RESEARCH ARTICLE
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Management of Adult Primary Immune Thrombocytopenia: Delphi-Based Consensus Recommendations

Demir A.M. et al: Management of Adult Primary ITP

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Abbreviations: ITP: Immune thrombocytopenia

ABSTRACT

Introduction: Primary immune thrombocytopenia (pITP) is an acquired autoimmune disorder related with increased destruction or/and impaired production of platelets. Diagnosis and management of ITP is challenging and require expertise and interpretation of international consensus reports and guidelines with national variations of availability. We aimed to assess the agreement of hematologists in Türkiye on certain aspects of both first line and second line management of patients with pITP.

Methods: As a modified Delphi method, Turkish National ITP Working Group (14 steering committee members) founded under Turkish Society of Hematology (TSH) developed a 21-item questionnaire consisting of statements regarding diagnosis-first line and second line treatments of pITP and 107 adult Hematologists working either in university or state hospitals voted for their agreement or disagreement of the statements for two consequential rounds.

Results: Participants have reached consensus on the use of corticosteroids as first line treatment and with limited duration. Methylprednisolone was the choice of corticosteroids rather than dexamethasone. Use of intravenous immunoglobulin was not preferred in patients without bleeding. It was also agreed that thrombopoietin receptor antagonists (TPO-RA) or rituximab should be recommended as second-line treatment, and that splenectomy could be considered 12-24 months after diagnosis in chronic pITP patients.
Conclusion: The optimization of the dose and duration of cortTPO-RAs in addition to corticosteroids is necessary to improve the management of patients with pITP.
Key words: Adult primary immune thrombocytopenia, Management, Delphi method

ÖZET
Giriş: Primer immün trombositopeni (pITP), trombositlerin artan yıkımı ve/veya bozulmuş üretimi ile ilişkili edinsel bir oto-immun hastalıktır. ITP'nin tanı ve yönetimi zorludur; ayrıca hem uzmanlık hem de uluslararası fikir birliği raporları ile kılavuzlarının, ulusal farklılıkları da göz önünde bulundurarak, yorumlanmasını gerektirir. Bu çalışmada Türkiye'deki hematologların pITP hastalarının birinci ve ikinci basamak tedavisinin belirli alanlarındaki fikir birliği düzeylerini değerlendirmeyi amaçladık.
Yöntem: Türk Hematoloji Derneği (THD) bünyesinde kurulan Türkiye Ulusal ITP Çalışma Grubu (14 yürütme kurulu üyesi), modifiye Delphi yöntemi ile pITP'nin birinci basamak ve sonraki tedavilerine ilişkin ifadelerden oluşan 21 maddelik bir anket geliştirdi. Üniversite veya devlet hastanelerinde çalışan 107 yetişkin hematolog, ardışık iki tur boyunca ifadelere katılıp katılmama yönünde oy kullandı.
Bulgular: Katılımcılar kortikosteroidlerin birinci basamak tedavi olarak ve sınırlı süreyle kullanılması konusunda fikir birliğine vardı. Metilprednizolonun, dekzametazondan ziyade tercih edilen kortikosteroid olduğu gözlendi. İntravenöz immünglobulin tedavisinin kanama dışında kullanımı tercih edilmez iken, trombopoietin reseptör antagonistleri (TPO-RA) veya rituksimab ikinci basamak tedavi olarak önerilebileceği, kronik pITP hastalarında tanıdan 12-24 ay sonra splenektomi düşünülebileceği konusunda da görüş birliğine varıldı.
Sonuç: pITP'li hastaların yönetimini iyileştirmek için kortikosteroidlerin yanı sıra TPO-RA'ların doz ve süresinin optimizasyonu gerekli olduğu konusunda fikir birliği sağlanmıştır.
Anahtar Kelimler: Erişkin primer immün trombositopeni, Hastalık yönetimi, Delphi metodu

Introduction

Primary immune thrombocytopenia (pITP) is an acquired autoimmune disorder characterized with reduced platelet counts related with increased destruction due to immune dysregulation and impaired production of platelets (1). Diagnosis is based on exclusion of conditions leading to platelet consumption or impaired thrombopoiesis related with stem cell disorders and the disease is classified as newly diagnosed (within 3 months), persistent (3-12 months) and chronic (≥12 months) (2).
With the classification being mainly based on disease duration, the goals of treatment have also been established. Rather than normalizing the platelet count (reaching beyond 100 $x10^9$/L), the long-term goal has been any platelet count above $30x10^9$/L without bleeding (2,3).
Data regarding the effectiveness of pITP treatments have been accumulating and practical recommendations towards the management of pITP have been needed. To provide such recommendations, as the national pITP study group, we would like to determine the actual needs as well as the views of the practicing hematologists in Türkiye and used a modified Delphi technique to constitute all aspects of management of pITP, from diagnosis to treatment.

