Comparison Of Treatment Regimens Used In Patients Diagnosed With Idiopathic Thrombocytopenic Purpura

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ABSTRACT

Objective: To compare the efficacy of different treatment regimens used in patients diagnosed with Idiopathic Thrombocytopenic Purpura, also called primary Immune Thrombocytopenia (ITP).

Methodology: Retrospective cross-sectional design used. 83 patients followed in hematology clinic at King Hussein Medical Center as Idiopathic Thrombocytopenic Purpura cases were included. Treatment options were classified as first, second and third lines. Treatment response defined according to The American Society of Hematology.

Results: Eighty three patients diagnosed with Idiopathic Thrombocytopenic Purpura, the median age was 30 years (18-70) and platelet count < 30,000/ µl. Majority of them were female (63.9%). Overall response rate (Partial Response and Complete Response) with first line therapy Prednisone was 90.4% (75/83), while response rate for those given second line Azathioprine and Danazol was 35.7% (17/49) and 57.1% (4/7) respectively. Moreover third line treatment response rate was as follow, Mycophenolate 31% (9/29), Rituximab 50% (7/14), and Splenectomy 70% (7/10). Out of 75 patients who responded to Prednisone, 35 patients were dependent on steroid and shifted to second line therapy. The results revealed statistically significant difference in treatment response at first and third month of treatment induction (p value = .001 and .032 respectively). Only three patients remained refractory to Splenectomy and to all used treatments.

Conclusion: Idiopathic Thrombocytopenic Purpura is an acquired bleeding disorder with complex pathophysiology. More than 50% of patients who responded to Prednisone therapy developed dependency; however it is effective treatment for Idiopathic Thrombocytopenic Purpura. Rituximab showed efficacy that is nearly equal to splenectomy which is still the treatment of choice for cases with steroid resistance.

Key words: Idiopathic Thrombocytopenic Purpura, Adult, Efficacy, Steroids, Splenectomy.

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Introduction

Nowadays, Idiopathic thrombocytopenic purpura (ITP) is called as immune thrombocytopenia, because of its immune etiology ITP is an acquired immune mediated disease that cause peripheral platelet destruction and impaired platelet production, leading to thrombocytopenia and spontaneous bleeding.[1] George et al (1996) rely on the absent of clinical associated conditions or causes in defining ITP.[2] ITP according to American Society of Hematology defined as a peripheral blood platelet count less than 100×10^9 /L with the absence of underlying cause.[2,3] ITP could be transient or persistent decrease of platelets count.[4]

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Another classification decided to avoid the term "idiopathic" preferring "immune" to emphasize the immune-mediated mechanism of the disease and choose "primary" (as opposed to idiopathic) to indicate the absence of any obvious initiating and/or underlying cause.

The term "purpura" was felt inappropriate, because bleeding symptoms are absent or minimal in a large proportion of cases. According to this classification it was divided into primary and secondary immune thrombocytopenia (ITP) according to the presence or absence of identifiable alternative etiologies such as infection, primary bone marrow disease, systemic immune deficiency, intravascular coagulation, vitamin deficiency, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. In this classification the disease was divided in three phases:

1. Newly diagnosed ITP: This is within 3 months from diagnosis.

2. Persistent ITP: Between 3 to 12 months from diagnosis includes patients not reaching spontaneous remission or not maintaining complete response off therapy.

3. Chronic ITP: lasting for more than 12 months.[5] Most of patients with ITP have less platelets count and higher bleeding manifestation than patient with secondary immune thrombocytopenia.[6] Usually ITP is a self limited disease and around 80% of the cases resolved within 6 to 12 months.[7]

Bleeding (bruising, epistaxis, gum bleeding and intracranial hemorrhage) [7,8] fatigue, and thrombosis are the most common clinical manifestation of ITP among adult patients.[7]

Although ITP as a disease have been studied over more than a century, its prevalence is not will characterized in general population.[9] ITP is more prevalent in adult female than male.[10,11,12] Gender difference about the prevalence of ITP is an age specific. Terrell et al (2012) identify the average annual prevalence with 12.1/100,000 adults and the prevalence was greater among female, but in contrast the prevalence among males was greater for patients above age of 70.[13]

