% (60.4%–88.2%), and the 12-month probability of continuous CR was 67.9% (47.3%–81.8%) (Figure 2c and 2d). For patients with positive antithyroid antibodies, the 12-month probability of SR was 82.6% (60.1%–93.1%), and the 12-month probability of continuous CR was 60% (35.7%–77.6%) (Figure 2e and 2f).

There were no statistical differences between ANA-positive and -negative patients in terms of the 12-month SR rate or 12-month continuous CR rate (Figure 2c and 2d). Similarly, there were no statistical differences between antithyroid antibody-positive and -negative patients in terms of the 12-month SR rate or 12-month continuous CR rate (Figure 2e and 2f).

Loss of therapeutic response

Among patients who achieved initial response and CR, the cumulative incidence of the loss of response to treatment at 12 months was 21.4% (11.2%–30.5%) and 11.3% (2.3%–19.5%), respectively. The rate of the loss of response to treatment in patients with initial response was slightly higher than that in patients with initial CR, but there was no statistical significance (Figure 3).

Safety

Two patients died during the follow-up period (2.8%). One died of intracranial infection, and the other died of cerebral herniation after intracranial hemorrhage. Ten patients developed hypertension after treatment (13.9%), and 11 patients developed hyperglycemia (15.3%). No femoral head necrosis was found during the follow-up of patients (Table 1).

Discussion

According to ITP international guidelines,[2,6] HD-DXM (40 mg/day × 4 days) or conventional-dose prednisone (1 mg/kg per day) is the first-line treatment. In a prospective multicenter randomized trial,[3] one or two courses of HD-DXM resulted in a higher overall initial response rate (82.1% vs 69.1%, p = 0.044) and CR rate (50.5% vs 26.8%, p = 0.001) compared with prednisone. In addition, patients treated with HD-DXM showed a shorter time to reach response and CR, and the therapy was generally well tolerated. A retrospective study reported by Sakamoto et al.[7] also showed that the response rate of patients treated with HD-DXM was higher than that for prednisone, and the time to obtain CR was shorter. Therefore, as an initial treatment of newly diagnosed ITP, HD-DXM exhibits better efficacy and safety than prednisone. However, in the study by Wei
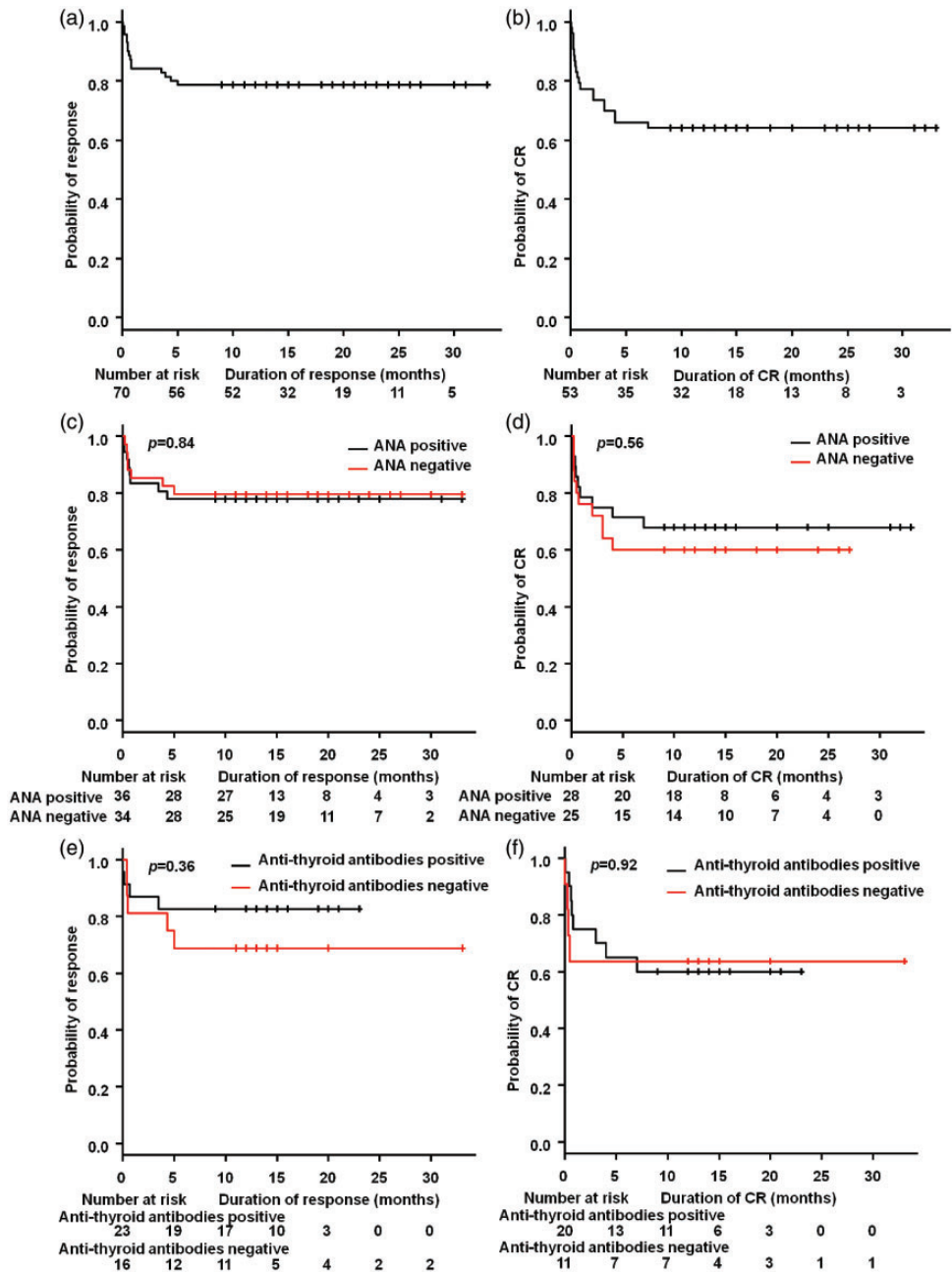
Figure 2. Twelve-month sustained response (SR) and complete remission (CR) in 72 newly diagnosed immune thrombocytopenia adult patients administered intravenous high-dose dexamethasone (40 mg/day × 4 days) with sequential oral prednisone maintenance therapy (1 mg/kg daily). The 12-month probabilities of SR and CR for patients who obtained initial response (a) and initial CR (b). There were no statistical differences between anti-nuclear antibody (ANA)-positive and -negative patients in terms of 12-month the SR rate (c) or 12-month continuous CR rate (d), and there was also no statistical differences between antithyroid antibody-positive and -negative patients (e and f).
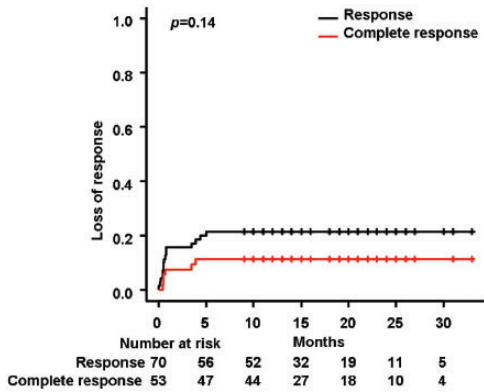
Figure 3. Loss of response in 72 newly diagnosed immune thrombocytopenia adult patients who achieved initial response and complete response (CR) after the administration of intravenous high-dose dexamethasone (40 mg/day × 4 days) with sequential oral prednisone maintenance therapy (1 mg/kg daily). The cumulative incidence of loss of response at 12 months for patients who achieved initial response and CR was 21.4% (11.2%–30.5%) and 11.3% (2.3%–19.5%), respectively (p = 0.14).

