ORIGINAL ARTICLE

Evaluation of First-line and High-altitude Alpine Therapies for Patients with Immune Thrombocytopenia

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Abstract

Introduction: Acquired thrombocytopenia is a condition that causes immune thrombocytopenia (ITP) and is characterized by a platelet count of 100 × 10^9/l. The main challenges faced by Kyrgyz patients with ITP include the lack of clearly defined therapeutic regimens, high rate of complications associated with glucocorticoid use, unpredictability in treatment outcomes, and limited access to novel drugs. We aimed to evaluate the safety and efficacy of initial and supplementary treatments for individuals with ITP. **Methods:** Between 2015 and 2022, data from two sites in Kyrgyzstan, one in the country's south and the other in the Republic, were retrospectively analyzed for 172 patients who met the inclusion criteria. The initial treatment regimen followed the current standards, consisting of several injection courses with a dose ranging from 0.4 to 1 g/kg over one to five doses. In addition, dexamethasone was delivered at a dosage of 40 mg orally or intravenously every day for 4 days, along with prednisone at a daily dosage of 1–40 mg for up to 4 weeks. **Results:** Only 22.4% of patients showed clinical and hematological improvement with prednisone treatment, and no partial or complete remission was observed. Of 91 patients, 57 (62.6%) experienced adverse events due to prednisone. The most common adverse events were hyperglycemia and metabolism (34.1%), followed by mental disorders (27.5%), sleeplessness (23.1%), hypertension (15.4%), and skin disorders (12.1%). **Conclusion:** In 45.4–77.6% of cases, conservative treatment approaches can effectively treat adult ITP patients. Current treatments include prednisone, dexamethasone, and the combined use of intravenous immunoglobulin, rituximab, and azathioprine.

Key words: Dexamethasone, immune thrombocytopenia, intravenous immunoglobulin, prednisone

INTRODUCTION

Low platelet counts, which are <100 × 10^9/l, are a defining characteristic of immune thrombocytopenic purpura (ITP), a condition in which the immune system attacks and destroys platelets.[1] This illness affects individuals of all ages, with the highest incidence occurring in children who experience repeated peaks in the condition. The differing prevalence of chronic ITP in different patients shows significant disparities in the underlying causes of the illness between adults and children.[2] Despite being typically a chronic illness in adults, ITP often resolves in young individuals.[3] There is no significant gender variation in the incidence of

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Received: 17-02-2024
Revised: 22-03-2024
Accepted: 30-03-2024

adult primary ITP up to the age of 60 years, which ranges from 3.3–3.9 cases/100,000 people annually. ITP symptoms and treatment outcomes can vary greatly from person to person.[2,3]

Patients with isolated primary ITP typically undergo a comprehensive evaluation to rule out more severe conditions, such as viral infections, autoimmune disorders, hematopoietic deficiencies, and bone marrow infiltration. A diagnosis of primary ITP is made when no abnormalities are detected and the patient has isolated thrombocytopenia (platelets $<100 \times 10^9$/l).[3,4] Bone marrow tests are often performed in patients with thrombocytopenia to exclude bone marrow disease. However, researches showed substantial bone marrow abnormalities are rare in asymptomatic individuals. Therefore, routine bone marrow testing is not recommended for patients without symptoms or other indications of an underlying disease, according to recommendations from the American Society of Hematology for ITP.[1,5,6] New drugs such as fostamatinib and avatrombopag offer promising treatment options for ITP.[1,5-7]

The American Society of Hematology recommends rituximab or thrombopoietin agonists (TPO-A) as second-line therapy for patients who relapse following the initial treatment according to their recommendations and modifications.[3,4] However, these drugs are costly and require government approval, rendering them inaccessible to Kyrgyzstan. In Kyrgyzstan, doctors usually administer glucocorticosteroids as well as a few additional second-line drugs.

The primary challenges faced by patients with ITP in Kyrgyzstan include the absence of well-defined therapeutic plans, a high rate of complications arising from glucocorticoid-induced side effects, unpredictable treatment outcomes, and limited access to advanced medications. Given that ITP therapy has shown some promise, it is crucial to address it in the high-altitude setting of Kyrgyzstan.[8] This study aimed to examine the safety and effectiveness of initial and additional treatments for individuals with ITP.