In United Kingdome the prevalence of ITP was 50.29/100,000 person and increased over time.[10] Segal JB and Powe NR (2006) reported the prevalence of ITP in United state of America as 9.5/100,000 person.[12] Prospective population based study in UK on newly diagnosed ITP patients above age of 16 years with platelet count of < 50 x 10^9 /l demonstrated an annual incidence 1.6 and the highest incidence was among individuals above age of 60.[14]

In comparison to general population morbidity and mortality rate of ITP patients is increased.[11,15] ITP patients have an increased mortality rate ranging from 1.3- to 2.2 fold than general population.[11,16,17] The excess of mortality rate of ITP patients has been recognized due to bleeding with severe thrombocytopenia, death due to infection [17,18] and death after splenectomy.[18] Risk for death was increased by age, refractory patients with a history of hemorrhage and patients with associated bleeding diatheses.[18,19]

In general, treatment of ITP patients depends on risk assessment of bleeding. Decrease platelet count, increase age, associated bleedings co-morbidities, and history of bleeding considered as a significant factors in risk assessments for bleeding.[19] Platelet count of less than 30,000/ µl is used as cutoff point to initiate treatment accompanied by strict risk assessment for lifestyle, age, and other medical conditions.[3,20]

Corticosteroid such as Prednisone and Dexamethasone recommended as a first line treatment of ITP, and if corticosteroids is contraindicated or there is a need for rapid increase of platelet count, intravenous Immunoglobulin (IVIg) or anti-D immune globulin (anti-D) consider drugs of choice as first line treatment [3] but it's not recommended for long term therapy because of long term toxicity.[21] The aim of first line treatment is inhibiting autoantibody production and platelet degradation by macrophages,[22] such as Corticosteroid action.[23] Long term therapy of corticosteroid should be avoided as much as possible because of adverse effect of the drug (e.g. hypertension, diabetes, osteoporosis, and increase weight).[24] Pirunsarn et al (2018) compared low dose of prednisone (7.5mg/d) versus observation for prevention of recurrence relapse ITP and concluded that there were no significant differences between prednisone group and control group, so prednisone didn't prolong relapse-free survival.[25]

IVIg act by decreasing destruction of platelets that have bound auto-antibodies through saturation of Fc receptors in the reticuloendothelial system.[23, 26] IVIg treatment showed an increase in platelet count within 24 to 48 hours in up to 85% of patients. [27] Moreover, additional therapy is needed if IVIg treatment response was transient and platelet count decrease less than 30,000/ µl.

IVIg compared with corticosteroid in treatment of ITP during pregnancy and both drugs gave favorable outcomes without fatal or severe maternal, fetal, or neonatal hemorrhages.[28]

Anti-D immune globulin (anti-D) was approved by in 1995 by Food and Drug Administration (FDA) for the treatment of non splenectomized ITP patients who have an Rh-positive blood type and approved dose was 50 microgram/kg. [26, 29] Anti-D immune globulin acts by blocking the macrophage system, neutralizing and binding

of auto-antibodies to platelets.[26] Rare but serious adverse effects have been reported during and after treatment with Anti-D immune globulin such as intravascular hemolysis,[30] acute renal failure,[31] and disseminated intravascular coagulation.[32] Most of these adverse effects occurred among patients with comorbid disease, so careful patients' selection and monitoring during and after treatment is needed for early detection of these adverse effects.[33]

Second and third lines of treatment mainly set aside for persistent and chronic ITP cases. Latest treatment guidelines recommended Rituximab and Splenectomy as second line of treatment, while in clinical practice they prefer to delay Splenectomy to third line of treatment options.[3,34] Second line therapy focuses on immunosuppression, whereas third line treatment focuses on stimulation platelets production by megakaryopoiesis.[22]

