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ORIGINAL ARTICLE

Immune thrombocytopenia: epidemiological and clinical features of 216 patients in northwestern Turkey

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Abstract We evaluated the clinical features, treatment modalities, treatment responses, and prognosis of our patients with immune thrombocytopenia (ITP). Furthermore, we estimated the frequency of ITP in the Thrace region of Turkey. Two hundred sixteen patients diagnosed with ITP between 2000 and 2012 at our center were retrospectively evaluated. Patients' clinical features, treatments, and responses to treatment modalities were recorded. The mean annual incidence of ITP was 2.92/100,000 (95%CI: 1.57–4.27). The overall prevalence of ITP was 35.1/100,000 (95%CI: 30.3–39.8). The administration of first-line therapy resulted in complete remission (CR) in 76.5 % of patients and partial remission (PR) in 13.6 %. After 5 years, 33 % of patients who were responsive to first-line therapy were still in relapse-free remission. Of patients who were given second-line therapy, CR was obtained in 71.3 % and PR in 14.9 %. The duration of relapse-free remission was longer with splenectomy than with steroids ($p<0.001$). Five years after splenectomy, 62 % of patients were in relapse-free remission; contrarily, this was lower with steroids (36 % at 5 years). The annual incidence and prevalence of ITP in northwestern Turkey was similar to data from western countries—at the lower limit for some countries. Effective treatment strategies seem to be steroids as first-line therapy and splenectomy in refractory cases.

Keywords Immune thrombocytopenia (ITP) · Incidence · Prevalence · Corticosteroids · Splenectomy

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Introduction

Immune thrombocytopenia (ITP) is a disease characterized by a shortened platelet life span, autoantibodies in the plasma against platelets, and megakaryocytes with ultrastructural abnormalities which means apoptosis and para-apoptosis in the bone marrow [1, 2]. It has acute, chronic, and recurrent forms: acute form is common in children, and chronic form is more frequent in young adults [3, 4].

The pathogenesis of ITP involves shorter platelet survival, autoantibodies against glycoproteins on platelet membrane, and complement activation. The platelet life span which is normally 7–10 days becomes as short as a few minutes to a couple of hours in ITP. The platelets are covered by IgG autoantibodies, and they are cleared from the circulation earlier than normal by macrophages in the mononuclear phagocytic system [5].

ITP is a rare disease, and the current literature about the epidemiology of adult ITP is mainly from Europe and the USA [6]. A recent review summarizing European-origin studies about ITP reported an annual incidence of 1.6 to 3.9/100,000 in adults [7]. In other studies, however, the prevalence was stated to vary between 4.0 and 23.6/100,000 patient-years [8]. One study from the USA reported that the average annual prevalence of ITP in adults was 12.1/100,000 [9]. In one British series, the prevalence of ITP in individuals older than 18 years was 50/100,000 [10]. Various pediatric and adult ITP series have been reported from Turkey [11–13]; however, no data about the prevalence and incidence of ITP in

Turkey has been published so far. It is quite difficult to perform an epidemiologic study because there are multiple pathogenic mechanisms in ITP and no laboratory or clinical data is characteristic for the diagnosis [4, 14]. In order to diagnose ITP, other causes of isolated thrombocytopenia should be excluded, and in fact, this is quite cumbersome [4, 15].

In this study, we evaluate the incidence and prevalence of ITP in our region based on patient admission into our center. In addition, we retrospectively determined the clinical features, treatment response, and prognosis in our ITP patients.

Methods

We retrospectively evaluated 216 adult ITP patients diagnosed at Trakya University Medical Faculty, Department of Hematology between 2000 and 2012. The names and hospital protocol numbers of all patients with ITP were extracted from our hospital's computer database by using the ICD code for ITP. The patients' hospital files (both inpatient and outpatient) were obtained from the archives, and required medical data were screened. Local ethical committee approval and written informed consent were obtained. The definition of primary ITP was that adopted by the International Working Group [4]. Bone marrow aspiration and/or biopsy were performed in patients ≥60 years of age, for patients scheduled for splenectomy, and for patients with suspected primary bone marrow disorders. Patients with secondary ITP [4] and/or dysplastic features on bone marrow analysis were excluded. None of the patients had history of thromboembolism, autoimmune disease, recent infection, or recent drug intake.

