Introduction and Aim: Immune thrombocytopenia (ITP) is an acquired thrombocytopenia characterized by a platelet count of 100x10^9/l and caused by immune-mediated destruction of platelets. This study aimed to assess the efficacy and tolerability of the first and subsequent lines of therapy for adult patients with ITP.

Materials and Methods: This retrospective study included 172 patients with ITP and a mean age of 44.2±5.71 years at the time of diagnosis and/or who were treated for ITP at participating centers such as south and republican centers in Kyrgyzstan during the study period from 2015–2022. Analyzing patient medical records yielded detailed data on treatment strategies and results.

Results: There was a significant difference in the mean number of platelets between clinical centers (26.2 versus 14.5x10^9 cells/l, p<0.05), and the mean number of platelets at admission to the hospital was 17.1±1.84x10^9 cells/l. 113 (65.7%) had primary ITP, and the remaining 59 (34.3%) had secondary ITP. 35.6% of patients with secondary causes were infected (including those with Helicobacter pylori but not others).

Conclusion: Patients with adult ITP can be effectively treated with conservative methods in 45.4–77.6% of cases. These treatments include prednisone, dexamethasone, and their combination with intravenous immunoglobulin, rituximab, and azathioprine.

Keywords: Immune thrombocytopenia; corticosteroids; high-altitude climatotherapy; platelets; intravenous immunoglobulin

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia characterized by a platelet count of <100x10^9/l and caused by immune-mediated destruction of platelets (1). With multimodal morbidity, it affects both adults and children; the first peak arises in childhood, while the second and third arise in young and elderly individuals. The incidence of chronic ITP in various patient groups suggests that the fundamental disease mechanism of ITP in children and adults may differ considerably (2). ITP is more frequently a chronic illness in adults, even though it typically subsides on its own in children (3).

Adults with primary ITP have an incidence of 3.3–3.9 per 1,000,000 per year, with little female predominance up to the age of 60, as it is more prevalent in men. The clinical presentation and response to therapy for ITP vary widely (2, 3). Even now, the diagnosis of ITP continues to be a diagnosis by exclusion. In order to rule out serious conditions such as hematopoiesis insufficiency, bone marrow infiltration, other autoimmune disorders, viral infections, etc., patients with isolated primary ITP undergo several kinds of examinations. Primary ITP is diagnosed if there are no deviations from the norm and only isolated thrombocytopenia (platelets <100x10^9/l) is seen (3, 4).

In older times, bone marrow tests were frequently carried out in thrombocytopenia patients in order to rule out bone marrow pathology. Studies have revealed that significant bone marrow pathologies are not often found in asymptomatic patients (4). Because of this, the most recent guidelines from the American Society of Hematology and the International Consensus do not advise regular bone marrow tests if there are no symptoms or signs of an underlying illness (1, 5, 6). Avatrombopag and fostamatinib, two recently produced extremely effective medications, increase the possibilities for treating this disease (1–5, 9).

The American Society of Hematology (ASH) has put out guidelines (3, 4) and updates (4) that recommend rituximab or thrombopoietin agonists (TPO-A) as second-line treatments for people who have had a relapse after first-line therapy. Unfortunately, Kyrgyzstan has limits on accessing these medications since they are expensive and require official authorization. As a result, most of the time, specialists...
in Kyrgyzstan prescribe glucocorticosteroids together with a few other second-line drugs.

Due to the inaccessibility of new medications, the imperfection of developed ITP therapy protocols, the high incidence of complications associated with glucocorticoid-induced reactions, and the frequent unpredictability of the expected response, it is essential to highlight the treatment of patients with ITP in the high-altitude climate of Kyrgyzstan, since it has demonstrated some efficacy (10).

Accordingly, the most serious problem affecting Kyrgyzstan at present is the treatment of adult patients with ITP. This study aimed to assess the efficacy and tolerability of the first and subsequent lines of therapy for adult patients with ITP.

