



Management of immune thrombocytopenia: 2022 update of Korean experts recommendations

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Abstract

Despite the availability of therapies to treat patients with immune thrombocytopenia (ITP), there is currently little data from randomized trials to assist clinicians in managing patients. The evidence-based guidelines of the Korean Society of Hematology Aplastic Anemia Working Party (KSHAAWP) are intended to support patients and physicians in the management of ITP. Experts from the KSHAAWP discussed and described this guideline according to the current treatment situation for ITP in Korea and finalized the guidelines. The expert panel recommended the management of ITP in adult and pediatric patients with newly diagnosed, persistent, and chronic disease refractory to first-line therapy with minor bleeding. Management approaches include observation and administration of corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, and thrombopoietin receptor agonists. Currently, evidence supporting strong recommendations for various management approaches is lacking. Therefore, a large focus was placed on shared decision-making, especially regarding second-line treatment.

Key Words Immune thrombocytopenia, Recommendation, Management

INTRODUCTION

Purpose of these guidelines

These guidelines aimed to provide helpful recommendations for managing adult and pediatric patients with immune thrombocytopenic purpura (ITP). In addition, these guide-

lines aim to provide clinical support for the decision-making process regarding different treatment courses.

Clinical situation and impact of ITP

ITP is an acquired autoimmune disorder characterized by low platelet count resulting from platelet destruction and impaired production. The incidence of ITP in Western

countries is 2–5 per 100,000 person-years [1–5]. In national studies using the Korea Health Insurance Research and Assessment (HIRA) database, the incidence rate of ITP for all ages is 5.3 per 100,000 person-years, while it is 13.39 and 18.1 per 100,000 person-years for children aged <18 years [6–8]. ITP can be an isolated primary event or secondary to other clinical conditions. ITP is a heterogeneous disorder with variable clinical symptoms and signs and remains a diagnosis of exclusion of other causes of thrombocytopenia [9]. The clinical course of ITP may also vary depending on whether it is primary ITP (not associated with other conditions), occurring in the setting of autoimmune cytopenia (Evans syndrome), a manifestation of primary immunodeficiency, or is associated with autoimmune or infectious causes (secondary ITP). In secondary ITP, treatment is often directed towards managing underlying causes.

Bleeding episodes are often unpredictable, and patients with ITP, even in severe thrombocytopenia, may not have bleeding, except bruising and petechiae [10–12]. However, severe bleeding may occur [11–13]. Serious bleeding was reported in 9.5% [95% confidence interval (CI), 4.1–17.1] of adults [11]. Adults with ITP have a 1.3–2.2-fold higher mortality rate than the general population due to cardiovascular events, infectious diseases, and bleeding episodes [14]. In addition, ITP has a significant impact on health-related quality of life (HRQoL) [15, 16].

Whether a patient can be observed without treatment or requires further treatment is complex and varies based on comorbidities, medications, and age, all of which affect the risk of bleeding [17, 18]. In addition, management approaches may vary according to the duration of the disease, accessibility to care, quality of life implications, and preferences of the patient and clinicians. Considering the inter-patient variability in the pathophysiology of immune dysregulation and the lack of effective predictors of treatment response, the choice of appropriate therapy may vary significantly among physicians when the treatment has been decided [19].

For the 2022 update, an expert panel reviewed the evidence published since the 2017 Korean recommendation [20]. In these guidelines, the expert panel recommended valuable principles for managing adult and pediatric patients with ITP based on evidence and expert opinions.

RECOMMENDATIONS

Management of adult patients with newly diagnosed ITP

Corticosteroids versus observation

Recommendation 1

In adult patients with newly diagnosed ITP and a platelet count $<20 \times 10^9/L$ without symptoms or with minor mucocutaneous bleeding, we recommend corticosteroids rather than observation.

To choose corticosteroid versus observation, physicians should consider the level of platelet count, additional co-

morbidities, use of anticoagulant or antiplatelet agents, need for subsequent procedures, and patient age.

