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Management of immune thrombocytopenia: Korean experts recommendation in 2017

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Abstract

Management options for patients with immune thrombocytopenia (ITP) have evolved substantially over the past decades. The American Society of Hematology published a treatment guideline for clinicians referring to the management of ITP in 2011. This evidence-based practice guideline for ITP enables the appropriate treatment of a larger proportion of patients and the maintenance of normal platelet counts. Korean authority operates a unified mandatory national health insurance system. Even though we have a uniform standard guideline enforced by insurance reimbursement, there are several unsolved issues in real practice in ITP treatment. To optimize the management of Korean ITP patients, the Korean Society of Hematology Aplastic Anemia Working Party (KSHAAWP) reviewed the consensus and the Korean data on the clinical practices of ITP therapy. Here, we report a Korean expert recommendation guide for the management of ITP.

Key Words Aplastic Anemia Working Party, ITP, Recommendation, Management

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune-mediated condition caused by antibody-mediated destruction of platelets and impaired platelet production of megakaryocytes [1, 2]. Management options for patients with ITP have advanced substantially over the past decades. In 2011, the American Society of Hematology (ASH) published a comprehensive guideline for ITP, which has become the standard reference for the diagnosis and treatment of ITP [3]. Most Korean hematologists refer to this evidence-based

practice guideline for ITP, ensuring that a larger proportion of patients are properly treated and are able to maintain normal platelet counts.

The National Health Insurance (NHI) is the only public medical insurance system operated by the Ministry for Health and Welfare in Korea. The Korean Health Insurance Review and Assessment Service (HIRA) is a government-affiliated organization created to build an accurate claims review and quality assessment system for the NHI. HIRA enforces ITP treatment options by reimbursing health insurance and Korean hematologists should follow this unified mandatory national insurance system.

Despite this uniform standard guideline and unified insurance system, there are several unsolved issues in real practice regarding ITP treatment such as the definition of medically unfit to splenectomy or optimal timing of secondary treatment options. To resolve these issues, an expert recommendation guide is needed in Korea. To optimize the management of Korean ITP patients, the Korean Society of Hematology Aplastic Anemia Working Party (KSHAAWP) reviewed the consensus and the Korean data on the clinical practices of ITP therapy. In this report, we propose an expert recommendation guide for the management of ITP.

CLASSIFICATION

ITP in adults

ITP is characterized by the autoimmune destruction of platelets and the suppression of platelet production from bone marrow (BM) megakaryocytes. A platelet count $<100\times10^9$/L was recently suggested as the upper threshold for the diagnosis of ITP in one report from an international working group [4]. The decrease in the platelet cut-off from 150×10^9/L to 100×10^9/L was based on a long-term outcome study of healthy individuals, that revealed that individuals with platelet counts between 100×10^9/L and 150×10^9/L had only a 6.9% 10-year probability of developing persistent platelet counts $<100\times10^9$/L [5]. ITP may be diagnosed as isolated thrombocytopenia without specific association with other diseases (primary) or together with other medical conditions that can cause thrombocytopenia (secondary) [4]. Common causes of secondary ITP include autoimmune diseases (including systemic lupus erythematosus, antiphospholipid syndrome), infections (cytomegalovirus, hepatitis C virus [HCV], human immunodeficiency virus [HIV], varicella zoster, and *Helicobacter pylori* [*H. pylori*]), lymphoproliferative neoplasms (chronic lymphocytic leukemia and lymphoma), immunodeficiencies (IgA deficiency and common variable hypogammaglobulinemia), therapy with certain drugs, and recent vaccination [1, 4, 5]. ITP can be further classified based on duration: newly diagnosed ITP, (<3 mo duration); persistent ITP (between 3 and 12 mo duration); and chronic ITP (>12 mo duration)[4]. Because the degree of thrombocytopenia is a surrogate for the risk of bleeding, although not always in good correlation, severe ITP is defined when patients have bleeding symptoms at presentation that require appropriate treatments or new bleeding symptoms requiring additional treatments or increase in drug dose [4]. Refractory ITP should be reserved for patients with severe ITP occurring after splenectomy.

ITP in pediatrics

Primary ITP is defined as an autoimmune disorder of isolated thrombocytopenia without other causes or disorders associated with thrombocytopenia, while secondary ITP is defined as all forms of immune-mediated thrombocytopenia except for primary ITP [3, 4]. For secondary ITP associated with underlying disorders, treatment is more challenging and complex; some patients may require tailored therapy specific to the underlying disease and others may require ITP-like therapy to normalize the platelet count [6, 7].