Second and third line of treatment also used in combination with steroids or immunosuppressive agents in refractory cases to enhance treatment response through targeting various mechanisms.[5,35] Rituximab acts by inhibition auto-antibodies production from B cells as well as reverting T-cell abnormalities in patients who respond to treatment.[22,36] Meta analysis conducted in 2011 aimed to investigate efficacy of Rituximab treatment before Splenectomy in adult ITP patients.[37] This Meta analysis included four RCT studies, nine prospective and six prospective studies. Seven studies defined complete response as a platelet count of >100 x 10^9/L and for the remaining studies was >150 x 10^9/L. Overall response rate (platelet count >50 x 10^9/L) after one year was 57%, whereas complete response was 41%. Another RCT study reported that Rituximab (375 mg/m^2) once weekly for four weeks plus Dexamethasone 40 mg/day for 4 days showed higher response rate and longer time of relapse than Dexamethasone monotherapy during 12 months of follow up.[38] In contrast, large double blind RCT showed failure of Rituximab treatment compared to placebo in reduction the rate of relapse in patients who previously treated with corticosteroids.[39]

Thrombopoietin receptor agonists (TPO-RA) therapy added clinical development in the landscape of second line therapy for the treatment of chronic ITP. TPO-RA such as Romiplostim and Eltrombopag are both approved by FDA. Eltrombopag achieved 66.7% of complete response (platelet counts>100,000 cells/ µL) and 5.7% partial response (platelet counts between 50,000 and 100,000 cells/ µL) in 18 patients with refractory ITP.[40] Another study reviewed 6 RCT studies include 611 patients confirmed that Eltrombopag significantly improved platelet counts (RR 3.42; 95% CI: 2.51-4.65) and reduced incidence of bleeding (RR 0.74; 95% CI: 0.66-0.83).[41] Moreover, J. R. Gonzalez-Porras et al suggested that patients who are not responsive to one treatments of TPO-RA or have adverse effects can switch to another type of TPO-RA treatment successfully.[42]

The American Society of Hematology (2011) recommended splenectomy as a second line treatment therapy and advises to delay this procedure 6 to 12 month after diagnosis.[3] 15% to 25% of ITP patients with refractory or relapse after first line therapy undergo splenectomy as treatment option.[43] Splenectomy is an effective treatment for refractory or dependent patient on medical treatments with response rate 70% to 90%. [2,44] On the other hand, splenectomy is an invasive procedure and there is a risk for infection, sepsis, thrombosis, and hemorrhage.[45] Literature demonstrated that age, low prednisone dosage (≤ 40mg/day) before splenectomy, higher preoperative minimum platelet count, and the lowest platelet count ≥ 50×10^9/L within 14 days after splenectomy are important predictive prognostic factors after splenectomy.[46]

Splenectomy was compared with Rituximab as a second line treatment for ITP and the result showed no significant difference between two types (OR 2.03, 95% CI (0.21–22.09), p = 0.549) [47]

In general, guidelines present different options for diagnosis and management of adult with ITP and literature reported different efficacy and response for these treatment options.

Method

This is a retrospective cross-sectional study reviewed data of adult patients who were diagnosed with ITP and followed in hematology clinic at King Hussein Medical Center from January 2017 to June 2018. Patients selected according to convenient sampling method. Inclusion criteria included all patients (male and female) with primary immune thrombocytopenia, while patients with secondary cause of immune thrombocytopenia (e.g.; malignancy, infections, etc...) were excluded.

Furthermore, patients' age between 18 and 70 years were selected. Cut off point for platelets count was 30,000/ µl and more than this was excluded.

Ethics review board committee at Royal Medical Services approved the study in September 2018.

Patients diagnosed with ITP received first line treatment with standard dose of steroids. They given prednisone 1 mg/kg/day for a period of 2-6 weeks then tapered over 3 to 6 months according to side effects and response. While those who developed resistance or dependence to steroid shifted to second line treatment that includes steroid sparing immunosuppressive agent Azathioprine (imuran) (150 mg/day for 3 months) and androgen

analogue Danazol (600 mg/day for 3 months). Moreover the third line treatment option was divided between Mycophenolate mofetil (MMF or CellCept) (2 g/day orally for 3 months), Rituximab (375 mg/m^2, once weekly for 4 weeks) and Splenectomy (mainly to steroid resistant patients).