The benefits cannot be estimated from the data because of the lack of direct comparison results [21–27]. The response rate of the platelet count at 7 days was 55.8% with corticosteroids; however, the overall remission rate was relatively low (30.2%) [21]. The harms and burdens could not be precisely estimated from the data because of the lack of direct comparison results. Undesirable adverse effects of observation exist in this setting, considering that thrombocytopenia is a surrogate for future bleeding events and treatment failure in adult patients. Bleeding episodes (3.3%) and mortality (5.7%) were only reported in the corticosteroid-treated group [26].

Recommendation 2

In adult patients with newly diagnosed ITP and a platelet count $\geq 20 \times 10^9/L$ without symptoms or minor mucocutaneous bleeding, we recommend observation rather than corticosteroids. For patients with a platelet count at the lower end of this threshold, those with additional comorbidities, anticoagulant or antiplatelet agents, or need to follow the procedures. Corticosteroid treatment may be appropriate for elderly patients (aged >60 yr).

The benefit cannot be precisely estimated from the data because of the lack of direct comparison results. However, major bleeding episodes were not different and low in both arms (corticosteroids vs. observation: 0.9% vs. 0%) [28–32]. Based on indirect evidence, the side effects of corticosteroids are not trivial; therefore, the undesirable adverse effects of corticosteroids are moderate.

Duration and type of corticosteroids

Recommendation 3

In adult patients with newly diagnosed ITP, we recommend a short course (≤ 6 wk) of prednisone rather than a prolonged course (>6 wk, including treatment and tapering).

No studies supporting short courses of prednisone are currently available, and this recommendation is based on expert experience [33–35]. It is presumed that a trivial benefit exists in continuing corticosteroids for more than 6 weeks, and many patients require additional treatment. For patients requiring further treatment, an alternative therapy is preferable to continued corticosteroid exposure. The likelihood of harm and risk of adverse events was enormous with the continuation of corticosteroids for more than 6 weeks. Adverse events included hypertension, hyperglycemia, sleep and mood disturbances, epigastric soreness, ulcer formation, glaucoma, myopathy, and osteoporosis.

Recommendation 4

In adult patients with newly diagnosed ITP, we recommend either prednisone (0.5–2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days) as the type of initial corticosteroid treatment. If we stress the rapidity of the platelet count response, dexamethasone may be preferable to prednisone,

considering that the response at 7 days was more desirable with dexamethasone.

Randomized study data showed an increased platelet count response at 7 days to dexamethasone [relative risk (RR), 1.31; 95% CI, 1.11–1.54] [21–23]. The remission rate was higher among the dexamethasone-treated patients than with prednisone (RR, 2.96; 95% CI, 1.03–8.45); however, the confidence level was low because the definition of remission applied by the trials was indirect, and the dose of corticosteroid was heterogeneous [21–23, 25, 28, 36, 37]. No clear benefit was found regarding the 1 month response rate, durable response rate, or incidence of major bleeding episodes. The duration of the initial response following a cycle of dexamethasone varied. We also recommend that the platelet count should be monitored frequently.

Despite the lack of direct evidence, the risk of adverse events in clinical practice varies according to the dose and duration of corticosteroid treatment, comorbidities, and patient age. Concerns regarding dexamethasone in patients with underlying diabetes and the elderly (aged >60 yr) also exist.

Recommendation 5

In adult patients with newly diagnosed ITP, we recommend corticosteroids alone rather than corticosteroids combined with rituximab as the initial treatment. An initial course of corticosteroids combined with rituximab may be preferable when the possibility of remission is higher than the concerns regarding the potential side effects of rituximab.