Similar to adult ITP, pediatric ITP is classified into newly diagnosed, persistent and chronic ITP depending on disease duration [3, 4].

Refractory ITP is a condition of severe ITP or risk of bleeding requiring therapy after splenectomy or relapse after splenectomy. However, splenectomy should be delayed as long as possible expecting spontaneous remission and benign courses in children. Therefore, when non-splenectomized children with ITP do not respond to conventional medical therapy, the term "unresponsive to the specified therapy" would be used instead of "refractory" [4].

DIAGNOSIS

ITP in adults

There are currently no golden standard tests that can reliably establish a diagnosis of ITP, which still relies on the exclusion of other possibilities. Essential components of the diagnosis of ITP include personal history, family history of inherited thrombocytopenia, physical examination, complete blood count with differential, reticulocyte count, and review of peripheral blood smear [8]. ITP is usually suspected when isolated thrombocytopenia is observed with no additional abnormalities except for anemia in the setting of bleeding. If patients present with typical ITP, a BM examination is not generally required to diagnose the ITP. However, if there are abnormalities in the complete blood counts or peripheral blood smear that indicate other diseases, further investigation should be conducted with a BM examination or other appropriate tests. BM examination may also be necessary in patients older than 60 years of age, who do not show appropriate response to first-line treatment, or in patients that are candidates for splenectomy. Additional serologic testing for hepatitis B virus, HCV, and HIV is recommended for all adult patients with ITP [8], because these infections may be associated with ITP and treatment depends on the management of the underlying condition. The effect of *H. pylori* eradication in patients with ITP is higher in countries with a high prevalence of *H. pylori* infection [9] including Korea [10]. Thus, the detection of *H. pylori* infection using a rapid urease test, urea breath test, or stool

H. pylori antigen assay needs to be considered in the work-up of adult patients with ITP. A recent prospective study in Korean patients with moderate thrombocytopenia showed that 57.7% of patients responded to *H. pylori* eradication [11]. However, antinuclear [12] and antiphospholipid antibodies [13] are insufficient for the routine evaluation of patients suspected with ITP. These tests should be included on the basis of relevant symptoms and signs of individual patients. Antiplatelet antibody testing is not recommended any longer, because of high inter-laboratory variability and poor sensitivity [14]. Table 1 shows the recommended work-up for the diagnosis of ITP in adult patients.

Table 1. Recommended work-up for the diagnosis of ITP in adult patients.

Essential evaluation	Potentially useful evaluation
Patient history	Bone marrow examination[b]
Family history	Antinuclear antibody test
Physical examination	Antiphospholipid antibody tests, including anticardiolipin antibody and lupus anticoagulant
Complete blood count with differential	Pregnancy test in women of child bearing potential
Peripheral blood smear	
Reticulocyte count	
Serology tests for HBV/HCV and HIV infection	
H. pylori tests[a]	
Blood group (Rh)	
Direct anti-globulin test	

[a]Include rapid urease test, urea breath test, or stool *H. pylori* antigen assay. [b]In selected cases with patients ≥60 years old, no appropriate response to therapy, or plan for splenectomy.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; *H. pylori*, *Helicobacter pylori*; Rh, rhesus.

Table 2. Causes of secondary ITP in children.

Antiphospholipid syndrome
Autoimmune thrombocytopenia (e.g. Evans syndrome)
Common variable immune deficiency
IgA Deficiency
Wiskott-Aldrich syndrome
Drug side effect
Infection (eg. CMV, *H. pylori*, HBV, HCV, HIV, VZV, parvovirus, etc.)
Lymphoproliferative disorders
Bone marrow transplantation side effect
Vaccination side effect
Systemic lupus erythematosus
Rheumatoid arthritis
Hypersplenism

Adapted from Neunert *et al.* [3]
Abbreviations: CMV, cytomegalovirus; IgA, immunoglobulin A; VZA, varicella zoster virus.

ITP in pediatrics

Exclusion diagnosis: ITP is basically diagnosed by excluding other causes presenting with thrombocytopenia through careful history consideration, physical examination, and lab-

Table 3. Diagnostic elements of ITP in children.

