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Mini review article

LEČENJE PRIMARNE IMUNOLOŠKE TROMBOCITOPENIJE U ERI NOVIH VODIČA I LEKOVA

TREATING ITP: WHAT ARE THE OPTIONS IN THE ERA OF NEW GUIDELINES AND NEW DRUGS?

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Abstract

Primary immune thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia. Treating ITP may be challenging since different treatment modalities are available. While choosing the suitable option for every patient, a physician should take into account both patient's medical characteristics and wishes. The first line treatment options include: corticosteroids, intravenous immunoglobulins and intravenous anti-D immunoglobulin. Second line treatment options comprise medical (thrombopoietin receptor agonists, rituximab, fostamatinib, azathioprine, cyclophosphamide, cyclosporin A, hydroxychloroquine, mycophenolate mofetil, danazol, dapsone, vinca-alcaloids) and surgical (splenectomy) approach. However, there are some treatment gaps which remain uncovered with existing treatment modalities. Therefore, development of novel therapeutic strategies is required. The aim of this review is to provide an illustrative overview of novel treatments for adult ITP.

Keywords:
ITP,
splenectomy,
romiplostim
eltrombopag
rituximab

Sažetak

Primarna imunološka trombocitopenija (ITP) predstavlja autoimunsko oboljenje koje se odlikuje izolovanom trombocitopenijom. Lečenje ITP-a često predstavlja izazov s obzirom na brojne terapijske modalitete. Izbor najprikladnijeg terapijskog pristupa za svakog pacijenta zavisi kako od bolesnikovog stanja i faze bolesti, tako i od bolesnikovih želja. Modaliteti prve terapijske linije su: kortikosteroidi, intravenski imunoglobulini i intravenski anti-D imunoglobulin. S druge strane, modaliteti druge terapijske linije se klasifikuju na hirurške (splenektomija) i nehirurške (agonisti trombopoetinskih receptora, rituksimab, fostamatinib, azatioprin, ciklofosfamid, ciklosporin A, hidroksihlorokin, mikofenolat-mofetil, danazol, dapson, vinka alkaloidi). Međutim, i pored širokog spektra postojećih terapijskih modaliteta, neophodan je dalji razvoj lekova koji bi doveli do izlečenja i poboljšanja kvaliteta života svih obolelih od ITP-a.

Cilj ovog preglednog rada je upoznavanje čitalaca sa novim terapijskim pristupima u lečenju ITP-a odraslih.

Ključne reči:
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Introduction

Primary immune thrombocytopenia (ITP) represents an acquired autoimmune disorder characterized by isolated thrombocytopenia (platelet count (PC) < 100 x10^9/L) in the absence of other causes of thrombocytopenia (1). The incidence of ITP ranged from 1.6 to 3.9 per 100 000 adults/year (2).

So far, different possible precipitating factors of thrombocytopenia were defined in pathogenesis of ITP (infection, environment, genetics). It is likely that a combination of these factors actually precipitates ITP (3). Different pathophysiologic mechanisms lead to decreased platelet count (PC). Abnormally activated T cells trigger B cells to proliferate and differentiate towards secreting antiplatelet antibodies. Those antibodies ameliorate platelet clearance through the enhancement of the phagocytosis by macrophages, complement-dependent cytotoxicity, and apoptosis mediated by CD8 T cells. The spleen is a major organ of platelet destruction in the greatest number of patients. On the other hand, small PC is usually a result of low platelet production. It is a consequence of megakaryocytes (MK) dysfunction/destruction caused by autoantibodies and CD8+ T-cells. Moreover, serum thrombopoietin (TPO) level is not notably different between persons with normal and those with low PC (4).

Different treatment modalities have been developed as a result of such a complex pathogenesis. Consequently, treating ITP could be challenging for both physicians and patients. While corticosteroids, intravenous immunoglobulins (IVIg) and intravenous anti-D immunoglobulin (IV anti-D) are used as a first line therapy for ITP, choosing second-line therapy option greatly depends on patient's characteristics (bleeding history, age, comorbidities and compliance), as well as on the availability of drugs. Second line treatment options could be classified into medical (thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, azathioprine, cyclosporin A, cyclophosphamide) and surgical (splenectomy) (5).