Treatment response was defined according to The American Society of Hematology (3) as:

- Complete response (CR): A platelet count > 100 x 10^9/L measured on 2 times >7 days apart with absence of bleeding and lasting for >4 weeks.
- Partial response (R): A platelet count > 30 x 10^9/L and a greater than 2-fold increase in platelet count from baseline measured on 2 times > 7 days apart with absence of bleeding and lasting for >4 weeks.
- No response (NR): A platelet count <30 x 10^9/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 times more than a day apart. Furthermore, no response occurs when the treatment stopped because of the side effects of treatments.

Platelet count at presentation, after 1 month; 3 months and 6 months from initial presentation and starting treatment analyzed. Data were analyzed with SPSS version 22. The Kolmogorov-Smirnov test used to evaluate the normality of the data. Mean, median and standard deviation used to express quantitative data, while qualitative data were expressed as frequency and percentage. The chi-square test or the Fisher exact test was used for comparison of qualitative variables. Significant level set as p value <.05.

Results

Over all, out of 83 patients diagnosed with ITP and platelet count < 30,000/ µl, 53 (63.9%) patients were females and the remainders (36.1%) males. The median age of the study sample was 30 years (range: 18-70). At time of diagnosis, median of initial platelet count was 19 for both females and males (range: 5-29). Majority of patients (78.4%) didn't have bleeding at diagnosis. The presenting demographics and clinical features for patients at diagnosis demonstrated in (Table I).

First line of treatment response:

The first line treatment regimen was standard dose of steroids. All patients received prednisone (1mg/kg) for a period of two to six weeks then tapered over three to six months according to side effects and response. Among 83 patients, 15 (18.1%) showed partial response and 25 (30.1%) complete response. On the other hand, 35 patients developed dependency on steroid therapy. First line treatment response summarized in (Table II).

Second and third line treatment response:

Patients who were unresponsive or dependent on first line of treatment received second line therapy that includes Azathioprine and Danazol. Out of 49 patients treated by Azathioprine, seven (14.3%) patients achieved complete response and 10 (20.4%) patients partial response. One female patient with splenomegaly was prescribed Azathioprine and achieved complete response. Regarding Danazol, one (14.2%) patient achieved complete response and three (42.9%) patients achieved partial response. During treatment with steroid sparing immunosuppressant no severe infection reported.

In total, 53 (63.9%) patients shifted to third line therapy, which is consist of Mycophenolate, Rituximab and Splenectomy.

Overall 14 patients received Rituximab and led to a response rate of 50% (21.4% complete response).

Mycophenolate was prescribed for 29 patients. Three patients had complete response and 6 patients partial response.

Ten (12.04%) patients underwent Splenectomy. Complete response was obtained in four (40%), partial response in three (30%), and no response was obtained in three (30%) patients. Follow up after splenectomy showed no serious infection reported.

(Table III) Shows mean response to second and third-line treatment regimens in ITP patients

In general, the results showed statistically significant differences in responses to different types of treatment regimens at one month post starting therapy (51.8%, 30.6%, 24.1%, 35.7%, 71.4%, 80% respectively); p value = .001. The highest treatment response was for Splenectomy, while the lowest treatment response was for Mycophenolate. Similarly, the researchers found statistically significant differences regarding responses to treatment regimens at third month of induction; p value=.032.

Splenectomy still has the highest response (70%), while Azathioprine has the lowest response (22.8%). In contrast, there was no statistically significant differences between all regimens after six month of treatment; p value =.097. Moreover, the researchers evaluated the response over one, three and six months for each treatment alone, Danazol showed a statistically significant treatment response (p value=.008) with decrease in treatment response from 71.4% at one month to 42.9% at six months. This can explained by the lowest number of patients treated with Danazol (seven patients) in comparison to other types of treatment. Similarly, Rituximab has

statistically significant response over time (p value=.043). Treatment response at different periods during study is shown in (Table IV).