History taking
Bleeding symptoms/history
Systemic symptoms (eg. fever, weight loss)
Autoimmune disorder symptoms (eg. arthralgia, skin rash, alopecia, venous thrombosis)
Risk factors for HIV, Hepatitis B or C
Drug and herbal medicines history (eg. heparin, alcohol, quinidine, sulfonamides, aspirin)
Transfusion history
Family history
Vaccination history (eg. MMR, Hepatitis A, Hepatitis B, Influenza, DTaP, Varicella, Pneumococcus, etc.)
[a]Alcohol history/pregnancy status
[a]Comorbid conditions (eg. GI/CNS/GU disease)
Physical examination
Bleeding sign
Lymphadenopathy/hepatomegaly/splenomegaly
Symptoms of autoimmune disease (eg. arthralgia, goiter, nephritis, vasculitis)
Symptoms of infection (eg. HIV, other viral infection)
Skeletal anomalies (eg. inherited/congenital thrombocytopenia)
[a]Symptoms of thrombosis
Laboratory test
Complete blood count
Reticulocyte count
Peripheral blood smear
Coagulation and platelet function screening test
Immunoglobulin level
Autoimmune profile
HIV, hepatitis B and hepatitis C screening
Baseline immunoglobulin levels
Direct antiglobulin test
Blood type
[a]Bone marrow examination (in selected cases)
[a]*H. pylori* (in selected cases)
Test of potential utility
Glycoprotein-specific antibody
Antiphospholipid syndrome screening
Antithyroid antibodies and thyroid function test
Viral PCR for parvovirus and CMV
[a]Pregnancy test (in women of childbearing potential)
[a]Antinuclear antibodies (in selected cases)
Test of unproven benefit
Thrombopoietin
Reticulated platelets
Platelet-associated immunoglobulin G
Bleeding time
Platelet survival study
Serum complement

Adapted from George *et al.* [39] and Provan *et al.* [8].
[a]Test in selected cases.
Abbreviations: CNS, central nervous system; DTaP, a vaccine for diphtheria, pertussis, and tetanus; GI, gastrointestine; GU, genitourinary; MMR, measles-mumps-rubella combined vaccine; PCR, polymerase chain reaction.

oratory evaluation such as complete blood count and peripheral blood smear [7, 15, 16]. The exclusion of secondary ITP is crucial (Table 2).

ITP is the "default" diagnosis for a patient with isolated thrombocytopenia that should be distinguished from pseudo-thrombocytopenia or laboratory errors by repeat test. Table 3 shows the diagnostic elements of ITP in children.

Special consideration

BM exam: BM exam is usually performed prior to therapy [e.g. administration of thrombopoietin-receptor agonists (TPO-RAs)], to ensure that BM is normal. BM exam is not necessary in children with typical ITP or even after failure to IVIg therapy [6, 7].

Vaccines and vaccination: Although vaccination provides protective immune responses, it may promote autoimmune diseases, such as ITP. Vaccine-associated autoimmunity can be caused either by antigen-mediated immune mechanisms or by vaccine constituents or adjuvants. However, most vaccine-associated ITP is mild and well-responsive to therapy. In contrast, because infections may trigger ITP causing severe consequences, it would be prudent to vaccinate children with previous history of ITP [17, 18].

Anti-platelet antibody: Not helpful for either exclusion or confirmation of the diagnosis of ITP.

Anti-nuclear antibody: Not necessary in children with suspected ITP.

ITP TREATMENT IN ADULTS

When is treatment required?

Generally, the majority of patients without bleeding who have persistent platelet counts above 20×10^9/L can be observed without treatment. Many adults with mild and asymptomatic thrombocytopenia appear to have a benign course without treatment [19, 20]. Treatment should be initiated in patients who have platelet counts persistently less than 10×10^9/L or symptomatic patients who have active bleeding symptoms, anemia induced by bleeding, and poor quality of life. Assessment of bleeding risk includes detailed history consideration, such as the timing, location, and severity of bleeding symptoms and also the use of antithrombotic agents, hypertension, peptic ulcer disease, or a potential for substantial trauma to the body with high-risk occupation.

The decision to treat adults with platelet counts between 10×10^9/L and 20×10^9/L depends on other risk factors such as age, comorbidities, patient's severity of bleeding, bleeding risk, activity level, expected side effects of treatment, patient's daily activities and preferences. Careful observation by a specialist may be an option for patients with platelet counts between 10×10^9/L and 20×10^9/L, unless the patient is characterized by additional risk factors. The platelet count offers an indication of bleeding risk; however, it is not the sole factor for the prediction of bleeding [21].