The main goal of ITP therapy is to maintain PC to a safe level in order to prevent severe bleeding and to minimize adverse events (AEs). Female sex and exposure to non-steroidal anti-inflammatory drugs or to anticoagulants, with PC <20×10^9/L, all represent risk factors for severe bleeding, and for that reason they should be always assessed in ITP patients (6). Moreover, treatment strategy should be based on the severity of bleeding, assessed by the validate scale as well. One of the widely used bleeding score is the one established by Khellaf and the associates. In this score, cut-off value of 8 is set to determine whether the bleeding is severe or not (7). However, the decision to initiate treatment should not be based only on the bleeding tendency and the PC. Moreover, disease stage (acute/persistent/chronic), side effects of treatment, comorbidities, concomitant diseases and therapy, access to specialist care and patients' preferences should be also taken into account (8).

The first line therapy

Corticosteroids

Corticosteroids are traditionally the first line therapy for ITP. They act by altering the imbalance between individual lymphocyte fractions (Th1 vs. regulatory T cells), by rising the amount of suppressor cells, by switching the balance between activator and inhibitor *FcγR* on monocytes, and increasing myeloid-derived suppressor cells in a murine model of ITP (3). Additionally, it has been shown that corticosteroids improve endothelial function and, therefore, reduce the bleeding (9). Steroid therapy encompasses oral prednisolone (0.5-2 mg/kg of body weight (BW)), IV methylprednisolone (1 mg/kg BW or pulse dose 500 mg to 1 g IV for 3 days) and IV dexamethasone (40 mg IV for 4 days). Each of the aforementioned steroids can be used with approximately the same effectiveness. (10). Namely, PC responses after six months showed no significant difference between the group treated with pulsed dose of dexamethasone and the group treated with standard dose prednisone in patients with acute ITP. However, response to pulsed dose dexamethasone was achieved more rapidly, with less severe bleeding, and less additional adverse events compared to prednisone. Dexamethasone could be administered in one to three cycles over a 6-month period (11). Furthermore, no significant difference in response rate was shown between the groups treated with IV methylprednisolone (1 mg/kg) and with oral prednisolone (1 mg/kg) (12). High-dose methylprednisolone could be also used in severe ITP, but it showed up to be less effective than IVIg (13). However, it may be used together with IVIg or azathioprine as an effective treatment option in ITP patients refractory to oral corticosteroids (5). After a certain period of use the potential benefits of corticosteroids are outweighed by the side effects. For the reason, ASH guideline panel recommends that the prednisolone treatment lasts < 6 weeks, including tapering period (14). The most common AEs of corticosteroid treatment are: cataract, nausea, vomiting and other gastrointestinal manifestations, sleep disturbances, fractures, osteoporosis, cardiac conditions, type 2 diabetes mellitus and arterial hypertension (15).

IVIg

Intravenous immunoglobulin (IVIg) may be used in patients where corticosteroids are contraindicated or can mask underlying disease in case of unclear diagnosis, as well as in cases with serious bleeding. The recommended dose is 1 g/kg on day one, repeated on day 2, if the response is inadequate. If the patients are older and/or with comorbidities (risk of thrombosis, renal insufficiency), IVIg should be administered in dose of 0.4 g/kg during 5 days (10). No differences in efficacy between those two modes of administration were observed. Its efficacy could be explained by blockade of *Fc* receptors on macrophages, its anti-inflammatory effects, effects on B and T cells, and effects on cell growth. Response was shown in 65 % to 80 % of the treated patients. However, it is transitory

and the relapse is common after a median of 11 days (16). Adverse events (AEs) related to the IVIg therapy could be immediate (headache, chest discomfort, fever, muscle and joint pain, gastrointestinal and cardiovascular symptoms) and late-onset (kidney disfunction, blood disorders, lung diseases, pseudohyponatremia, neurotoxicity, thromboembolic events, arthritis). Severe anaphylactoid reactions after the IVIg infusion are uncommon. They might occur in IgA-deficient patients in which macromolecular complexes with anti-IgA antibodies of the recipient are formed (17).