et al.[3] the SR rates obtained by the two regimens were similar (p = 0.884), and the incidence of SR and persistent CR in the HD-DXM cohort was only 40.0% and 27.4%, respectively. Although the response rate was 100%, and the CR rate was 90.3% in patients receiving HD-DXM in the study by Sakamoto et al., the response gradually disappeared over time. Specifically, the rate of SR after 1 year was only 42.7%.[7] Both of the above studies indicated that short-term HD-DXM achieved a high initial response rate, but the long-term efficacy was poor. However, in this study, the long-term efficacy was superior to previously reported studies (summarized in Table 2) as 97.2% and 73.6% of patients achieved response and CR, and 76.4% and 54.2% of patients achieved SR and continuous CR, respectively.

The pathogenesis of ITP is particularly complex and not fully understood. Similar to other acquired autoimmune diseases, genetic susceptibility,[8–10] immune

imbalance[11] and abnormalities of the bone marrow immune microenvironment lead to the development of ITP.[12,13] Therefore, immunosuppressive therapy, especially corticosteroid treatment, is the first-line treatment for ITP. It has been demonstrated that the immune imbalance in ITP patients is attributed to abnormalities in B cells, T cells, macrophages, and other immune cells. As a result, short-term HD-DXM treatment is unable to completely suppress the abnormal immunity in ITP or achieve sufficient long-term efficacy. Although the disease course is self-limiting in some patients, 70% of patients eventually develop chronic ITP, resulting in a poor quality of life.[1] In this study, HD-DXM with sequential prednisone maintenance therapy resulted in more adequate immunosuppression, which explains the superior clinical efficacy of this treatment approach compared with that in previous reports (Table 2). Furthermore, we found that the morbidity and severity of steroid-related adverse events were within an acceptable range. Therefore, we consider that HD-DXM with sequential prednisone maintenance therapy might be recommended as a preferred first-line treatment for newly diagnosed ITP patients.