METHODS

A retrospective analysis of individuals with ITP treated by hematology specialists at two locations in Kyrgyzstan, one in the south and the other in the Republic, was conducted between 2015 and 2022. This study included data from the Department of Hematology at the Osh Inter-Regional Clinical Hospital, which covers three southern regions of the country, and the Department of Adult Hematology at our hospital. The local Committee on the Ethics of Human Research at I. K. Akhunbaev Kyrgyz State Medical Academy authorized this study on March 10, 2020, and assigned Protocol Number 17.

The following individuals were included in this study: Patients who were diagnosed with ITP received treatment at participating institutions between 2015 and 2022 and were at least 18 years old. Patients without sufficient medical records were excluded from the study. As all eligible patients were included in the research sample, a separate calculation of the sample was not performed. The records of all hospitalized individuals who were assigned the diagnosis codes ICD-10 D69.6 (thrombocytopenia) or D69.3 [ITP] during the study period were reviewed.[9]

Examining the patients' medical records yielded a wealth of information about their treatments and outcomes. Over the course of the trial, data on treatments and responses were collected retrospectively, including during the hematologist's follow-up phase. Due to the limitations of the available data, it was not always possible to determine the cause of any follow-up loss. To maintain precision and uniformity, we included the quality of response, severity of illness, and duration of response duration of response in adherence to the standards set forth by the international working group.[1] Tuya-Ashu Pass, which stands at an elevation of 3200 m above sea level, is where the high-altitude hospital of the I.K. Akhunbaev Kyrgyz State Medical Academy is located. Located within the Tengri Tagh mountain, this pass is the location of the tunnel highway connecting Bishkek and Osh. The region experiences a diverse range of weather conditions throughout the day, including sun, clouds, rain, snow, and hail. The summer season is short, lasting between 60 and 75 days, with temperatures ranging from 17°C to 22°C. With an annual precipitation of 753 mm, the region receives approximately two-fold rainfall as Bishkek does. Because of these geographical and meteorological factors, high-altitude hospitals are only accessible during the warm season, spanning from June to August. The 40-bed alpine base is a single-story facility that includes a ward, residential room, kitchen, dining area, and treatment room. Patients were provided with a well-planned, high-protein and-calorie diet three meals daily.

Statistical analysis, version 11.5 of the Statistical Package for the Social Sciences was employed. The results are presented as mean ± standard deviation and *n* (%), and a paired *t*-test was used to evaluate the variations in treatment and outcomes across the participating sites. The test assumed equal variances for both samples, and the findings indicated statistically significant differences in platelet count, length of therapy, hospitalization duration, and demographic characteristics ($P < 0.05$). However, due to the small sample size, no additional analyses were performed for these subgroups.

RESULTS

One hundred and seventy-two individuals who have an average age of 46.3 ± 2.86 are presented in Table 1. Of the total, 104 (60.5%) individuals were women and 68 (39.5%) were men. The mean age of individuals at the beginning of therapy was consistent across both centers.

Table 1: Common features of individuals compared between the two centers

Treatment centers	*n (%)*	Women (%)	Mean age	No. of bed-days	No. of thrombocytes
Southern	78 (45.3)	56.4	45.1±4.82	13.9±2.41	26.2±2.77
Republican	94 (54.7)	60.6	47.4±4.90	15.4±2.84	14.5±1.93
Total	172 (100.0)	104 (60.5)	46.3±2.86	14.8±2.92	17.1±1.84

Data presented as *n* (%), N: No. of patients, m±M: Mean±standard deviation

The platelet count varied significantly across clinical sites, ranging from 26.2–14.5 × 10^9 cells/l ($P < 0.05$). On being admitted to the hospital, the average platelet count was 17.1 ± 1.84 × 10^9 cells/l. Over 11% of the study, participants had a platelet count below 20,000 cells/l, which indicates severe ITP and more than 90.7% of them had bleeding that required hospitalization upon arrival, according to the World Health Organization.[9] There was no significant difference in the average length of hospital stay between the two facilities at the time of treatment, which was 14.8 ± 2.92 days.