Intravenous anti-D (IV anti-D)

The mechanism of action is unknown; however, it is believed that anti-D coats the red blood cells of Rh-positive patients and either blocks *FcγR* on phagocytic cells, or modulate the immune system resulting in an increase in the PC (10). A single dose of 50-75 mg/kg is recommended (5). The prerequisites for anti-D treatment in ITP are that the patient should be Rh (D) positive, with a hemoglobin level > 10 g/dL. Patient should not have undergone splenectomy and coexisting hemolytic anemia should be ruled out. A response rate is approximately 70 %. The effect of therapy lasts > 21 days in 50 % of the responders (18). Only one product of anti-D is approved for ITP and it is only available in USA (8). Most patients exhibit a mild hemolysis (decrease in Hb concentration of 0.5 to 2 g/dL over the 3 to 7 days). Anti -D therapy carries black box warning that requires observation of the patients for 8 hours after administration, due to risk of intravascular hemolysis and disseminated intravascular coagulation (19).

The second line treatment

Medical treatment

TPO-RA

The most commonly used TPO-RAs are eltrombopag and romiplostim. Eltrombopag is applied orally at the initial dose of 25 or 50 mg/day. If the favorable effect is not reached, dose could be increased up to a maximum of 75 mg/day (5). Certain interactions with the food are noted and for that reason it should be administered 2 hours before, or 4 hours after products containing polyvalent cations. The EXTEND (Eltrombopag extended using) study has shown that nearly 70 % of patients achieved a continuous PC of ≥30 × 10^9/L, for more than 25 weeks (20). Similarly, a sustained platelet response for 9 out of 12 weeks was achieved by 68 % of splenectomised and 80 % of nonsplenectomised patients given romiplostim (21). Romiplostim is applied initially at the dose of 1 mcg/kg weekly subcutaneously. If the response fails to occur, dose could be increased up to 10 mcg/kg per week (5). Romiplostim and eltrombopag bind to the thrombopoietin (TPO) receptor, inducing conformational change in the TPO receptor, alongside the activation in subsequent signal pathways. The final results are increased MK progenitor proliferation and increased platelet production. While romiplostim binds directly and competitively at the TPO binding site, eltrombopag binds at a trans-membrane site. There are also differences in the activation of other signaling pathways in MK. Furthermore, romiplostim mostly stimulates mature precursors, while eltrombopag appears to stimulate MK precursor cells and MK differentiation (22). Therefore, switching to the second TPO-RA, if the favorable response is not achieved with the first one, should be taken into consideration. Switching proved to be effective in almost 60 % of cases (23). On the other hand, avatrombopag is representative of newer generation of TPO-RAs. It is similar to eltrombopag in binding to the TPO-receptor in the transmembrane domain, being available orally and in its efficacy. However, no interactions with food were recorded (24). The TPO-RAs are still developing.

So far, following AEs are recorded in patients treated with TPO-RAs: headaches, joint and muscle pain, stomach complaints, bone marrow fibrosis, and thromboembolic events. Fluctuating PC and neutralizing antibody development are the AEs mostly associated with romiplostim. On the other hand, patients treated with eltrombopag are in risk of treatment-related cataract, transaminitis and skin toxicity (itching, redness, maculopapular exanthema). Furthermore, rebound thrombocytopenia occurs after abrupt cessation of treatment (8, 22). Termination of TPO-RA treatment is recommended after the favorable response is attained for 6 months continuously. In order to avoid rebound thrombocytopenia, it is advised to gradually lower the dose of TPO-RA before its definite cessation (27).

Rituximab

Rituximab is a second line treatment option with the achievement of a PC > 50x10^9/L in 62.5 % of adults. However, sustained response is rare among those patients (28). Depletion of B-cells is marked as a major mechanism of action of rituximab (29). The recommended dose is 375 mg/m^2/week i.v. for 4 weeks. The low dose rituximab regiments were tested (100 mg/m^2/week i.v. for 4 weeks) with similar efficacy (30). Younger women (< 40 years old) have the higher probability of achieving long term response (31). The AEs related to rituximab are: infusion-related AEs (weakness, nausea, fever, chills, headaches), anaphylactic reaction (rare), increased risk of infections and progressive multifocal leukoencephalopathy (rare). Before the introduction of the rituximab viral hepatitis should be excluded (8).