Estimation of prevalence and incidence

Our university hospital is located in the city of Edirne, in Thrace region of Turkey. Edirne is located in northwestern Turkey and makes borders with Greece and Bulgaria. Our hospital is the only tertiary referral center for hematology patients who live in Edirne and Kirklareli cities. The city of Kirklareli is also in Thrace region. Our center has served in the diagnosis and therapy of hematological diseases (both benign and malignant) for a mixed rural and urban population of 616,000 people for longer than 16 years (316,000 males, 300,000 females). There is no other hospital or any other health institution which has hematologists in their staff in the Thrace region. The population number was obtained from the 2011 census data of the Turkish Statistical Institution. Pediatric age group patients (<16 years) were not included.

Thrace population is composed of Balkan-origin Turks who have been inhabitants in the region starting from the time of the Ottoman Empire. The population is very static, and there have been absolutely no internal and external migrations. We recorded down the general features of ITP patients who were diagnosed at our center within the last 12 years. The incidence rates per 100,000 population aged ≥16 years were calculated. Clinical features and survivals of ITP patients were also evaluated. Any patient diagnosed with ITP in our region in November 2011 was defined as a prevalent case. Prevalence of ITP was calculated by dividing the number of prevalent cases by the population in this area in November 2011.

Follow-up and treatment

Inpatient and outpatient files of ITP patients were investigated. Demographic and clinical features at the time of initial diagnosis were determined. Age, sex, initial platelet count, bleeding symptoms, and findings at initial diagnosis were recorded. Bleeding symptoms were classified into petechiae, ecchymoses, easy bruising, epistaxis, gingival hemorrhage, hemorrhagic bullae in the oral cavity, genitourinary bleeding, gastrointestinal bleeding, and intracranial bleeding. The severity of bleeding was assessed by the World Health Organization (WHO) Bleeding Score.

Antinuclear antibody (ANA), antiphospholipid (APL) antibody, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) serologies were obtained from medical charts. Other investigations included chest X-ray, abdominal ultrasound, and further tests according to the clinical condition. Bone marrow biopsy results were recorded if they were available. Patients were hospitalized if the platelet count was <20,000/mm^3 and/or if they had bleeding including ecchymosis or purpura. All patients with anemia according to the definition of WHO (hemoglobin <12 g/dl in females, and <13 g/dl in males) were initially screened for the presence of iron deficiency anemia by serum iron, total iron binding capacity, and ferritin levels. Patients who were found out to have iron deficiency anemia were investigated for the source of bleeding when needed (upper gastrointestinal endoscopy, colonoscopy, and gynecologic examination in females). In anemic patients without iron deficiency anemia, hemoglobin electrophoresis was performed to screen for hemoglobinopathies.

The need for therapy was assessed in accordance with the American Society of Hematology (ASH) guidelines [16, 17]. All treatment modalities for ITP, response to therapy, blood tests at the time of relapse and remission, and complications related to therapy were recorded. For patients who were lost to follow-up, missing data were tried to be retrieved by giving the patients phone calls. When interpreting the results of therapy, patients whose treatment data were missing were excluded from analysis.

ASH ITP Guidelines (2011) were also used to evaluate response to therapy [17]. High-dose methylprednisolone was defined as pulse dose or 1 mg/kg/day. If the daily dose of

methylprednisolone was 0.5 mg/kg/day or less, it was defined as of low-dose. Dexamethasone therapy was administered as 40 mg/day for consecutive 4 days at every 28-day cycles for 1 to 4 cycles. Other treatment modalities included intravenous immunoglobulin (IVIG), anti-Rh immunoglobulin (anti-D), azathioprine, vincristine, rituximab, and eltrombopag. IVIG and anti-D therapies used for increasing the platelet counts temporarily before splenectomy were not evaluated.

The 95 % confidence intervals (CI) were calculated based on a Poisson distribution and the standard error of a Poisson distribution is based on the square root of the numerator. When comparing categoric parameters between the groups, Chi-square test and when appropriate Fisher's exact test were used. Continuous variables between the groups were compared with the unpaired test. We used the Kaplan-Meier curve to determine duration of disease-free remission. In order to compare disease-free remission durations of different groups, log-rank test was utilized.