Of the individuals examined, 113 (65.7%) were diagnosed with primary ITP, and 59 (34.3%) were diagnosed with secondary ITP. Secondary ITP cases were caused by infections in 35.6% of the patients, including those with Helicobacter pylori in 13 patients (22.0%) but excluding others, antiphospholipid syndrome in 11 patients (18.6%), hematological malignant neoplasms in 6 patients (10.1%), and systemic lupus erythematosus in 5 (8.5%) individuals [Figure 1]. Other additional factors were medication responses, gestation, connective tissue disorders, and autoimmune illnesses not associated with systemic lupus erythematosus, impacting three individuals. Patients with secondary ITP had a significantly longer hospital stay than those with primary ITP (18.5 compared to 8.4 days). Furthermore, individuals diagnosed with secondary ITP had a lower probability of receiving the first drug therapy (25.4% compared to 91.1%) and did not receive further medication (0% compared to 33%).

Of the 172 individuals evaluated, 141 (82%) were initially treated, whereas 31 (18%) were not. The average age at diagnosis in the treated group was 41.7 years, which was significantly higher than the 28.5 years observed in the untreated group ($n = 141$, $P < 0.05$).

The patients in the treatment group had a lower median number of platelets at the time of admission (13.7 × 10^9 cells/l) and a higher prevalence of bleeding symptoms at the initial therapy (94.3%). Individuals who presented with bleeding symptoms had a significantly longer duration of hospitalization than those without such symptoms, with an average of 14.9 compared to 6.3 days, $P = 0.01$). Additionally, patients with ITP resulting from infection, Helicobacter pylori infection, or hematological malignancies were less likely to exhibit bleeding at the time of admission, with rates of 28.5%, 33.3%, and 38.5%, respectively, all of which were below the overall average of 94.3%.

The recommended initial dosage regimen followed the current guidelines, which prescribed prednisone at a dose of 1–40 mg

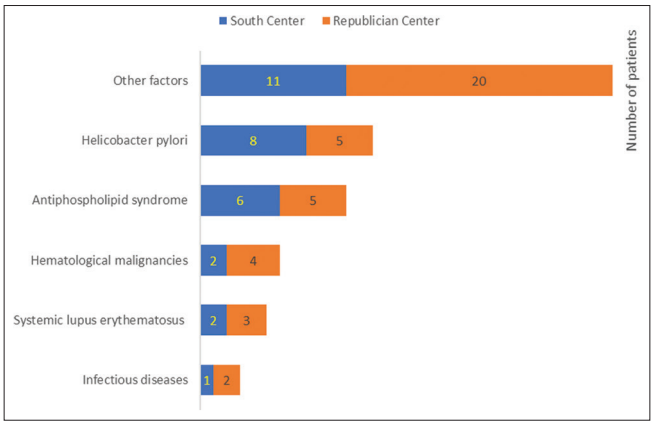

Figure 1: Various diseases in patients with immune thrombocytopenic purpura from two centers

daily for a period 1–4 weeks, along with dexamethasone at 40 mg administered orally or intravenously per day for 4 consecutive days. In addition, 0.4–1 g/kg was administered via multiple injections in 1–5 doses.[6]

Individuals in the study received prednisone as their primary treatment, with no significant difference in the average age at diagnosis or duration of hospital stay observed between those receiving prednisone and those receiving alternative first-line treatments. All patients were treated with prednisone for an average of 177 days, although the duration of treatment varied notably between medical facilities. Unfortunately, prednisone did not result in any partial or complete remission, as only 22.4% of patients experienced clinical and hematological improvement. Among the 91 individuals, 57 (62.6%) experienced adverse events from the prednisone treatment. The most common adverse events were related to metabolism and high blood glucose (34.1%), followed by mood disturbances (27.5%), sleep disorder (23.1%), high blood pressure (15.4%), and skin issues (12.1%).

A cohort of 21 individuals with a mean aged of 38.5 years, was administered dexamethasone tosustain their response [Table 2]. Following statistical analysis, no significant differences were observed in age, platelet count, or hospital stay duration between this group and the larger population of patients receiving therapy ($P = 0.7$, 0.8, and 0.5, respectively). Among the 21 patients, 16 (76.2%) needed additional dosagesof dexamethasone to maintain response. While undergoing dexamethasone treatment, 61.9% of the patients revealed improvements in both their clinical and hematological conditions, but none of the patients achieved