Materials and Methods

The Delphi method is a survey-based process where certain statements were reviewed and scored for a few rounds by a predefined group of experts to until consensus is achieved. The group freely and anonymously votes for their agreement/disagreement of the statement in a graded manner. After the results are collected and reviewed by the committee, the statements are evaluated in terms of agreement rates as well as the supporting evidence by the published guidelines or the lack of agreement and its possible contributing factors (4,5).
National ITP Study Group (consisted of 14 steering committee members) has been founded under Turkish Society of Hematology and Hemostasis and Thrombosis Scientific Subcommittee by Hematologists with significant expertise on ITP. A questionnaire consisting 21 items regarding first line (9 items) and second line treatments (12 items) of ITP were developed. 107 adult hematologists of varying ages and facilities agreed to participate to the study. 77 have participated the first round (71,9%) and 72 have participated the second round of voting (93,5%). 68 of the votees were under 50 years (88,3%). Thirty one votees were working at University Hospitals (40,2%) while 43 were working at State Hospitals (55,8%) and the remaining votees were working at private practices.
The hematologists as votees, were asked to consider each statement and select their level of agreement using a 5-point Likert-type scale (1=disagree-never, 2=somewhat disagree-rarely, 3=neither disagree-sometimes nor agree,

4=somewhat agree-often, 5=agree-always). Consensus of agreement was regarded and expressed within this text as the sum of percentage of votes that somewhat agree-often and agree-always.

Results and Interpretations

1. First line treatment of pITP

1.1 Statement

In newly diagnosed pITP patients who are asymptomatic or with minor bleeding and platelet count <30 x10^9/L, treatment shall be commenced.

Agreement: 90% in favor of commencing treatment

Though the risk of bleeding is not corelated with any platelet count, it is accepted that risk of bleeding is higher in patients with platelet counts <20 x10^9/L (2). The panel recommends commencing treatment in patients who are asymptomatic or has minor bleeding and has platelet counts <30 x10^9/L.

1.2 Statement

In young patients with newly diagnosed pITP and platelet count <30 x10^9/L, dexamethasone 40 mg/day for four consecutive days within 28 days' cycles should be commenced.

Agreement: 30%

1.3 Statement

In young patients with newly diagnosed pITP and platelet count <30 x10^9/L, methylprednisolone 0.5-2.0 mg/kg/day should be commenced.

Agreement: 71%

In patients diagnosed with ITP and who are in need of treatment, corticosteroids are recommended (2,3). In a randomized controlled trial comparing dexamethasone with prednisone, both type of corticosteroids has been well tolerated though dexamethasone has resulted better short-term but poorer long-term responses (6).

1.4 Statement

In patients with newly diagnosed pITP and platelet count is <30 x10^9/L, how long shall the corticosteroids be used?

Agreement: 72%, less than 6 weeks, not more than 12 weeks

Duration of corticosteroids is recommended to be limited to 6 (maximum 8 weeks) including the tapering period even though the platelet count decreases (2,3). The use of prolonged use of corticosteroids is not recommended since there is no evidence in favor with the use of corticosteroids more than 6 weeks (3). We have observed a tendency to limit the use of corticosteroids in Türkiye.

1.5 Statement

The treatment of patients with pITP who are asymptomatic or has minor bleeding and platelet counts <30 x10^9/L can be managed in outpatient setting.

Agreement: 75%

In patients with pITP, treatment and follow up can be managed in an outpatient setting if there is no active bleeding and other conditions (such as in need of an anticoagulant treatment) and in patients who have platelet counts >20 x10^9/L (3). The panel also stated that there are factors other than the clinical condition and platelet counts such as distance to the facility, available beds etc. may be taken into account in the decision of hospitalization.

1.6 Statement

In patients with newly diagnosed pITP, corticosteroids shall be combined with rituximab as first line treatment.

Agreement: 73% in disagreement to use corticosteroids and rituximab as combination.

Rituximab is not recommended outside the setting of patients who have relapsed or refractory to corticosteroids, IVIG or splenectomy and the practice in Türkiye has been consistent with international guidelines (2,3,7).

1.7 Statement

In patients with pITP without bleeding, IVIG shall be used as treatment

Agreement: 88% against the use of IVIG in patients without bleeding.

The panel recommends the use of IVIG in patients with pITP who have bleeding, who are in need of an intervention in doses of 1g/kg/day in two consecutive days. IVIG may also be considered in newly diagnosed pITP patients in case corticosteroids are contraindicated (2,3,8,9).