Results

Annual incidence of ITP

Of 216 ITP patients, 159 (73.6 %) were females and 57 (26.4 %) were males (female/male: 2.8). During the study period, the mean annual incidence rate of ITP was 2.92/100,000 (95%CI: 1.57–4.27). The mean annual incidence of ITP in women was 4.42/100,000 (95%CI: 2.04–6.8), and in men, it was 1.5/100,000 (95%CI: 0.15–1.85).

Prevalence of ITP

By November 2011, the overall prevalence of ITP in our region was 35.1/100,000 (95%CI: 30.3–39.8) in the population aged ≥16 years. The prevalence in women (53/100,000, 95%CI: 44.8–61.2) was higher than the prevalence in men (18/100,000, 95%CI: 15.4–20.6).

General features of ITP patients

The mean age of ITP patients at the time of diagnosis was 42.3 years (median age: 40, range: 17–87). The mean age in females was 42.6 years, and the mean age in males was 41.2 years. Bleeding symptoms were present in 115 (53.2 %) patients. Three patients (1.4 %) had bleeding which caused a fall in hemoglobin level; in one patient admitted with periodic paralysis, the platelet count could not be determined and cranial computed tomography showed hemorrhage. The frequency of various bleeding symptoms were as follows: ecchymoses, 46.9 %; easy bruising, 42.9 %; petechiae, 37 %; gingival hemorrhage, 15.7 %; epistaxis, 14.9 %; genitourinary bleeding, 11.4 %; gastrointestinal system bleeding, 5.6 %; and hemorrhagic bullae in the oral cavity, 2.7 %.

Laboratory values

The median platelet count at the time of diagnosis was 12,000/mm^3 (range: 3,000–99,000/mm^3). At initial diagnosis, 45.3 % patients had a platelet count <10,000/mm^3; 67.9 % had a platelet count <30,000/mm^3; and 82.6 % had a platelet count <50,000/mm^3. Anemia was present in 65 (41.5 %) females and 7 (12.3 %) males ($p<0.05$). Fifty-eight female patients and six male patients had iron deficiency anemia; β-thalassemia minor was diagnosed in seven females and one male patient. Antinuclear antibody was positive in 18.5 % (28/151), and anti-DNA was present in 1.6 % (2/121) of patients in which they were available. None of the patients had findings of systemic lupus erythematosus (SLE) or other autoimmune rheumatic diseases at initial presentation. Therefore, none of the patients with positive ANA or anti-DNA fulfilled the classification criteria for SLE. APL antibodies were positive in 29.3 % (24/82) of the patients in which they were available. Nevertheless, except one, all were IgM antibody positivity at low titers. None of the cases with positive APL antibodies had history of thrombosis or abortion. When Sydney criteria were considered, there was no patient with APL syndrome.

HBsAg was positive in 3.7 % (7/187) and anti-HCV in 1.1 % (2/187) of patients. None of the patients with HBsAg or anti-HCV positivity had clinical and/or laboratory features of acute hepatitis or cirrhosis; their HBV-DNA and HCV-RNA were negative. Therefore, these patients were included into the study. Anti-HIV was negative in all 187 patients.

During follow-up, two patients developed nonHodgkin lymphoma (after 2 and 4 years), and two patients were diagnosed with myelodysplastic syndrome (3 and 6 years later). After 2, 5, and 6 years of follow-up, three female patients developed SLE. In three ITP patients, Coombs-positive autoimmune hemolytic anemia was diagnosed after 18 months, 2 years, and 27 months of follow-up, and they were later designated as Evans syndrome. All of the above-mentioned patients had been excluded from the study.

Treatment and follow-up

Fourteen of the patients were lost to follow-up after first-line therapy; therefore, 202 patients were evaluated. There was an indication for treatment in 162 (80.2 %) patients; 40 (19.8 %) patients were followed up without any therapy. Of the 162 ITP patients who were given first-line therapy, there was complete response (CR) in 124 (76.5 %) and partial response (PR) in 22 (13.6 %); 16 (9.9 %) patients were nonresponsive to therapy. First-line treatment modalities and responses are seen in Table 1.