Table 2: Characteristics of patients with ITP who underwent primary treatment

Early therapy	N	Mean age	Gender (men/women)	Bleeding	Mean no. of thrombocytes	Average bed-days	Response duration
Prednisone	85	45.2	27/64	69.2	11.9	10.2	12.7
Dexamethasone	21	38.5	8/13	85.7	13.7	9.6	10.2
Prednisone+IVIg	14	50.1	9/5	78.6	10.7	12.4	9.6
Dexamethasone+IVIg	11	39.6	5/6	72.7	18.6	15.1	17.3
Prednisone+Dexamethasone+IVIg	4	29.9	2/2	50.0	23.5	10.7	15.3
Rituximab	3	33.4	2/1	100.0	16.0	13.8	12.5
Azathioprine	3	27.8	1/2	100.0	12.7	15.2	13.8
Total patients for treatment	141	48.3	51/90	73.0	17.3	13.9	8.2
Splenectomy	18	30.3	7/11	100.0	13.9	19.3	16 complete remission
Without treatment	31	40.4	17/14	74.2	28.8	8.5	1.4
Total number of patients	172	44.2	68/104	73.2	14.8	12.8	13.9
Alpine climatotherapy	51	38.2	31/20	-	21.3	34.2	12 complete remission

Data presented as n (%), N: No. of patients, m±M: Mean±standard deviation, IVIg: Intravenous immunoglobulin, ITP: Immune thrombocytopenic purpura

either partial or total remission. Approximately 57.1% of the patients experienced adverse effects from dexamethasone, with the most common being related to metabolism, including hyperglycemia (38.0%) and mood (14.3%).

Determining the most effective first-line treatment options for patients with particular characteristics, including platelet counts, age at treatment initiation, bleeding rates at admission, and length of hospital stay, proved to be difficult due to the limited sample size and wide confidence intervals of the study. Of the 57 patients in the present study, 67.0% responded well to the initial treatment and did not require further therapy with second-line medications.

A notable percentage of the patients, comprising 21 (12.2%) individuals, exhibited a positive response to second-line therapy, thereby avoiding the need for further intervention. Among these individuals, 18 (10.5%) experienced complete recovery from both clinical and hematological perspectives after undergoing open-access splenectomy. Furthermore, 51 (29.7%) individuals underwent five rounds of high-altitude climatotherapy at the Tuya-Ashu base situated at an elevation of 3200 m above sea level, ultimately achieving remission.

Three patients received rituximab as follow-up treatment, and two patients received it as second-line treatment. The most common dosage regimen consisted of administering 100 mg of rituximab weekly for 4 weeks at a moderate dose, which resulted in a full response in 64.7% of cases. The average reaction duration for every individual who were administered rituximab was 25.2 ± 3.81 days, and the mean response duration was 27.3 ± 3.72 months. Two individuals using corticosteroids had an average response time of 12.9 days and an average response duration of 21.1 months, as compared to 25.2 days and 27.3 months, respectively, for those receiving rituximab alone. The hematological and clinical statuses of 66.6% of the patients improved during treatment, but no partial or total remission was observed. Every individual experienced adverse events of rituximab, with headache being the most commonly reported adverse effect. One patient experienced infusion response.

Sympathectomy, a second-line therapy, was administered to 18 individuals, who exhibited an mean response duration of 41.0 months and a response duration of 10.2 ± 1.90 days. Additionally, 11 patients underwent an average 28-day corticosteroid therapy, resulting in an mean response duration of 37.1 months for these patients, compared to 14.9 days for the other patients. Patients who underwent splenectomy alone had an average response time of 42.8 months, while the other patients had a mean response duration of 5.6 days. Throughout the therapy, 88.9% of the patients achieved complete remission, whereas the remaining patients achieved partial remission. An infection was the most common adverse event that three (16.7%) individuals encountered following splenectomy.

In 7.5% of cases, azathioprine was administered to three individuals as a second-line therapy option. Two of these individuals were administered 50 mg daily, whereas the remaining one received 100 mg each day. The mean response duration for every individual taking azathioprine was 22.9 ± 3.13 days, which translates to 28 months. Among the patients who received corticosteroids in addition to azathioprine, the mean response duration was 16 days, which was shorter than that of patients who only received azathioprine ($P < 0.05$). The mean reaction duration for these patients was 9.3 months, while those who received azathioprine alone had a much longer overall response time

of 28 months. Throughout the treatment period, 88.9% of the individuals reported improvements in their hematological and clinical states, with one patient remaining unchanged. Approximately 23.1% of patients experienced side effects from azathioprine, with nausea being the most common. It should be noted that the study only included individuals who were taking azathioprine 100 mg daily, which is a high dosage and has adverse effects.