MATERIALS AND METHODS

A retrospective study of patients treated for ITP by hematologists in two participating centers such as south and republican centers in Kyrgyzstan from 2015–2022 was conducted. The centers included the Department of Hematology of the Osh Interregional Clinical Hospital, serving three regions of the southern region of Kyrgyzstan, and the Department of Adult Hematology of the National Center of Oncology and Hematology of the Ministry of Health of the Kyrgyz Republic, serving patients from all over the country. The I.K. Akhunbaev Kyrgyz State Medical Academy’s local Committee on Ethics of Human Research approved this study (Protocol No. 17 dated March 10, 2020).

This study included all patients aged 18 years and older who were diagnosed with ITP and/or who were treated for ITP at participating centers during the study period (2015–2022). Exclusion criteria included incomplete medical records of patients. The study sample included all patients in participating institutions who met the inclusion criteria, so a separate quantitative assessment of the sample size was not carried out. The reports of all patients admitted to the hospital during the study period (2015–2022) and who received the diagnostic code ICD-10 D69.6 (thrombocytopenia) or D69.3 (ITP) were reviewed (11).

Analyzing patient medical records yielded detailed data on treatment strategies and results. Retrospective data on treatment and response was obtained during the course of the study, including the follow-up period with the attending hematologist. Losses for follow-up were not separately accounted for since it was not always feasible to ascertain the reason for the end of observation due to the nature of the available data. It was determined to define the terms “disease severity,” “quality of response,” and “duration of response” considering guidelines from the international working group (1).

High-altitude climatotherapy took place over a period of 30–40 days undertaken at the I.K. Akhunbaev Kyrgyz State Medical Academy which is situated 3200 meters above sea level on the Tuya-Ashu Pass, which is a part of the Tien Shan Mountain range. Through the pass lies the highway tunnel Bishkek-Osh. The weather in the Tuya-Ashu pass varies greatly throughout the day; it might be sunny, cloudy, or rainy, then snow or hail. Summers are typically brief (60–75 days), with daytime temperatures of 17°C and low temperatures of 22°C. With 753 millimeters of precipitation annually, it receives about twice as much as Bishkek. Owing to these geographic and climatic factors, the high-altitude hospital is only open from June to August during the warm season. The alpine base is a one-story facility with 40 beds. The facility has a dining area, kitchen, resident’s room, treatment room, and wards. A well-organized, high-calorie meal three times a day was included.

Statistical analysis was carried out using the Statistical Package for the Social Sciences, version 11.5. The obtained data are shown as mean ± standard deviation and n (%). Paired t-tests (two samples provided equal variances) were used to assess differences in treatment and outcomes between participating centers. Differences were determined to be statistically significant at p<0.05 in demographic characteristics, duration of hospitalization, platelet count, and duration of treatment. Statistical analysis was not used for these subgroups due to the limited sample size.

RESULTS

172 patients with a mean age of 44.2±5.71 years at the time of diagnosis were included in the study (Table 1). Men were 68 (39.5%) and women were 104 (60.5%) of the total number of patients. In both participating centers, the average age of the patients at the start of therapy was the same.

Fig. 1: High-altitude base Tuyu-Ashu (3200 meters above sea level)
There was a significant difference in the mean number of platelets between clinical centers (26.2 versus 14.5×10^9 cells/l, p<0.05), and the mean number of platelets at admission to the hospital was 17.1±1.84×10^9 cells/l. According to the World Health Organization, 90.7% of the patients included in this study had bleeding at admission that needed hospitalization and a platelet count of fewer than 20,000, which is eligible for severe ITP (11). At the time of treatment, the two centers' average length of hospital stay was 14.8±2.92 days, and there was no statistically significant difference between them.