Increasing age is a major risk factor for bleeding when platelet counts are less than 20×10^9/L [19]. However, treatment-related toxicities also increase with age [22]. Comorbidity is also an important factor for treatment decision. For patients, who require anti-platelet agents or anticoagulation after percutaneous coronary artery stents or cardiac valve replacement surgery, the recommended platelet count is above 50×10^9/L. However, myocardial infarction can be observed in patients with platelet counts less than 20×10^9/L. A careful assessment of bleeding and thrombosis risk and treatment decision should be made on an individual basis in these groups of patients.

First-line therapy

The recommended treatment option as a first-line treatment in adult ITP patients includes corticosteroids, intravenous immunoglobulin (IVIg), and anti-D immunoglobulin (anti-D).

Corticosteroids: One mg/kg/day of prednisolone or 40 mg/day of dexamethasone are usually the initial doses for patients who are not contraindicated for corticosteroid treatment. Longer courses of corticosteroids (e.g. prednisolone 1 mg/kg orally for 3–4 weeks then tapered off or dexamethasone 40 mg/kg for 4 days and dexamethasone/prednisolone maintenance [23, 24]) are recommended over shorter courses of corticosteroids (e.g. one course dexamethasone 40 mg orally for 4 days or high-dose pulse of methylprednisolone) or IVIg alone, because they were associated with prolonged responses in one randomized study [25]. However, short courses of corticosteroids also showed high rates of sustained responses in other non-randomized studies [23-26]. Single course or repeated courses of high dose dexamethasone are also reasonable treatment options in frontline setting, which showed comparable or even better outcomes in one randomized study [27]. After a short course of the initial dose, rapid tapering schedule should be considered to minimize the potential toxicities of long-term use of corticosteroids.

The addition of rituximab (375 mg/m^2 weekly for 4 wk) to high dose of dexamethasone (40 mg/day for 4 days) as frontline therapy in adult ITP patients, improved their response (63% vs. 36%, P=0.004). However, the high rate of protocol violations, dropouts, unclear presentations regarding duration of corticosteroid treatment, and increased rate of complications in the rituximab arm limit recommendation of this combination treatment as a standard first-line therapy [28].

IVIg or anti-D: IVIg or anti-D should be considered in cases of life-threatening bleeding or prior to surgery, because of the relatively rapid and high initial response rate. Contraindication to corticosteroids is also an indication to IVIg and anti-D. Concurrent use of IVIg and corticosteroids could be considered for emergency situations with extremely low platelet counts ($<5\times10^9$/L) or significant bleeding. In case IVIg is used, an initial single dose of 1 g/kg should be administered. The recommended usage of IVIg is 1 g/kg/day for 2 days [29]. Major adverse effects of IVIg include renal

failure, thrombotic events, aseptic meningitis, hemolytic anemia, and erythema [30]. In case anti-D is chosen as the first-line therapy, the risk of severe hemolysis and disseminated intravascular coagulation should be carefully considered [31].

Second-line therapy

The main goal of second line therapy is to achieve an increase in platelet count that will prevent major bleeding rather than normalizing the platelet count. Splenectomy and rituximab treatment are potential options to induce a long-term remission, while immunosuppressants, steroids, and TPO-RAs are agents that require chronic administration.

Splenectomy: For decades, surgical splenectomy was the treatment of choice; however, recent data suggest that less than 30% of patients with ITP undergo splenectomy [32], despite long-term response rates of 60-70% [33, 34]. Risk of infection (5- to 30-fold increase in the first 90 days and 1- to 3-fold life-long increased risk of invasive bacterial infection and sepsis), risk of thrombosis (>30-fold compared to the general population) as well as reports of pulmonary hypertension and immediate post-operative complications may have contributed to decreased splenectomy rates [34-36]. Therefore, it is recommended to delay splenectomy for at least 6 months to one year after diagnosis even if splenectomy is considered as a useful second-line treatment [3].

According to the 1996 and 2011 ASH guidelines, further treatment of patients, with platelet counts $>30\times10^9$/L in the absence of bleeding who have failed to respond to splenectomy, is not recommended. However, further treatment was recommended for patients with platelet counts $<30\times10^9$/L who have active bleeding [3].