Eleven patients were prescribed dexamethasone as a follow-up treatment, primarily as second-line therapy, at a dosage of 40 mg/day for 4 days. The average duration of response was 8.8 ± 1.31 days. Dexamethasone had a shorter response length (average reaction time of 8.2 months) when used as a second-line medicine compared to other medications. Although only 54.6% of patients experienced clinical and hematological improvements, the majority of patients (81.8%) experienced side effects, with anxiety, headaches, and sleep disturbances being the most frequently reported side effects. Individuals with chronic and resistant ITP were treated with high-altitude alpine therapy as second-line therapy in this study. Among the individuals, 74.5% achieved clinical and hematological remission, with 52.2% experiencing full remission and 22% experiencing partial remission. The likelihood of achieving full remission was higher in patients who had been ill for to 1–3 years. A 35-year-old patient achieved complete remission after two consecutive 40-day periods at altitude following failed hormone and interferon therapy. The average length of remission was 2.35 years, with a standard deviation of 0.41 years. The remission rates were not significantly different among patients who received conservative treatment. However, the results of high-altitude climatotherapy were markedly different from those of the medication.

DISCUSSION

The standard treatment for ITP is intravenous immunoglobulin (IVIg), which can be administered either alone or in conjunction with corticosteroids. While there is limited evidence to support the use of these alternative treatments, healthcare professionals may still consider them.[1-6,10] These additional therapies typically produce a moderate response rate; however, they can also cause adverse effects that may require discontinuation.

The use of corticosteroids is frequently prioritized as a primary treatment option; however, extended utilization can result in severe adverse effects, especially those related to metabolism, which may call for discontinuation. Moreover, the study revealed that patients, on average, required 2.17 treatment lines to attain an ongoing response, underscoring the prevalence of the inadequacy of first-line therapy.

For individuals with chronic ITP, oral corticosteroids are often suggested as the first-line therapy unless there are contraindications or a need for a faster increase in platelet count because of severe bleeding. Prednisone is the most commonly used corticosteroid, typically administered at a dose of 0.5–2 mg/kg/day for 2–3 weeks. The dosage should be gradually reduced with the aim of discontinuing by 6–8 weeks.[10-12] First, 70–80% of individuals exhibit a response, but permanent cure rates are poor, and the prevalence of recurrences is significant.[13]

Some studies included patients with ITP who were either receiving treatment in a hospital setting or monitored by a hematologist. In patients with severe and chronic conditions, respectively. The social and demographic features of the study cohort corresponded with the findings of previous investigations, comprising 58% of female patients and a mean age of 48.85 years at the time of diagnosis.[3,4]

Information on the ethnicities of individuals undergoing therapy in public medical centers in Kyrgyzstan is usually never gathered, hindering the identification of hereditary or social-cultural variables that might impact treatment effectiveness or tolerance. Moreover, inadequate data in medical records hinder the collection of data for patients, especially those in need of blood or platelets for transfusions.

Prednisone, either alone or in combination with IVIg, was the main treatment option for most patients. All treatment centers followed the current therapy recommendations for the initial treatment period, which usually lasted between 5 and 8 days. Although precise information regarding prednisone dose at the time of discontinuation was not available in this study, it was observed that the weaning process took an average of 67–392 days across various centers.

CONCLUSIONS

In 45.4–77.6% of cases, conservative treatment approaches can effectively treat adult ITP patients. Current treatments include prednisone, dexamethasone, and the combined use of IVIg, rituximab, and azathioprine. When medication fails to cure chronic ITP, splenectomy is the most effective treatment plan. Although patients with ITP may benefit from high-altitude climatotherapy, further research is required to support this treatment choice.

ACKNOWLEDGEMENT

None.

AUTHOR'S CONTRIBUTION

Clinical management: AZ, DA, EB, AE, BM, OE, UK, SM; Performed work: AZ, DA, EB, SM: Designed and generated idea; AE, BM, OE, UK, MP, KK; Prepared manuscript: BM, OE, UK, SM, MP, KK.

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Source of Support: Nil. **Conflicts of Interest:** None declared.