113 (65.7%) had primary ITP, and the remaining 59 (34.3%) had secondary ITP. 35.6% of patients with secondary causes were infected (including those with Helicobacter pylori but not others). There were also 13 patients with systemic lupus erythematosus (SLE), which is 22.0%; 11 patients with hematological malignant neoplasms, which is 18.6%; 6 patients with antiphospholipid syndrome, which is 10.1%; and 5 patients with H. pylori, which was 8.5% (2/3 people). Also, secondary causes included drug reactions, pregnancy, connective tissue problems, and autoimmune diseases that were not linked to SLE. These happened in 3 patients (Figure 2). In patients with secondary ITP, the mean duration of hospitalization was significantly higher than in patients with primary ITP (18.5 vs. 8.4 days). Compared with primary ITP, patients with secondary etiology were less likely to receive treatment with first-line drugs (25.4% vs. 91.1%) and did not receive second-line drugs at all (0% vs. 33%).

Of the 172 patients included in the study, 31 (18%) patients did not receive treatment at the initial treatment. In this group, the mean age at diagnosis was younger (mean age 28.5 years) than in the group that was getting treatment (mean age 41.7 years; n = 141, p<0.05). They also had more platelets at admission (the average number of platelets is 41.7×10^9 cells/l), less bleeding at admission (9.1% vs. 39.7%), and were in the hospital for less time (7.7 days vs. 14.5 days) than the group that was getting treatment.

The majority (82%) of patients in the study population who were admitted to the hospital with newly diagnosed ITP received treatment. In this group (n=141), the average number of platelets was 13.7×10^9 cells/l. The incidence of bleeding symptoms at the first treatment was 94.3% among patients treated at the first treatment. Patients with bleeding symptoms at the time of admission had a statistically significantly longer average duration of hospitalization of 14.9 days compared with 6.3 days in patients without bleeding symptoms (p=0.01 according to the paired t-criterion). Patients with ITP due to infection (28.5%), H. pylori (33.3%), and hematological malignancies (38.5%) were less likely to be bleeding at admission than the average (94.3%).

The initial dose of treatment corresponded to modern treatment recommendations that is (3, 4), prednisone 1 mg/kg to 80 mg daily for 1-4 weeks, followed by gradual withdrawal of the drug dexamethasone 40 mg orally or intravenously per day for 4 days to three, and, if necessary, repeated courses of injection of 0.4–1 g/kg per dose in 1–5 doses (6).

Patients in the study population most frequently received prednisone monotherapy as their first-line treatment. Patients receiving prednisone monotherapy and all other patients receiving first-line treatment did not significantly differ in terms of mean age at diagnosis or length of hospital stay. All patients received the prednisone drug for a mean of 177 days; however, the length of prednisone treatment varied significantly across the participating centers. During prednisone monotherapy, there was no partial or total remission; instead, 77.6% of patients only had clinical and hematological improvement. Of the 91 patients, 57 (62.6%) had side effects from their prednisone. The most frequent effects were those relating to metabolism and hyperglycemia (34.1%), then effects on mood (27.5%), insomnia (23.1%), hypertension (15.4%), and dermatological issues (12.1%).

Dexamethasone monotherapy was used in 21 patients with an average age of 38.5 years (Table 3). Compared with the general population of patients receiving treatment, these patients had no statistically significant difference in age (p=0.7), platelet count (p=0.8), or duration of hospitalization (p=0.5).

Table 1: General characteristics of patients in the comparative aspect between the centers

<table>
<thead>
<tr>
<th>Treatment centers</th>
<th>No. of patients</th>
<th>Women %</th>
<th>Average age (m±M)</th>
<th>Bed days (m±M)</th>
<th>Tp number (m±M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern center</td>
<td>78 (45.3%)</td>
<td>56.4%</td>
<td>43.1±4.82</td>
<td>13.9±2.41</td>
<td>26.2±2.77</td>
</tr>
<tr>
<td>Republican center</td>
<td>94 (54.7%)</td>
<td>60.6%</td>
<td>45.4±4.90</td>
<td>15.4±2.84</td>
<td>14.5±1.93</td>
</tr>
<tr>
<td>Total</td>
<td>172 (100.0%)</td>
<td>60.5%</td>
<td>44.2±5.71</td>
<td>14.8±2.92</td>
<td>17.1±1.84</td>
</tr>
</tbody>
</table>

Fig. 2: Etiology of patients with ITP

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

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

Of the 21 patients who received dexamethasone alone or in combination with other drugs, 16 (76.2%) required repeated doses to maintain the response. During dexamethasone monotherapy, 61.9% showed clinical and hematological improvement; there was no partial or complete remission. Side effects from dexamethasone treatment were observed in 57.1% (12/21) of patients. The most frequent were hyperglycemia and metabolic effects (38.0%), then mood-related effects (14.3%).