1.8 Statement

During the taper of corticosteroids, if the platelet count decreases, corticosteroid dose shall be increased.

Agreement: 48%

If a response to corticosteroids is observed (increasing to >50 x10^9/L), the use of corticosteroids is not recommended to be prolonged more than 6 weeks (8 weeks maximum) including the taper period even with a decrease in platelet count (2,3). The lack of consensus in this statement demonstrates a need to increase the awareness and education in the definitions of corticosteroid dependency and refractoriness and the need to limit the prolonged use of corticosteroids.

1.9 Statement

In patients who have responded to corticosteroids, second line treatment is indicated for a relapse within the first year.
Agreement:63%
In adult patients, the natural course of pITP is still unclear. 20-45% of patients are reported to reach remission within 6 months however spontaneous remission beyond 6 months is regarded as relevant. In patients with persistent or chronic pITP who are refractory or dependent to corticosteroids or who have relapsed after corticosteroids, the panel recommends the use of TPO-RAs or rituximab. Re-use of corticosteroids in patients who have responded as first line but relapsed, is not recommended (2,7).

2. Treatment of Relapsed pITP

2.1 Statement

Bone marrow biopsy shall be performed in all patients requiring second line treatment
Agreement: 35%
Bone marrow evaluation should be performed in patients who have additional abnormal blood counts or who are nonresponsive to first line treatment or for whom splenectomy is considered (2,3,7).

2.2 Statement

For relapsed pITP patients with bleeding, TPO-RA shall be preferred as treatment.
Agreement: 62%
For patients with persistent pITP who are refractory or dependent to corticosteroids, either eltrombopag or romiplostim as a second line treatment is recommended (2,3).

2.3 Statement

The decision to use TPO-RAs (eltrombopag or romiplostim) shall be individualized in respect to patients' preference
Agreement: 88%
Since the availability of each TPO-RA vary within countries, international guidelines have suggested the decision be based on both resources and patients' preference (2,3). The panel recommends patients' preference to be taken into account in this decision as once weekly subcutaneous administration of romiplostim or daily oral route whilst fasting may be burdensome for patients.

2.4 Statement

TPO-RAs shall be used as second line treatment before splenectomy.
Agreement: 71%

2.5 Statement

Rituximab shall be used as second line treatment before splenectomy
Agreement: 49%.
Rituximab has been recommended in patients who prefer a limited duration of treatment. However it may have adverse effects such as secondary immune deficiency and hepatitis B reactivation. Recent pandemic with SARS-CoV-2 have also limited the use of rituximab. The panel have taken these perspectives into account and regarded rituximab and TPO-RAs as alternatives before splenectomy.

2.6 Statement

For patients with chronic pITP (>12 months) who are refractory to available treatments and have relapsed, splenectomy shall be performed
Agreement: 71%.

2.7 Statement

For patients with persistent pITP (3-12 months) who are refractory to available treatments and have relapsed, splenectomy shall be performed
Agreement: 34%
With the short term and long-term complications of splenectomy have been recognized, the worldwide use of splenectomy has observed to be decreased. Spontaneous remission rates within the first year and fifth year of ITP diagnosis has been reported as 30% and 80% respectively. International guidelines have recommended splenectomy to be postponed at least 12-24 months for possible spontaneous remission. For patients with persistent ITP who are refractory or dependent to corticosteroids, rituximab or TPO-RAs are recommended rather than splenectomy (2,3,7). Regarding this statement, votees who are younger than 40 years have voted against the use of splenectomy, while votees who are older than 40 have voted in favor of the use of splenectomy in this setting (p=0.013).

2.8 Statement

For patients with pITP who have reached platelet counts >30 $x10^9$/L after splenectomy, prophylactic anticoagulation shall be considered.
Agreement: 65%
Postoperative prophylaxis against thromboembolism is recommended for all patients with platelet counts >30-50 $x10^9$/L.

2.9 Statement

If a TPO-RA is not effective, switching to another TPO-RA shall be considered
Agreement: 30%
Switching to another TPO-RA or sequential treatment with TPO-RAs have been demonstrated to improve the rates of efficacy while decreasing the rates of adverse events (2,3). The panel have observed a lack of consensus majorly due to romiplostim being approved but only conditionally reimbursed in Türkiye.

2.10 Statement

In patients who have sustained platelet counts >100 x10^9/L, TPO-RA shall be tapered and be discontinued.
Agreement: 46%

2.11 Statement

In patients who have sustained platelet counts >50 x10^9/L, TPO-RA shall be used in the minimum effective dose possible.
Agreement: 88%
The optimal duration of treatment with TPO-RAs, once they are effective has not been established. For patients who have reached sustained platelet counts >50 x10^9/L, tapering and discontinuation of TPO-RAs may be considered after 6-12 months (2,3,7). The panel tended to regard the treatment with TPO-RA as a long-term treatment even in tapered doses.