Table 1 First-line treatment modalities in ITP patients and response rates

Treatment	Complete response	Partial response	Nonresponsive
High-dose methylprednisolone, *n* (%)	58 (78.3)	9 (12)	7 (9.4)
Low-dose methylprednisolone, *n* (%)	53 (80)	9 (13.6)	4 (6)
Dexamethasone, *n* (%)	6 (67)	3 (33)	0 (0)
Intravenous immunoglobulin, *n* (%)	4 (50)	1 (12.5)	3 (37.5)
Other therapies, *n* (%)	3 (60)	0 (0)	2 (40)
Total, *n* (%)	124 (76.5)	22 (13.6)	16 (9.9)

In 9 of the 40 patients who had no treatment indication initially, treatment had to be administered after a median of 15 months (range 5–70 months). No treatment indication arose in the remaining 31 patients after a median follow-up of 7 months (range 3–97 months). Eight patients with treatment indication were given steroids, and IVIG was administered to only one patient. CR and/or PR were obtained in six patients; one patient was steroid-refractory and underwent splenectomy which resulted in CR; the response to therapy could not be evaluated in two patients.

At a median of 13.5 months (range 0–71 months), 10 of the 40 patients (25 %) had a fall in their platelet counts which were within treatment limits. The other 30 patients had no further fall in their platelet counts at a median of 7 months (range 3–98 months).

Seventy-three (50 %) of the 146 patients who obtained response (CR + PR) with first-line therapy relapsed at a median of 6 months (range 2–98 months). The median follow-up in patients who did not relapse was 11 months (range 2–108 months). The frequencies of relapse-free remission in patients who were responsive to first-line therapy were 56 % at 1 year, 49 % at 2 years, 54 % at 3 years, and 33 % at 5 years. Figure 1 shows the Kaplan-Meier curve.

Second-line therapy was administered to 99 patients who were nonresponsive to first-line therapy or who relapsed after an initial response. Five patients were lost to follow-up after second-line therapy. Second-line treatment modalities and response rates are seen in Table 2. Thirty-nine patients (48.1 %) who were responsive to second-line therapy (CR + PR) relapsed at a median of 5.5 months (range 2–83 months). Twenty-five patients (53.2 %) who were steroid-responders relapsed at a median of 6 months (range 2–83 months). Ten patients (34.5 %) who were responsive to splenectomy relapsed at a median of 6.5 months (range 2–54 months).

Splenectomy

Splenectomy was performed in 49 ITP patients. In 30 patients, it was the second-line treatment modality; in 13 patients, it was third-line; and in 6, it was fourth-line therapy. Splenectomized patients were followed up for a median of 35.5 months (range 2–187 months). The median duration from diagnosis until splenectomy was 7 months (range 2–102 months).

Of 49 patients who underwent splenectomy, 43 (87.8 %) had CR and one (2 %) had PR. Five (10.2 %) patients were