Moderate effects were observed with concomitant corticosteroids and rituximab, particularly a higher durable response rate (RR, 1.70; 95% CI, 1.34–2.16) and remission rate (RR, 1.58; 95% CI, 1.00–2.52) [38–40]. No difference was observed regarding the impact on the response rate at 1 month, prevention of major bleeding episodes or mortality, and no data on HRQoL. The certainty level in the evidence for benefits was extremely low due to the absence of HRQoL data, unknown and non-standardized corticosteroid doses for comparison, and the absence of long-term follow-up results. The prioritized outcome of infection was not different between the two treatments, even though the CI was significant (RR, 3.18; 95% CI, 0.13–76.25).

Management of adult patients with corticosteroid-dependent or refractory ITP

Eltrombopag versus romiplostim

Recommendation 6

In adult patients with corticosteroid-dependent or refractory ITP for more than 3 months, we recommend a thrombopoietin receptor agonist (TPO-RA), either eltrombopag or romiplostim. Physicians should consider the preferences of individual patients when choosing daily oral medications or weekly subcutaneous injections.

A comparison was made between the durable response rates of eltrombopag and romiplostim (odds ratio=0.20; 95% CI, 0.01–2.13) [41–43]. The major bleeding rates and dis-

continuation or reduction rates of corticosteroids could not be estimated from the data because of a lack of comparisons. However, the desirable effects were minimally different. There were no significant differences in the outcomes, including durable response, bleeding, and corticosteroid discontinuation or reduction rates. The undesirable effects are trivial. Elevation of alanine/aspartate transaminase related to eltrombopag was mild and reversible in most participants; therefore, it did not affect the balance of undesirable events. No net health benefits or harmful differences related to eltrombopag or romiplostim were observed. Based on the available evidence, it is presumed that there is no difference between the two treatments. Preference of the patients for the route of administration – oral daily medication compared with weekly subcutaneous injection – likely affects treatment decision-making.

Second-line therapies: TPO-RA and splenectomy

Recommendation 7

In adult patients with ITP lasting ≥ 3 months who are corticosteroid-dependent or unresponsive to corticosteroids, we recommend TPO-RA rather than splenectomy. Splenectomy should be postponed for at least 12 months after diagnosis because of the possibility of spontaneous remission in the first year. For patients with ITP lasting >12 months, a splenectomy can only be performed in those with limited indications.

The American Society of Hematology (ASH) guidelines suggest either splenectomy or TPO-RA for corticosteroid-dependent patients or do not respond to corticosteroids [44]. Despite the lack of direct evidence, both treatment options are associated with a more durable response. No difference in major bleeding was observed between the patients treated with splenectomy and those treated with TPO-RAs (4.6% and 3.5%, respectively). As there is no single treatment optimal for all patients with ITP, treatment should be individualized based on the duration of ITP, age of the patient, medical condition, and patient preferences [44].

For patients with ITP of 3–12 months, because of the possibility of spontaneous remission in the first year, it is recommended to postpone splenectomy to 12 months from diagnosis [45–50]. For such patients, TPO-RA is the primary treatment option because of its greater response durability. Splenectomy and TPO-RA can be viable options for patients with ITP lasting >12 months [51–66]. A splenectomy is an option for patients who prioritize durable responses and avoid long-term treatment. Currently, the use of splenectomy as a second-line treatment for ITP is gradually decreasing. In a Korean ITP study, only 3% of treated patients received splenectomy as a second-line treatment [6]. This low incidence of splenectomy for ITP results from high post-splenectomy morbidity and mortality related to the operation and long-term complications, such as infection, cardiovascular events, and venous thromboembolism, especially in older patients [6]. Alternative effective treatment options, such as TPO-RA, are also available for adult nonsplenectomized patients who have a medically unfit condition to splenec-