2.12 Statement

Rituximab may be used in patients with pITP who have been non responding to TPO-RAs
Agreement: 75%
For patients who have failed to respond to multiple treatment alternatives, use of other available treatments such as mycophenolate, fostamatinib, rituximab, azathioprine, dapsone or danazol are recommended (2,3).
Statements with consensus and the recommendations of international guidelines are summarized in the Table, as a supplementary file to this article.

Discussion

Until the availability of TPO-RAs, management of ITP has mainly been founded on expert opinions. With the development of TPO-RAs, there has been a huge leap in understanding the pathophysiology of megakaryopoiesis as well as future possibilities of further treatment options. Nevertheless, diagnosis and management of ITP is still mainly based on expert opinions and consensus statements. One of the major perspectives of this course of development is the perception of ITP as a non-malignant disease of platelet counts alone without any implications on life expectancy. However, we are now aware of how quality of life is affected in patients with ITP with fatigue, lack of concentration and productivity and a dependency to a facility at all times (9).
One of the other perspectives that contribute to the lack of solid evidence is the discrepancy of treatment alternatives within countries. Besides corticosteroids as being the first line and all available treatment method in every country, TPO-RAs (and each distinct TPO-RA), rituximab, fostamatinib and other acknowledge subsequent treatment method may not be approved by national health authorities. This very perspective has been the main objective this study group aimed to address.
The goal of treatment of pITP is to prevent or decrease the risk of significant bleeding, rather than to normalize the platelet count. However, the risk of bleeding for each individual patient might not be easy to estimate. Patients who have a history of bleeding, who have platelet counts <10 x10^9/L and who are older than 60 years are generally accepted to have a higher risk (2,3). The management of pITP should start with the decision as whether treatment is indicated then proceed with the individualization of the goal of treatment, the platelet threshold the patient would require. We observed that our expert panel have been congruent with the international guidelines on commencing treatment for patients with newly diagnosed pITP who have platelet counts <30 x10^9/L.
The choice of initial treatment has been corticosteroids for patients who are asymptomatic or who have minor cutaneous bleeding with either oral 1mg/kg methylprednisolone or 40mg/day dexamethasone for four consecutive days (2,3,7). For patients who have received methylprednisolone, total duration of treatment (including the taper period) should not exceed 6-8 weeks (maximum of 12 weeks) (2,3). Though a single type of corticosteroid is not recommended worldwide, methylprednisolone is the preferred type of corticosteroid rather than dexamethasone in Türkiye. Furthermore, other forms of corticosteroids such as prednisone and prednisolone have not been the regular practice in Türkiye probably due to availability.
While limiting the use of corticosteroids is intended, we have observed a significant hesitation when platelet counts decrease during tapering. Practices in prolonged use of corticosteroids in other hematological or rheumatological conditions may also contribute to this hesitation and should be addressed with educative programs.
Complete long term remission rates with first-line corticosteroids have been reported as 20%, and the majority of the patients will probably relapse (2,3). However, spontaneous remissions may occur up to 10-20% most frequently within the 6 months after diagnosis. TPO-RAs, Rituximab, and splenectomy are the options for second-line treatment and the decision shall be individualized. We have observed that hematologists younger

than 40 years of age tend to delay splenectomy as long as possible, and this inconsistency needs to be addressed with educative programs. With the possibility of a spontaneous remission within the 12 months of diagnosis, our expert panel has reached a consensus to delay splenectomy for relapsed and refractory patients.

Conclusion

As the Turkish National ITP Working Group, we have observed a need to improve national management of ITP in the first line setting as to limit the prolonged use of corticosteroids, in the second line setting as to optimize the dose and duration of TPO-RAs. This survey would serve as a guide for educative programs to improve the management of ITP.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee (Trakya University Medical School Scientific Ethics Committee: TUTF-BEK 2023/322). Informed Consent: All of the participating physicians provided their written informed consent.

Authorship Contributions

Concept- A.M.D., Design- A.M.D., E.G.U, M.Ayr., M.C.A, M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Data Collection or Processing- A.M.D., E.G.U, M.Ayr., M.C.A, M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Ü.Ç., Analysis or Interpretation- A.M.D., E.G.U, M.Ayr., M.C.A, M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Literature Search- A.M.D., E.G.U, M.Ayr., M.C.A, M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Ü.Ç., Writing- A.M.D., E.G.U, M.Ayr., M.C.A, M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y.,

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