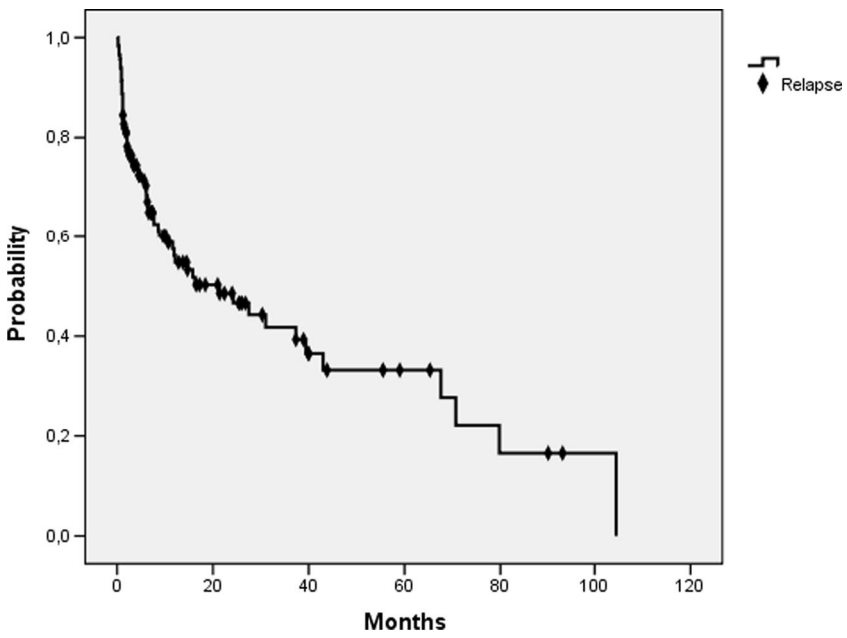

Fig. 1 Kaplan-Meier curve showing duration of relapse-free remission in patients who responded to first-line therapy which was 56 % at 1 year decreasing gradually to 33 % at 5 years

Table 2 Second-line treatment modalities and response rates in ITP patients

Treatment	Complete response	Partial response	Nonresponsive
Corticosteroids, *n* (%)	36 (63.2)	11 (19.3)	10 (17.5)
Splenectomy, *n* (%)	28 (93.3)	1 (3.3)	1 (3.3)
IVIG, *n* (%)	2 (50)	1 (25)	1 (25)
Other therapies, *n* (%)	1 (33.3)	1 (33.3)	1 (33.3)

nonresponsive to splenectomy. Nine of the 44 patients (20.5 %) relapsed at a median of 24 months (range 5.5–141 months). The median duration of remission in 35 patients (79.5 %) who did not relapse after splenectomy was 30.5 months (range 2–84 months).

The median platelet count after splenectomy was 462,000/mm^3 (range 189,000–1,000,000/mm^3). The mean maximum postsplenectomy platelet counts between patients responsive and nonresponsive to splenectomy were compared. The mean maximum platelet count in the group responsive to splenectomy was higher (508,000 vs. 296,000/mm^3), but the difference was not significant (p=0.08). Similarly, the mean maximum platelet count in the group which did not relapse after splenectomy tended to be higher than in the relapsing group (538,000 vs. 351,000/mm^3, p=0.07).

When splenectomy and steroids were compared as second-line treatment options, it was observed that CR rate was higher with splenectomy (p=0.002) and total response (CR + PR) tended to be better (96.7 vs. 82.5 %, p=0.09). Patients responsive to steroids as second-line therapy tended to relapse more frequently than patients treated with splenectomy (53.2 vs. 33.3 %, p=0.088).

When relapse-free remission durations with splenectomy and steroids were compared, it was seen that it was longer with splenectomy (p<0.001) (Fig. 2). The relapse-free remission rates after splenectomy were 90 % at 1 year and 62 % at 5 years. These rates were lower with steroid therapy (45 % at 1 year, 36 % at 5 years).

Severe complications and mortality

One ITP patient developed pulmonary tuberculosis, one had aseptic necrosis of the femoral neck, and one patient had intracranial nocardial abscess. One patient initially diagnosed with ITP and who developed SLE during follow-up died because of treatment-refractory pulmonary infection. One patient was admitted with central nervous system bleeding and was followed up in the neurosurgery department for some time. Two patients with gastrointestinal bleeding had to be transfused heavily and were followed up in the gastroenterology intensive care unit for a few days. All three patients survived the bleeding episodes.

Discussion

In our study, the mean annual incidence of ITP was 2.92/100,000 and the overall prevalence was 35.1/100,000. Our series was similar to the published series [11] in the ratio of females/males which was threefold. In our study, the frequency of ITP was close to western studies, although it was somehow lower. The median age in our series was 40 years which was in accordance with literature data.

Bleeding symptoms were present in 61 % of our patients; however, there was no requirement for erythrocyte transfusions in most of them. When types of bleeding were evaluated, skin and mucosal bleeding were seen to be more frequent than life-threatening bleeding, like gastrointestinal and intracranial bleeding which were rare. Although almost 70 % of our patients had a platelet count of less than 30,000/mm^3, only 37 % had petechiae. It is known that there is not always a linear association between platelet counts and the severity of bleeding manifestations [8]. Some patients with higher platelet counts do bleed, whereas those with lower counts do not manifest any bleeding symptoms [8, 18]. It was noteworthy that female patients in our study more frequently had signs of bleeding, like ecchymosis and easy bruising, when compared to males. In addition, iron deficiency anemia was relatively more common in female ITP patients which might be explained by heavier menstrual bleeding episodes secondary to thrombocytopenia.