Table I: Demographic and clinical characteristics of 83 patients diagnosed with ITP

	Male	Female	Total
	(n=30, 36.1%)	(n=53, 63.9%)	(n=83, 100%)
Median age (range)	27 (18-70)	44 (18-70)	30 (18-70)
Initial platelets counts (10^9/l) median (range)	19 (10-28)	19 (5-29)	19 (5-29)
Bleeding presence			
Presence	9 (30%)	9 (17%)	18 (21.6%)
Not presence	21(70%)	44 (83%)	65 (78.4%)

Table II: Mean response to first-line treatment regimen in ITP patients

	Patients (%)	Dependent (%)	No response (%)	PR (%)	CR (%)
Prednisone (1 mg/kg)	83 (100%)	35 (42.2%)	8 (9.6%)	15 (18.1%)	25(30.1%)

Table III: Mean response to second and third-line treatment regimens in ITP patients

	Patients (%)	No response (%)	PR (%)	CR (%)
Azathioprine	49 (100%)	32 (65.3%)	10 (20.4%)	7 (14.3%)
Mycophenolate	29 (100%)	20 (69%)	6 (20.7%)	3 (10.3%)
Rituximab	14 (100%)	7 (50%)	4 (28.6%)	3 (21.4%)
Danazol	7 (100)	3 (42.9%)	3 (42.9%)	1 (14.2%)
Splenectomy	10 (100%)	3 (30%)	3 (30%)	4 (40%)

Table IV: Treatment response at different periods of time during study

Types of treatment	**Response at 1 month** PR+CR/Total No (%)	**Response at 3 months** PR+CR/Total No (%)	**Response at 6 months** PR+CR/Total No (%)	P value
Prednisone	43/83 (51.8%)	40/83 (44.5%)	37/83 (48.2%)	.067
Azathioprine	15/49 (30.6%)	18/49 (22.8%)	18/49 (22.8%)	.239
Mycophenolate	7/29 (24.1%)	11/29 (37.1%)	9/29 (31.1%)	.128
Rituximab	5/14 (35.7%)	8/14 (57.1%)	8/14 (57.1%)	.043
Danazol	5/7 (71.4%)	4/7 (57.1%)	3/7 (42.9%)	.008
Splenectomy	8/10 (80%)	7/10 (70%)	6/10 (60%)	.081
P value	.001	.032	.097	

Discussion

This study is the first research that compares all lines of ITP treatment in Jordan and regional countries.

In this study, our primary objective was to study the efficacy of different treatment regimens (6 types) used for adult diagnosed with ITP and compare effectiveness of these regimens with each other, in increasing the platelet count and stop bleeding if present. The choice of starting treatment depends on platelet count (<30,000/ µl), and presence of bleeding or bleeding risk at time of diagnosis. All patients selected in this study diagnosed as Primary Immune Thrombocytopenia by exclusion of all secondary causes of thrombocytopenia and only patients with primary ITP were included in the study. In addition, patients with unusual presentation, extreme age or

refractory to treatment where investigated by Bone Marrow (BM) study, which revealed in all cases normal BM examination and thrombocytopenia secondary to peripheral destruction.

Our results showed rapid response for Prednisone, where 90.4% of patients in study responded to this type of treatment, with either complete or partial response. But on the other hand, 47% of patients who achieved response to Prednisone attained dependency on therapy during tapering period (over 3 to 6 month) and shifted to second line therapy. Response to steroids was similar to the result of Matschke J et al (2016), who compared Prednisone (1-2 mg/kg/day for 2-4 weeks) with six cycles (3-weeks) of pulsed Dexamethasone (0.6 mg/kg/day) and both types of treatment showed 100% response (48). In contrast, patients in Matschke J et al study tended to have more infections, while in our study most patients had no infections. In literature Dexamethasone considered more effective than Prednisone in management of ITP, however Dexamethasone adverse effects less favorable (49, 50). Liu et al reported that high dose Dexamethasone pulse therapy more effective in modulation and regulation of cells polarization which represent a new approach for immune-regulation in ITP. (51).

Regarding Intravenous Immunoglobulin (IVIg), it was used among 7 patients.

Five of steroid resistant patients were planned to undergo spleenectomy after failure of all lines of treatment, so IVIg was used as bridging treatment for temporary increment of platelet count in order to have safe level for surgery without risk of bleeding. All the 5 patients received IVIg 400 mg/kg/day for 5 days, where all of them reached Platelet count more than 60.000 in 4th to 5th day. In addition no side effects have been noticed in any of them. Then all of them underwent the surgery without complications.