The small sample size and wide confidence intervals made it impossible to draw any statistically significant conclusions about the first-line therapy groups (prednisone and dexamethasone, prednisone and IVIg, and combinations) based on platelet count, age at the start of treatment, bleeding rate at admission, and length of hospital stay. 57 (67.0%) people had a stable response to first-line treatment, and they did not require treatment with second-line drugs during the study period.

Twenty-one patients (12.2%) received a sustained response to second-line treatment and did not need further lines of therapy. In 18 (10.5%) patients, clinical and hematological recovery was achieved after open-access splenectomy. The remaining 51 (29.7%) patients received a five-time course of high-altitude climatotherapy to achieve remission of the disease at the Tuya-Ashu high-altitude base. Rituximab was used as a follow-up therapy in 3 patients, and it was used second-line in 2 patients out of this number. The most commonly used dosing strategy was low doses of rituximab (100 mg) weekly for 4 weeks. A complete response was observed in 64.7% of cases. The average response time for all patients receiving rituximab was 25.2±3.81 days, and the average response time was 27.3±3.72 months. Two patients in this group were additionally prescribed corticosteroids. These patients had a shorter average response time (12.9 days vs. 25.2 days) and response duration (21.1 months vs. 27.3 months) compared to patients receiving rituximab alone. In the course of therapy, 66.6% had clinical and hematological improvement; there was no partial or complete remission. All patients had side effects from the use of rituximab, in the form of headaches, and one infusion reaction was registered.

In 18 patients, splenectomy was performed as a second-line treatment. All patients receiving splenectomy had an average response period of 10.2±1.90 days, with an average response time of 41.0 months. Additional corticosteroid treatments, lasting an average of 28 days, had to be administered to 11 patients. The average response time for patients receiving further steroids was 37.1 months, while the average response time for other patients was 14.9 days. The average response time for patients who had a splenectomy alone was 42.8 months, whereas the average response time for other patients was 5.6 days. 88.9% of patients received complete remission throughout treatment, while the other patients experienced partial remission. Following splenectomy, 3 patients (16.7%) experienced adverse effects, with infection being the most common.

In three patients, azathioprine was administered as a treatment after the initial treatment. In 7.5% of cases, this option was chosen as a second-line option. Each of the two patients who were not receiving 100 mg was given 50 mg daily. When all patients receiving azathioprine were combined, the average response time was 22.9±3.13 days, or 28 months. In addition to azathioprine, one patient out of three received corticosteroids. The average response time in these patients was 16 days as opposed to 22.9 days, p<0.05, which was shorter than in patients receiving...
azathioprine alone. The average response time was 9.3 months instead of 28 months in the patient who received additional corticosteroids, which resulted in a much lower total response time. 88.9% of patients showed improvement in their hematological and clinical status throughout treatment, whereas one patient noticed no change. Azathioprine caused adverse effects in all patients (23.1%), with nausea being the most common side effect. Only patients receiving a relatively higher dosage of azathioprine 100 mg daily with side effects of Dexamethasone at a dose of 40 mg daily for 4 days was used as a follow-up line of therapy in 11 patients, mainly as a second line. The average response time was 8.8±1.31 days. When used as a second-line drug, the response duration was also short compared to other drugs (the average response duration is 8.2 months). In the course of therapy, 45.4% showed clinical and hematological improvement; in the remaining patients, the effect was short-term. Most of the patients (81.8%) had adverse events when taking dexamethasone, most often anxiety, headaches, and sleep disorders. Finally, high-altitude climatotherapy was used as a second option for 51 patients with chronic and refractory ITP. It led to clinical and hematological remission in 74.5% of patients; complete remission was achieved in 52% of patients; and partial remission was achieved in 22% of patients. The quality of the response to treatment directly depends on the duration of the disease. In cases where the disease experience is small (1-3 years), complete remission was achieved. It should also be noted that 1 patient, 35 years old, after unsuccessful treatment with hormones and interferon preparations and staying at altitude twice in a row for 40 days (1 time a year in the summer), achieved complete clinical and hematological remission. The average follow-up period from the moment of achieving remission was 2.35±0.41 years (from several months to 5 years). A comparison of remission rates showed that the probability of remission in adults after conservative therapies is not statistically different. The indicators of remission after high-altitude climatotherapy differ significantly from the indicators of remission achieved after the use of drug therapy.