Antiphospholipid syndrome or antibodies were reported to be present in 10 % of ITP patients in various series. As long as APL syndrome does not end up with thrombosis, it does not alter the general approach to thrombocytopenia [19]. In our study, history of thrombosis or abortion was not present in patients with positive APL antibodies. Therefore, none of our ITP patients with positive APL antibodies were assigned as APL syndrome. ANA positivity was present in 18.5 % of ITP patients. These patients did not have any symptoms associated with SLE or other autoimmune diseases. It was reported that 2–5 % of ITP patients developed SLE during long-term follow-up; we excluded these patients from our study. Patients with positive hepatitis B and hepatitis C serologies were included because they had no findings of acute or chronic liver disease, and their HBV-DNA or HCV-RNA were negative.

Treatment indication was present in 80 % of our ITP patients. Steroids still have the priority as the standard first-line therapy of ITP [15]. In our study, CR rate with low-dose and high-dose steroids was similar, around 80 %. In one ITP series reported from our country, similar to our study, a relatively good response rate was achieved with low-dose methylprednisolone [11]. In recent studies, high-dose dexamethasone yielded high response and long remission rates. In another study, the response rate was 86 %, and 74 % of the patients stayed in remission for about 8 months [20]. In our

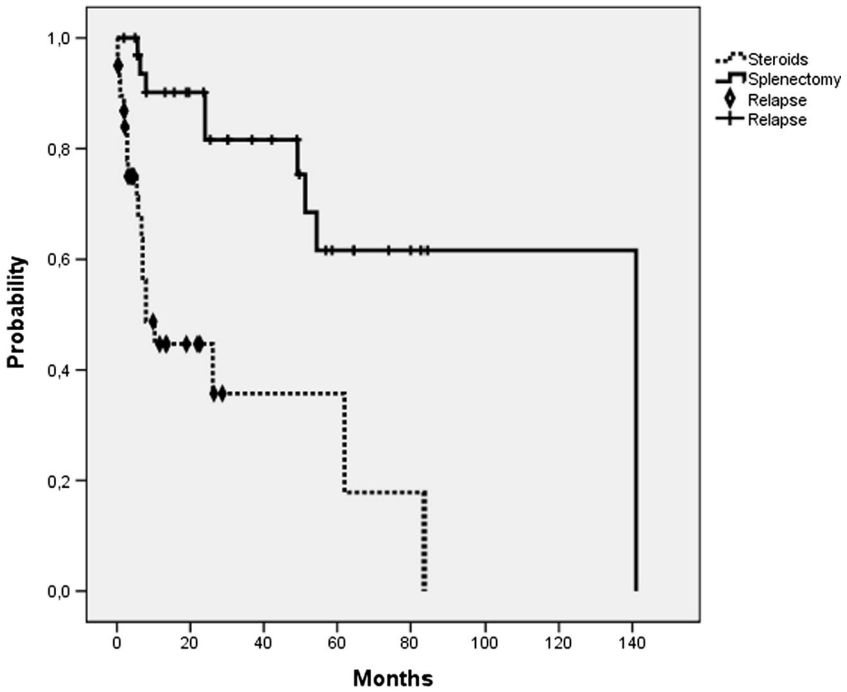

Fig. 2 Kaplan-Meier curves comparing relapse-free remission durations in patients who were responsive to second-line splenectomy vs. steroids. Durations of relapse-free remission were significantly longer with splenectomy than with steroids (62 vs. 36 % at 5 years) (log-rank test, $p<0.001$)

study, dexamethasone was opted as first-line therapy in nine patients. All patients responded to therapy, including CR in six of nine patients and PR in three. In addition, about one fourth of the patients without any treatment indications at initial presentation needed some form of therapy during follow-up.