In conclusion, this study indicates that the short- and long-term efficacies of HD-DXM with sequential prednisone maintenance therapy for newly diagnosed ITP are superior to those of the first-line treatment (HD-DXM or conventional prednisone) recommended by international guidelines. The morbidity and severity of adverse events were both acceptable. Although the clinical efficacy of this treatment approach is encouraging, this research has some limitations. First, this was a non-prospective and non-controlled study performed in a single center. Additionally, there was no grading of ITP, the initial treatment of HD-DXM was combined with high-dose IVIG in 61.1% of patients, and the number of patients was small.

Second, the observation period was short. For instance, there were at least 42 patients (58.3%) whose observation period was less than 18 months. Third, as a symptom of ITP, fatigue combined with corticosteroid-related adverse events may negatively affect the quality of life of patients. These limitations might have led to overly optimistic conclusions in the present study. We plan to conduct a prospective randomized multicenter clinical trial to expand the sample size and further verify the clinical efficacy of HD-DXM with sequential prednisone maintenance therapy for newly diagnosed adult ITP patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

Jin Xu collected and analyzed data and wrote the original paper. Changcheng Zheng designed the research, performed the research, analyzed and interpreted data, completed the tables and figures and critically reviewed the manuscript. All authors participated in patient care and contributed to data interpretation.

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References

1. Cooper N and Ghanima W. Immune Thrombocytopenia. *N Engl J Med* 2019; 381: 945–955.

2. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv* 2019; 3: 3780–3817.

3. Wei Y, Ji XB, Wang YW, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. *Blood* 2016; 127: 296–302.

4. Frederiksen H and Ghanima W. Response of first line treatment with corticosteroids in a population-based cohort of adults with primary immune thrombocytopenia. *Eur J Intern Med* 2017; 37: e23–e25.

5. Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med* 2003; 349: 831–836.

6. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115: 168–186.

7. Sakamoto K, Nakasone H, Tsurumi S, et al. Prednisone versus high-dose dexamethasone for untreated primary immune thrombocytopenia. A retrospective study of the Japan Hematology & Oncology Clinical Study Group. *J Thromb Thrombolysis* 2014; 37: 279–286.

8. Takahashi N, Saitoh T, Gotoh N, et al. The cytokine polymorphisms affecting Th1/Th2 increase the susceptibility to, and severity of, chronic ITP. *BMC Immunol* 2017; 18: 26.

9. Rischewski JR, Imbach P, Paulussen M, et al. Idiopathic thrombocytopenic purpura (ITP): is there a genetic predisposition? Pediatr Blood Cancer 2006; 47: 678–680.

10. Rezaeeyan H, Jaseb K, Alghasi A, et al. Association between gene polymorphisms and clinical features in idiopathic thrombocytopenic purpura patients. *Blood Coagul Fibrinolysis* 2017; 28 617–622.

11. Fischer A, Provot J, Jais JP, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J Allergy Clin Immunol* 2017; 140: 1388–1393.e8.

12. Li J, Sullivan JA and Ni H. Pathophysiology of immune thrombocytopenia. *Curr Opin Hematol* 2018; 25: 373–381.

13. Song Y, Wang YT, Huang XJ, et al. Abnormalities of the bone marrow immune microenvironment in patients with immune thrombocytopenia. *Ann Hematol* 2016; 95: 959–965.

14. Sadeghi A, Hosseini SF and Jouzdani SR. Evaluation of treatment plan by three-period pulses of high-dose dexamethasone among patients with primary immune thrombocytopenia on platelet count response and adverse events: A randomized Clinical trial. *J Res Med Sci* 2020; 25: 88.

15. Takase K, Nagai H, Kadono M, et al. High-dose dexamethasone therapy as the initial treatment for idiopathic thrombocytopenic purpura. *Int J Hematol* 2020; 111: 388–395.

16. Yu Y, Wang M, Hou Y, et al. High-dose dexamethasone plus recombinant human thrombopoietin vs high-dose dexamethasone alone as frontline treatment for newly diagnosed adult primary immune thrombocytopenia: A prospective, multicenter, randomized trial. *Am J Hematol* 2020; 95: 1542–1552.