Furthermore, IVIG was used in other 2 patients; who needed to have rapid increment in their platelet count. One of them was young female in early twenties at her presentation with ITP; platelet count was 5.000 with menorrhagia, significant ecchymosis and symptomatic anemia secondary to her menorrhagia.

She responded very well to treatment with intravenous immunoglobulin; her platelet count reached 50.000 in day 3 of initiation the therapy.

While the other was a male in 5th decade, with recent diagnosis of ITP; he needed to do coronary artery bypass surgery. He did not respond despite of 5 days therapy with IVIg and his platelet count wasn't raised beyond 30.000 post complete treatment, for which his surgery was postponed till combination of steroid and Azathioprine built their effect over 4-5 weeks of treatment.

Patients who showed dependency or unresponsiveness to Prednisone shifted to second line, so they were given Azathioprine and/or Danazol. Overall response for Azathioprine was 34.7% (CR and PR), while 65.3% had no response. However response for Azathioprine increased after 3 months of treatment without significant p value (= .239). In contrast, Poudyal et al reported that response rate on the start and day 90 post Azathioprine induction was highly significant (p value 0.000) and overall response was 75% (52). The most common side effects of Azathioprine included gastrointestinal intolerance, and infection. Regarding Danazol, 7 patients given the therapy with overall response 57.1%. Moreover, response rate was significantly different at first, third and sixth month of treatment initiation (p value=.008) but, this result can't be generalized because the number of patients treated with Danazol was so small. Most common adverse effects during treatment were abdominal distention, acne, hyperglycemia, amenorrhea and weight gain.

In third line therapy, Mycophenolate used in 29 patients (34.9%), majority of them (69%) showed no response. Slight headache, diarrhea and nausea recorded in 4 of 29 patients. Therapeutic effects were found to be almost equal for both males and females (5 males and 4 females showed response). In contrast, other studies showed better overall response to Mycophenolate therapy than our study (53, 54).

Regarding Rituximab, out of 14 patients treated with Rituximab, 7 (50%) accomplished overall response. Moullis et al (2013) compared efficacy and safety of Rituximab versus splenectomy in adult with ITP, after 12 months of therapy, response rate for Rituximab was 69% versus 87.9% for splenectomy (55). Mild to moderate adverse effects occurred during treatment with Rituximab includes abdominal pain, bronchitis, throat irritation, and upper respiratory tract infection. However, literature reported severe and life threatening adverse effects during treatment with Rituximab including anaphylaxis, bronchospasm, infections and chest pain (38, 56).

Ten patients were treated with Splenectomy; overall response achieved was 70%, which is within the range of response rates reported in literature (2, 44).

Most intriguingly, Splenectomy is an effective therapy for steroid resistance or dependent patient and appears to be independent of previous therapies. In this study 3 patients did not respond to Splenectomy, 2 of them were steroid dependent.

Although Thrombopoietin receptor agonists (TPO-RA) therapy has been approved by FDA as a second line therapy for treatment of ITP and its efficacy in treatments of refractory cases well reported in literature (40, 41), the issue of unavailability and high cost over extended period of time prevent the use of this type of treatment in

our patients. However; this line of treatment would be very helpful in refractory cases. In those cases; it will be cost effective and improving the quality of life in addition to decrease ITP related complications.

Limitations of the study:

Since ITP is an uncommon disease (10, 12, 13, 14), our sample size is relatively small, some minor complications of the disease and side effects of some drugs may be missed because of retrospective nature of the study. Therefore wider scale studies via different national medical institutions to compare all lines of treatment and assess efficacy and side effects of each medication is needed to establish optimal therapeutic strategies for Jordanian patients with ITP.

Conclusion:

ITP is an acquired bleeding disorder with complex pathophysiology. More than 50% of patients who responded to Prednisone therapy developed dependency; however it still effective treatment for ITP.

Rituximab showed efficacy that is nearly equal to splenectomy which is still the treatment of choice for ITP with steroid resistance.

Overall, patients who received all lines of treatment obtained statistically significant differences in treatment response at first and third month of therapy induction (p value = .001 and .032 respectively). Splenectomy attained the best treatment response compared to other treatment options over 3 month's period.

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