Rituximab: Previous studies have demonstrated the efficacy of rituximab as an alternative option to splenectomy for patients who have failed after frontline therapy. Using the standard dosing of 375 mg/m^2/dose×4 doses resulted in initial response rates of 40–60% including complete response rates of 20–40% [37]. However, rituximab did not show a comparable long-term response rate to splenectomy with sustained response rates of less than 20% at 5 years. In addition, there was no difference in complete response rates when standard dosing of rituximab and placebo were compared [38]. Many patients, who initially responded to rituximab, can respond to subsequent doses; however, the safety and efficacy of repeated dosing of rituximab has not been evaluated.

TPO-RAs: Two TPO-RAs were subsequently developed and are now in clinical use for ITP. Eltrombopag is a small molecular weight agonist of the thrombopoietin receptor, which is orally administered and results in a significant increase in platelet counts in patients with ITP as well as healthy individuals. Romiplostim, in contrast, is a recombinant polypeptide that binds to and activates the thrombopoietin receptor despite having no amino acid homology to endogenous thrombopoietin. It also increases platelet counts in patients with chronic ITP as well as healthy individuals but it has not been associated with induction of anti-thrombopoietin antibodies.

Table 4. Definition of medically unfit condition to splenectomy recommended by the Korean ITP Expert Group.

Elderly: age more than 65 years old
DM, Hypertension, cardiac disorder requiring treatment
Asthma, COPD, common variable immune deficiency
History of extensive abdominal surgery
Extreme obesity: BMI more than 30 kg/m^2
Allergy to vaccine
[a]Poor responder to IVIg or anti-D

[a]Platelet counts less than 30×10^9/L or not increasing to double from the baseline.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

According to the 2011 ASH guidelines [3], TPO-RAs are recommended only if patients are at risk of bleeding and relapsed after splenectomy or have a medically unfit condition to splenectomy and have failed at least one other therapy (grade 1B). Unlike the ASH guidelines, International Consensus Report guidelines place TPO-RAs at the same level of evidence as splenectomy [8]. According to the ASH guidelines, rituximab and TPO-RAs are suggested for consideration with grade 2C in patients at risk of bleeding who have either failed to one line of therapy such as corticosteroids, IVIg, splenectomy or rituximab, or did not undergo splenectomy.

There is no definition of medically unfit condition to splenectomy in any published guidelines. Table 4 indicates the definition of medically unfit patients to splenectomy recommended by the Korean ITP expert group. Another issue regarding TPO-RAs usage in Korean ITP patients is the duration of treatment. HIRA guidelines determined a fixed duration of 6 months TPO-RAs treatment, but there is no supporting evidence. Therefore, HIRA guidelines should be revised shortly.

Others: Azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, and vincristine can cause variable responses in platelet counts after days to weeks of administration, depending on the individual patients [8, 39]. Each agent has unique potential toxicities such as immune suppression, secondary malignancies, hypertension, hepatic toxicity, etc [8, 39].

ITP TREATMENT IN PEDIATRICS

First-line therapy

IVIg: According to the ASH 2011 guidelines, a single dose of IVIg (0.8 to 1 g/kg) or a short course of corticosteroids should be used as first-line therapy for pediatric patients

requiring treatment (grade 1B) and IVIg can be used when a more rapid increase in the platelet count is desired (grade 1B) [3]. A meta-analysis study that compared IVIg and corticosteroid treatment reported that the relative risk (RR) (corticosteroids vs IVIg) of achieving a platelet count $>20\times10^9$/L at 48 hours was 0.74 (95% CI 0.65–0.85) [40].

Many hematologists prefer the convenience of a 1 g/kg/day infusion for 1–2 days among various IVIg regimens [41]. The Korean multicenter study from the Korean Society of Pediatric Hematology/Oncology reported that IVIg was the most commonly used regimen. In the group treated with IVIg alone, the platelet count began to rise above 50×10^9/L at 2.6 days on average, and above 100×10^9/L at 3.7 days. IVIg increases the platelet count in 70%–80% of treated patients. Recent retrospective studies from Korea showed that only 14.1–17.5% of the patients had chronic ITP, regardless of treatment [42, 43].