DISCUSSION

Intravenous immunoglobulin (IVIg) with or without corticosteroids is the standard first-line treatment for ITP. In addition to the first-line drugs such as thrombopoietin agonists, rituximab, danazol, dapsone, mycophenolate mofetil, cyclosporine A, azathioprine, and cyclophosphamide (1–7), doctors can use a lot of other drugs, most of which have very little evidence that they work to treat ITP. These medications commonly have a moderate response rate and a range of adverse effects that could require discontinuing the medication. Corticosteroids remain the primary means of therapy, but their long-term use is linked with considerable adverse effects, especially metabolic, which may result in their discontinuance. Furthermore, patients in this study used an average of 2.17 treatment lines before an ongoing response to treatment was seen, demonstrating the widespread failure of first-line therapy.

Unless corticosteroids are contraindicated or an additional quicker platelet rise is required owing to severe bleeding, oral corticosteroids are the recommended first-line treatment for patients with chronic ITP. Oral prednisone at 0.5–2 mg/kg/day for 2–3 weeks is the most often used corticosteroid; it should be tapered, with an aim of stopping by 6–8 weeks (7, 12, 13). 70–80% of patients respond at first, but long-term remission rates are poor and recurrence rates are significant (14).

The patients included in the study were either hospitalized with ITP or were under the supervision of a hematologist, and some of the patients had severe and/or chronic ITP. The demographic characteristics of the group under study were in accordance with the characteristics presented in other studies, with a 58% female prevalence and an average age of 48.85 years at the time of diagnosis (3, 4).

In Kyrgyzstan, demographic data on the ethnicity of patients receiving treatment in public hospitals is typically not gathered, despite the fact that this information may be helpful in determining genetic or sociocultural variables that impact the efficacy or tolerance of the studied treatments. Additionally, there was limited data in medical records, which made it impossible to collect the data needed for patients, including bleeding that required a transfusion of blood or platelets.

Most of the patients were treated with prednisone alone or in combination with IVIg, and all centers followed the current guidelines for the initial course of therapy (5–8). Different centers found that weaning off prednisone took an average of 67–392 days, despite the fact that this study lacked information on the precise dose of prednisone at the time of stopping the drug. A ketogenic diet has been found to be useful in treating multiple illnesses, such as tumors, elevated cholesterol, epileptic seizures, heart illness, and type 2 diabetes mellitus (15, 16). Combining glucocorticoids and a ketogenic diet together may improve therapeutic results. Considering everything, treating ITP, which may come on for a variety of reasons, with a ketogenic diet is a safe and affordable option (17).

CONCLUSION

Patients with adult ITP can be effectively treated with conservative methods in 45.4–77.6% of cases. These treatments include prednisone, dexamethasone, and their combination with IVIg, rituximab, and azathioprine. The most efficient way to treat chronic
ITP when drug therapy is ineffective is to include splenectomy in the treatment regimen. While high-altitude climatotherapy is seen as a viable therapeutic option for adults with ITP, more studies are needed to promote high-altitude climatotherapy.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

REFERENCES