tomy, as suggested by the Korean ITP guidelines in 2017. Unlike the ASH guidelines, the International Consensus Report (ICR) guidelines recommend splenectomy only after medical treatment failure [67]. Based on the current data, splenectomy should be performed under limited indications considering the age, comorbidities that can worsen the risk of surgery, and patient preference [activity levels, occupation, need for procedures, acceptance of minor bleeding, the persistence of treatment duration (chronic therapy vs. limited therapy), preference for daily tablets or weekly injections, and financial ability]. Young patients with an active lifestyle, including those who participate in high-risk activities, may prefer splenectomies. In addition, other patients who do not comply with the medication (dietary restriction for eltrombopag and weekly injection of romiplostim) may consider splenectomy. For patients who prefer medical treatment and prioritize avoiding surgery, a suitable option is the TPO-RA. The common adverse effects of TPO-RA are gastrointestinal symptoms, mild transaminase elevation, and headache, most of which are mild. Bone marrow fibrosis is a potential side effect of concern with the use of TPO-RAs; however, the risk of clinically meaningful fibrosis seems to be low. Thrombotic events of TPO-RAs should be considered in patients with ITP with significant risk factors for venous and arterial thrombosis. In addition, the disadvantage of a relatively high cost due to the long-term use of a TPO-RA should be considered when discussing treatment options. Most importantly, for patients who prioritize achieving a durable response, the best option is TPO-RA. An individualized approach for selecting second-line treatment based on ITP duration and patient preference is shown in Fig. 1.

Fig. 1.

Management of pediatric patients with newly diagnosed ITP

Treatment vs. observation

Recommendation 8

In pediatric patients with newly diagnosed ITP without bleeding or with minor bleeding, observation rather than corticosteroids is recommended.

There was no perceived benefit of corticosteroids in terms of durable platelet response (78.5% with corticosteroids and 87.3% with observation), remission (76.6% with corticosteroids and 63.6% with observation), or reduction in major bleeding (0% for both treatments) in this setting [68-69]. In addition, the undesirable effects of corticosteroids increase in proportion to the treatment duration.

Recommendation 9

In pediatric patients with newly diagnosed ITP without bleeding or with minor bleeding, we recommend observation rather than intravenous immunoglobulin (IVIG) or anti-D immunoglobulin.

A randomized trial of IVIG over observation showed no differences in outcomes at 12 months and durable response. The incidence of bleeding and mortality was similar between the two groups (0.6% and 1.8% with IVIG and 0% and 0% with observation for bleeding and mortality, respectively) [69-73]. Although there was a lack of direct comparisons, there was only a small benefit from anti-D immunoglobulin. No data are available on major bleeding and mortality associated with anti-D immunoglobulins. IVIG has side effects, such as infusion-related symptoms, thrombosis, and acute renal failure, and anti-D immunoglobulins such as intravascular hemolysis [69-73].

Type and duration of corticosteroids

Recommendation 10

We recommend 7 days or shorter courses of corticosteroids rather than longer than 7 days in pediatric patients with