In relapsing ITP patients, the administration of steroids as second-line therapy led to lower CR rates (63.2 %) than first-line steroids. Although the CR rate was relatively good, nearly half of these patients relapsed at a median of 6 months. As a result, it is obvious that steroids as second-line therapy help obtain good results, though this is not as high as the response rate with first-line steroids. The major problem in an important proportion of ITP patients is relapse.

Very high response rates of around 65–80 % were reported with IVIG therapy within a short time [21]. This response is generally temporary, and there is usually relapse within 10–14 days. It is recommended to use steroids with IVIG as the combination might yield better response rates and causes less infusion reactions [21]. In our study, IVIG was combined with methylprednisolone when a rapid platelet response was desired. First-line IVIG was used in eight patients with CR in four and PR in one. Three of these five patients relapsed.

The response to splenectomy was reported to be 80 %, and 66 % of these patients were still in remission after 5 years [22–24]. There was relapse in 20 % of responding patients and no response at all was obtained in 14 % [4, 22]. In our study, splenectomy was performed in ITP patients nonresponsive to first-line treatment or those who relapsed after an initial response. CR was obtained in most of the splenectomized patients (87.8 %). At a median of 24 months, 20.5 % of splenectomized ITP patients relapsed. When splenectomy and steroids were compared as second-line treatment options, the splenectomy arm had a better response rate, a lower relapse rate, and a longer remission duration. Therefore, it is obviously seen that splenectomy still holds the first place for steroid-refractory patients.

In one study evaluating 402 splenectomized ITP patients, it was stated that the maximum platelet count after splenectomy could be a determining factor for response to therapy and relapse [22]. In our study, patients responsive to splenectomy tended to have higher mean maximum platelet counts in the postsplenectomy period than the nonresponsive group. A similar relationship existed between the maximum postsplenectomy platelet count and relapse after splenectomy. In the postsplenectomy nonrelapsing ITP group, the mean maximum platelet count after splenectomy tended to be higher than in the relapsing group.

Recently, thrombopoietin receptor agonists (romiplostim, eltrombopag) were added into the armamentarium of ITP treatment with satisfactory results [25, 26]. A placebo-controlled study with eltrombopag yielded 16 % response in placebo arm, while platelet values above 50,000/mm^3 were reached in 59 % of patients in eltrombopag arm [27]. Eltrombopag was given to only two patients in our study: both patients who were refractory to multiple lines of previous therapy were nonresponsive to eltrombopag.

In our treatment-refractory ITP patients, we considered inherited thrombocytopenias in differential diagnosis. Nevertheless, none of our patients had any family history of thrombocytopenia, any physical findings like cafe au lait spots (as seen in Fanconi anemia), or specific features which might be seen on peripheral blood smear, like macroplatelets and Döhle

bodies in neutrophils (suggestive of MYH9-related disorders), or microplatelets (as in Wiskott-Aldrich syndrome) [8, 28]. Our facility does not provide genetic testing for the inherited thrombocytopenias, but none of our patients had any features that required testing.

Our study had some limitations. The structure of the data could have been affected by our institution which is a tertiary center and by contacting patients by phone, if they were lost to follow-up. In addition, during the time of data collection (2000–2012), the ASH guidelines, the International Consensus Report [15], and other key literature were published; guidelines and consensus reports were revised which led to new knowledge of pathophysiology of ITP, the introduction of new laboratory tests and new platelet-enhancing drugs, and changed recommendations for the management of patients with ITP. However, eltrombopag has been approved for use in Turkey in recent years, and romiplostim is still not available. Therefore, we can say that the results of our study were not affected by these literature data to a large extent.

As a conclusion, the annual incidence of ITP was 2.92/100,000 and the overall prevalence was 33/100,000 in our tertiary care center in Turkey. Most ITP patients were females and they had more prominent signs of bleeding than males. Steroids seemed effective as first-line treatment of ITP. Although steroids had less efficacy as second-line therapy, still they proved effective, albeit with high relapse rates. Splenectomy seems to be the treatment of choice for second-line therapy. Response rates are higher and relapse rates are lower with steroids when compared to splenectomy.

Conflict of interest The authors declare no conflicts of interest for this manuscript.

Informed consent Written informed consent was given by all subjects in this study.

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