Corticosteroids: Corticosteroids remain a commonly used first-line therapy for ITP. A course of prednisone 1–4 mg/kg/day for 1–2 weeks with or without tapering is the popular regimen for newly diagnosed childhood ITP. Labrosse et al. reported that the use of prednisone at 4 mg/kg/day for 4 days without tapering was well tolerated and that there was no difference in the incidence rate of persistent ITP compared to longer use of prednisone [44]. In addition, the complications related to treatment were extremely rare in patients treated with short-course of prednisone, compared to patients treated with IVIg, who may develop severe headaches and aseptic meningitis frequently. However, many concerns remain regarding the complications of longer course of corticosteroids. In case corticosteroids are chosen as initial therapy, long-term use of corticosteroids should be avoided in children with acute ITP because of side effects [3].

Anti-D immunoglobulin: The ASH 2011 guidelines suggested that the anti-D therapy is not appropriate for children with a decreased hemoglobin concentration, because of bleeding, or with the evidence of autoimmune hemolysis (grade IC) [3]. Three randomized trials that compared therapies between anti-D and IVIg regimens showed that anti-D regimens with different doses had a higher incidence of hemolytic complications with less effectiveness than IVIg regimens [45-47]. Anti-D should be reserved only for patients who are Rhesus-positive, who have a negative direct antiglobulin test, and who have not undergone splenectomy.

Second-line treatment

The primary goal of treatment for pediatric patients with chronic ITP is not to achieve complete remission of disease, but to maintain a safe platelet count to prevent bleeding. Therefore, observation is suitable for these patients, if there is no significant bleeding. Long-term corticosteroid treatment needs to be minimized and cytotoxic drugs should be used very carefully in children.

Rituximab: Rituximab is a chimeric monoclonal antibody that depletes B lymphocytes by binding to the CD20 antigen surface marker. There is no randomized controlled study using rituximab for children with chronic ITP; however, a systematic review of 14 studies with 323 children revealed that 39% of patients showed a complete response (platelet count $\geq100\times10^9$/L) and 68% a partial response (platelet count $\geq30\times10^9$/L), with a median response duration of 12.8 months [48]. Therefore, rituximab may be considered for pediatric patients with chronic ITP with the dose of 375 mg/m^2 per week for 4 times. The most frequent adverse effects of rituximab are allergic reactions including pruritus, urticaria, chills and fever, which can be managed by the use of antihistamines, paracetamol, and corticosteroids [49]. Serum sickness after rituximab has been reported more frequently in children than adults [49]. The risk of progressive multifocal leukoencephalopathy (PML) after rituximab in children remains uncertain, but most cases with PML have been reported in pediatric patients with immunodeficiency following bone marrow transplantation [49]. Testing for hepatitis B status before receiving rituximab is recommended because of risk of viral reactivation. In addition, children should be vaccinated either before therapy with rituximab or until recovery of B cell function after rituximab therapy because of impaired humoral responses to vaccination after rituximab [50].

High dose dexamethasone: Several studies of dexamethasone in children with chronic ITP have been reported, but these studies have included less than 20 patients [51-54]. Dexamethasone was administered orally at a dosage of 20–40 mg/m^2/day for 4 consecutive days for each cycle. In a study of 13 children with chronic ITP who received dexamethasone (40 mg/m^2/day for 4 consecutive days every 28 days for 6 cycles), complete or partial responses were found in 46.2% of patients [51]. Side effects have been reported, such as bloating, nausea, vomiting, insomnia, anxiety, depression, aggressive behavior, and transient glucosuria [51-53].

Splenectomy: Spleen is thought to be the main location of both platelet destruction and antiplatelet-antibody production. Thus, splenectomy has been a treatment modality for children with chronic ITP. However, because remissions of ITP in children are often delayed and children <5 years of age are more susceptible to fatal sepsis caused by encapsulated organisms such as *Streptococcus pneumoniae*, *Hemophilus influenza* type b, and *Neisseria meningitidis*, the 2011 ASH guidelines recommended splenectomy to be considered for children with chronic ITP and who had bleeding symptoms [3]. Due to shorter hospital stay and less blood loss, laparoscopic splenectomy is preferred over open splenectomy in children with chronic ITP [55]. Children should complete vaccinations for encapsulated organisms at least 2 weeks prior to splenectomy, and prophylactic antibiotics are required for 2 years after splenectomy. Complete response rates of splenectomy are around 70–80% [56, 57].

TPO-RAs: TPO is a signaling peptide that stimulates thrombopoiesis in the bone marrow. However, because recombinant TPO may produce neutralizing antibodies to inhibit endogenous TPO, recombinant TPOs are not used in ITP [58]. Instead, TPO-RAs, which activate platelet production via the TPO pathway, have been developed. Currently, two drugs, eltrombopag and romiplostim, are available for use in adults and children with chronic refractory ITP.