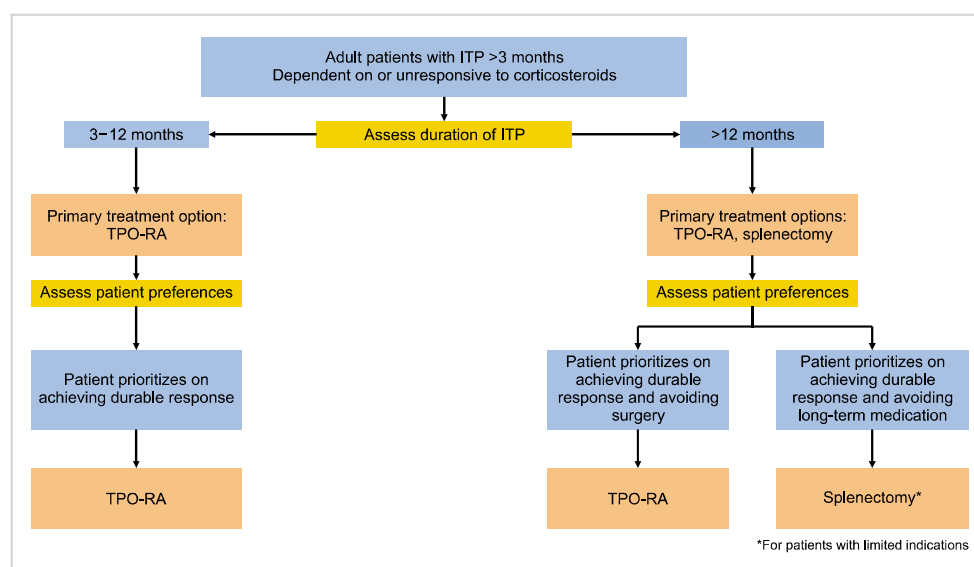


Fig. 1. Algorithm for the selection of second-line therapy in adult patients with ITP.

newly diagnosed ITP with non-life-threatening mucosal bleeding and diminished HRQoL. In addition, we recommend 2–4 mg/kg/day of prednisolone (maximum 120 mg/day) for 5–7 days, rather than 0.6 mg/kg/day of dexamethasone (maximum 40 mg/day) for 4 days.

Given the low rate of bleeding, high rate of spontaneous remission, overall low morbidity in the pediatric population, and lack of evidence for the benefit of long-term corticosteroids, there was likely a small benefit in continuing corticosteroids for longer than 7 days [44]. A longer course of corticosteroids (>7 days) is likely to increase the risk of adverse events, resulting in poor treatment adherence in this population. In the absence of increased benefits with a longer course of corticosteroids and the side effects associated with prolonged corticosteroid exposure, we recommend that the balance of effects favored 7 days or shorter course of corticosteroids over longer periods [44]. There are limited data on treatment with dexamethasone compared with prednisolone in the pediatric population. Higher corticosteroid doses of dexamethasone used in adult trials are deemed potentially intolerable by some pediatric patients with regard to short-term side effects. In the absence of data, there is no strong evidence suggesting that dexamethasone is superior to prednisolone.

Treatment of pediatric patients with non-life-threatening bleeding and diminished HRQoL

Recommendation 11

In pediatric patients with newly diagnosed ITP with non-life-threatening bleeding and diminished HRQoL, we recommend corticosteroids rather than anti-D immunoglobulins or IVIG.

Based on randomized trial data, only trivial benefits were observed with IVIG compared with corticosteroids regarding durable response, remission rate, prevention of bleeding events, and mortality [44, 70–73]. In addition, a short course of corticosteroids is usually associated with mild side effects in most pediatric patients. However, some concerns related to anti-D immunoglobulins and IVIG, leading to the need for additional medical interventions.

Management of pediatric patients with ITP who are unresponsive to first-line treatment

Recommendation 12

In pediatric patients with ITP with non-life-threatening mucosal bleeding and diminished HRQoL who do not respond to first-line treatment, we recommend using TPO-RAs rather than rituximab or splenectomy.

Although there are no data available for direct comparison of TPO-RAs with either rituximab or splenectomy, TPO-RAs show a moderate benefit over rituximab and splenectomy in various studies of pediatric patients with ITP who are unresponsive to first-line treatment [44, 74–76]. Compared with rituximab and splenectomy, TPO-RAs provide a stable long-term platelet response and reduce bleeding events [74–76]. However, there is concern about developing persistent hypogammaglobulinemia after rituximab treatment in

the pediatric population [44, 74–76]. In addition, operative complications associated with splenectomy were identified in 5.9% of children [44]. However, thrombosis was not observed in any children [44].

Maintenance for responders to a TPO-RA

Recommendation 13

In adult patients with ITP who respond to TPO-RAs, we recommend using the lowest dose of TPO-RAs, sufficient to maintain a platelet count $\geq 50 \times 10^9/L$.