Fostamatinib

Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor which has been used for treatment of chronic ITP in adults who have been unresponsive to previous treatment modalities. Syk has the significant role in cell cycle, immune regulation and cytoskeletal rearrangements during phagocytosis. Hence, Syk inhibition would lead to the inhibition of phagocytosis of antibody coated platelets. Double-blind, randomized trials showed that 18 % of chronic ITP patients, who were unresponsive to prior ITP treatments, achieved a stable response after fostamatinib treatment.

Initial dose used in this study was 2 x 100 mg/day, with a dose increase to 2 x 150 mg if the low PC persisted at week 4. The AEs recorded in this study were: diarrhea, hypertension, nausea, and transaminitis (32).

Other medical treatment options

Azathioprine is an antimetabolite with the efficacy in ITP treatment of 51 to 64 %. It is suppressor of B and T lymphocytes. The recommended dose is 1 - 3 mg/kg daily. Median time to response is 2 - 3 months and it lasts for approximately 3 - 84 months (33). Most common AEs are: elevated transaminase levels and leukopenia (34).

Cyclophosphamide is immunosuppressant whose efficacy in refractory ITP patients is around 55 %, and the response takes an average of 3 months (35). The most severe AEs described are: hemorrhagic cystitis, leukopenia and risk of secondary malignancies (33).

Cyclosporin A is an effective T cell inhibitor (inhibition of activation of CD4+ lymphocytes and IL2 production). In a small series of adult refractory ITP patients, complete remission was achieved by 41 % patients. However, potential AEs outweigh therapeutical benefit. Most common AEs are: fatigue, hypertension, gingival hyperplasia, hypertrichosis, impaired kidney function, dyspepsia and paresthesias (36).

Mycophenolate mofetil (MMF) is one more drug in the ITP treatment targeting T-cells. Response to MMF in refractory ITP was seen in 40 % of patients. The most common AEs are headache, abdominal pain, diarrhea, nausea, hypertension and hematological toxicity (38).

Danazol is traditionally used in treatment of thrombocytopenia of different etiology. In ITP it is usually applied in dose of 400 to 800 mg daily. It has shown its effectiveness in more than a half of patients with ITP which lasts for ≥ 3 months. Time to response varied between 2 and 3 months. Its most common AEs are: amenorrhea, acne, masculinization, liver function tests abnormalities, weight gain, headaches, or intracranial hypertension (39). For that reason, it should not be given to women in reproductive period (8).

Dapsone used in dose of 75 - 100 mg daily has been effective in > 50 % of ITP patients. Time to response is between 1 and 2 months. Following AEs were described: hemolysis with/without anemia, methemoglobinemia, nausea, vomiting, headache (39). Moreover, in Mediterranean's a deficiency or defect of glucose-6-phosphate dehydrogenase must be excluded before initiating dapsone (8).

Vinca-alkaloids, vincristine and vinblastine, are used in dose of 2 and 10 mg IV, respectively. Maximal cumulative dose is established due to potential AEs; for vincristine it is 6 mg and for vinblastine 30 mg (5). Vinca-alkaloids act through inhibition of phagocytosis. Median time to response is 9 days after the first dose. The overall response rate is 75 %. Almost half of patients treated with vincristine expressed some of the AEs (peripheral neuropathy, abdominal cramps, alopecia) (40).

Splenectomy

For decades, splenectomy has been the standard therapy for ITP patients unresponsive to corticosteroids. The role of the spleen in platelet pathogenesis is multiple. On the one hand, it presents the place where anti-platelet antibodies are synthetized and on the other it is the site where platelets are destroyed in the majority of patients (4). Normal PC after splenectomy was achieved in more than 60 % of patients, while PC > 50 x 10^9/L was attained in > 80 % of ITP patients. Relapse rate after splenectomy is estimated at 15 % with a median follow-up of 33 months (range, 3 - 153 months), and it increases with the duration of follow-up. Complications were noted in 12.9 % patients treated with laparotomy, and in 9.6 % patients treated with laparoscopic splenectomy (41). Complications associated with splenectomy can be categorized as: perioperative/short-term (postoperative bleeding, infections, perioperative thromboembolism, death (around 1 %)) and long-term (venous and arterial thromboembolism, infections, pulmonary arterial hypertension) (42). It should be underscored that splenectomised patients are at greater risk of these complications for life. Bacteria with polysaccharide capsule (e.g. *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*) are the most frequent pathogens that cause infections among splenectomised patients. For the reason, vaccination against these species is recommended a couple of weeks before splenectomy, or as soon as possible after emergency splenectomy (43). In order to prevent late-onset infections, annual influenza vaccine is required as well. Since the splenectomy associated complications are relatively frequent, and novel drugs are more available, it is performed less frequent nowadays. However, splenectomy is still a treatment of choice for those willing to live actively without frequent check-ups and drugs intake, as well as for those with ITP which is unresponsive to medical therapy (42). Moreover, splenectomy should be avoided within the first 12 months after ITP diagnosis to allow for spontaneous or therapy-induced remissions (5).