Eltrombopag is an oral, non-peptide TPO-RA administered daily, which activates the thrombopoietic receptor through the transmembrane domain [7]. It has been approved in the United States and Europe for children ≥1 year of age with chronic ITP who have not achieved an appropriate response with other drugs or splenectomy [59]. Approval was based on two randomized, double-blind, placebo-controlled trials (PETIT and PETIT2) of children aged 1 to <18 years old, which used eltrombopag at a starting dose between 12.5 and 50 mg daily depending on age and ancestry. In PETIT trial, 62% of the eltrombopag-treated group achieved a response with platelets $\geq 50\times10^9$/L at least once without rescue compared to 24% of the placebo-treated group [60]. PETIT2 trial showed that 40% of the eltrombopag-treated group maintained a platelet count of $\geq 50\times10^9$/L for 6 weeks or more compared with 3% of the placebo-treated group [61]. These studies indicated that eltrombopag increased platelet counts and reduced the need for rescue therapy compared with placebo in children with chronic ITP. Adverse effects included headache, upper respiratory tract infection, diarrhea, nausea, and vomiting. Of note, liver enzyme may increase with eltrombopag administration; therefore, monitoring of liver function is required.

Romiplostim is a peptide TPO-RA administered by subcutaneous injection once a week. In a phase 3, randomized, double-blind, placebo-controlled study for children with persistent or chronic ITP, the dose of romiplostim was calculated based on weight and varied between 1 and 10 μg/kg. Platelet responses were found in 52% in the romiplostim-treated group and 20% in the placebo-treated group (P=0.002) [62].

In previous studies, reticulin fibrosis in bone marrow biopsies was observed after treatment with TPO-RAs [63, 64]. However, systematic investigations of bone marrow fibrosis have not been conducted in children.

Others: Immunosuppressive agents including azathioprine, cyclophosphamide, danazol, dapsone, cyclosporine, sirolimus, and mycophenolate mofetil have been used in children with chronic ITP. However, the use of these drugs is not recommended in children due to lack of evidence.

SPECIAL CONSIDERATION

H. pylori infection

As the prevalence of *H. pylori* infection in adults is high and increases with age in Korea [65], routine testing is recommended for adult patients with ITP.

In a systematic review of 696 eligible patients that examined the efficacy of *H. pylori* eradication among *H. pylori*–positive patients, the overall response (platelet count ≥30×10^9/L and at least double from the baseline count) was 50.3% (95% CI 41.6%–59.0%) [9]. Response rates appear to be higher in patients with lesser degree of thrombocytopenia and in countries with a high prevalence of *H. pylori*. A similar result was also observed in a Korean phase II trial [11].

Emergency managements

A rapid increase in platelet count may be necessary for some ITP patients that 1) require surgical procedures, 2) are at high risk of bleeding, or 3) with active central nervous system, gastrointestinal, or genitourinary bleeding.

Although changing from corticosteroids to IVIg or anti-D regimens may be effective in emergency settings, the combination of first-line therapies is appropriate: prednisone and IVIg are recommended for the emergency treatment of patients with uncontrolled bleeding [25]. High-dose methylprednisolone may also be helpful in this setting.

However, because of the critical nature of the disease, physicians desire the modality of more rapid responses than those of IVIg and/or corticosteroids. Platelet transfusion ranging from every 30 minutes to 8 hours and platelet transfusions in conjunction with a continuous infusion of IVIg are suggested as urgent options in case of clinically significant bleeding [66]. These treatments may result in either a rapid reduction in bleeding and/or an improvement in the platelet count.

Vincristine induces a platelet count increase in a small fraction of chronic ITP patients. However, when combined with other agents it may be a useful approach in patients requiring emergency treatment [67].

Tranexamic acid (1 g, 3 times daily orally) and epsilon-aminocaproic acid (1–4 g every 4–6 hours [maximum dose, 24 g/day]) may be helpful in certain dental or surgical procedures; however, efficacy has not been evaluated by randomized trials in ITP patients [68].

CONCLUSION

This expert recommendation guide from KSHAAWP was developed to provide Korean hematologists with proper clinical practice guidance. Although we were not able to provide strong evidence in some key issues, we will update this recommendation when there are major changes in the management of ITP patients.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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