Supportive treatment

Bleeding caused by ITP could be managed with antifibrinolytics. E-aminocaproic acid and tranexamic acid showed success in bleeding control (44, 45). In order to reduce gynecological bleeding hormonal contraception and hormonal substitutive treatments could be used. However, the risk of thrombosis should be considered, especially in splenectomised patients and patients taking TPO-RA (46).

Platelet transfusions may be helpful in cases of life-threatening bleeding, especially intracranial hemorrhage (5).

Table 1. Updated recommendation for ITP management

Treatment modality	International consensus report (5)	American Society of Hematology (14)	JWG of DGHO, ÖGHO, SGH, GPOH, and DGTI (8)
Corticosteroids	-Prednisolone (1 mg/kg; max. dose 80 mg); -Dexamethasone (40 mg/day; 4 days) -Methylprednisolone (high-dose; emergency)	-Prednisolone (0.5 - 2 mg/kg); -Dexamethasone (40 mg/day; 4 days)	-Prednisolone (1 - 2 mg/kg) -Dexamethasone (40 mg/day; 4 days) -Methylprednisolone (125 - 1000 mg i.v; 1 - 5 days)
IVIg	-1 g/kg/day (1 or 2 days) -0.4 g/kg/day (5 days)*	-not addressed	-0.4 – 1 g/kg/day -emergency treatment
IV anti-D	-50 - 70 μg once (USA)*	-not addressed	-not approved in EU -emergency treatment
TPO-RA	-eltrombopag (max. dose 75 mg/day) -romiplostim (1 - 10 μg/kg/week) -avatrombopag (20 - 40 mg/day) -high response rate (irrespective of splenectomy)	-eltrombopag (max. dose 75 mg/day) -romiplostim (1 - 10 μg/kg/week) -avatrombopag (research priority) -TPO-RA over rituximab	-eltrombopag (max. dose 75 mg/day) -romiplostim (1 - 10 μg/kg/week) -avatrombopag (not addressed)
Splenectomy	-not until 12 to 24 months from diagnosis -high response rate -high risk of complications	-not until 12 months from diagnosis -patients wishing to achieve a durable response and to avoid long-term medication	-not until 12 months from diagnosis -patients with severe bleeding (WHO III, IV) who are irresponsive to other treatments
Rituximab	-375 mg/m^2 (4 doses) -response rate of 60%	-rituximab over splenectomy -TPO-RAs over rituximab -patients wishing to avoid surgery and long-term medications	-375 mg/m^2/week (4 weeks) -after failure of steroids and TPO-RA -early (after first infusion) and late responders
Fostamatinib	-2*100 mg/day (could be increased to 2*150 mg/day) -response rate of 43%	-research priority	-not addressed

*Patients with higher tendency of bleeding, corticoresistant patients, or those in need of surgery, or with contraindications to corticosteroid therapy (insulin-dependent/uncontrolled diabetes, psychiatric disorder).

First line treatment | Second line treatment | Third line treatment

Conclusion

Despite the constant development of novel ITP treatment options, it is still not possible to establish precise treatment algorithm suitable for all patients. The main reason for this is because there is usually no strong evidence supporting the recommendations. However, everyone agrees that AEs should be avoided as much as possible.

Besides, many of the specific drugs (i.e. TPO-RAs, fostamatinib) considered in the guidelines are unavailable in certain countries, at least not for a routine use. Hence, other drugs must not be overseen in treatment algorithms. Moreover, studies regarding those medications should be encouraged. However, the clinical practice should be beyond every guideline with the aim of choosing the best treatment option for every patient individually.

Lastly, it should be also noted that there are still some patients who remain unresponsive to the existing therapy. Consequently, further research is needed in order to establish the new treatment modalities.

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