TPO-RAs are generally used as a maintenance treatment for ITP. However, the optimal dose of TPO-RAs and the platelet count target necessary to maintain response and reduce bleeding in responders to TPO-RAs differ slightly depending on the study [77, 78]. In published studies on romiplostim, most adult patients who responded to romiplostim achieved and maintained a platelet count $\geq 50 \times 10^9/L$ with a median dose of 2 mcg/kg (up to 10 mcg/kg) [78]. In prescribed information of two TPO-RAs, the lowest dose of TPO-RAs was recommended to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. In a single-arm phase II study of romiplostim in adults with primary ITP who had received first-line therapy (remission study), 75 patients who achieved a response started tapering and discontinuation of romiplostim [79]. Patients with a platelet count $\geq 50 \times 10^9/L$ at 12 months started to receive a dose taper, in which the romiplostim dose was decreased, and the platelet count was maintained. In this study, 32% (24/75) of patients who discontinued romiplostim maintained platelet count $\geq 50 \times 10^9/L$ without any additional treatment for 24 consecutive weeks.

Other treatments for adult patients with ITP

Rituximab is a monoclonal antibody against the CD20 antigen that targets the B cell-producing antibodies for platelets. Rituximab is usually administered at 375 mg/m² intravenously every 4 weeks. In adults with ITP who fail to respond to TPO-RA or experience relapse after discontinuing TPO-RA, rituximab can be administered as a third-line therapy [80].

Azathioprine is administered at an oral dose of 50–200 mg/day in adult patients and is sometimes administered with danazol; however, there is little data to support an improved response to the combination. It takes several months to have a full effect on ITP. Azathioprine is one of the drugs deemed “safe” for patients with ITP in pregnancy, without increased risk of fetal malformation, and safe during lactation. Major adverse events included nausea, infection, liver function abnormalities, neutropenia, and anemia [81].

Cyclophosphamide is a chemotherapeutic agent that has been used since 1959 to treat malignant disease at high doses and as an immunosuppressive agent to treat autoimmune disorders at low doses. Cyclophosphamide is usually delivered as an oral dose of 50–200 mg/day for adult patients. Major adverse events include bone marrow suppression, infection, infertility, secondary malignancies, and hemorrhagic cystitis. However, its use is contraindicated during pregnancy

and lactation [82].

Cyclosporine A levels were adjusted by monitoring drug levels. However, the usual starting dose is 3–6 mg/kg/day, with a maximum dose of 200 mg for adult patients. Major adverse events were gingival hyperplasia, hypertension, renal toxicity, and emesis. Therefore, its use is contraindicated during pregnancy and lactation [83].

Danazol is usually administered at an oral dose of 200–800 mg/day in adults. Its androgenic effects are related to major adverse events (especially in women), transaminitis, weight gain, acne, rash, mood changes, amenorrhea, and virilization. Therefore, clinicians should perform liver function tests at least once a month. However, they are contraindicated during pregnancy and lactation. It has sometimes been used in combination with azathioprine, but there is little evidence to support the added benefits of this combination [84].

Dapsone is administered orally at 50–100 mg/day to both adult and pediatric patients. The treatment was generally well-tolerated. However, mild hemolysis occurs in most patients, whereas significant hemolysis is less common. Therefore, clinicians should monitor for the potential development of methemoglobin [85–89].

Mycophenolate mofetil is administered orally at 500–2,000 mg/day to adult patients. Serious adverse events include diarrhea, neutropenia, anemia, and viral infections. Prolonged drug use increases the risk for malignancy and progressive multifocal leukoencephalopathy. It has also been associated with pure red aplasia. It is a teratogen that should not be prescribed during pregnancy or lactation [90–92].

Vinca alkaloids can be used as treatment options for ITP. Patients can achieve a rapid response at 7 days with vincristine (1–2 mg per dose once weekly for 2–4 wk in adult patients) or vinblastine (10 mg per dose once weekly for 1–3 wk in adult patients). Almost all patients experience adverse events, such as vincristine neuropathy, vinblastine-associated bone marrow suppression, constipation, hyponatremia, and infusion site vesication. Vinca alkaloids are contraindicated in pregnancy and lactation [93–95].

Authors' Disclosures of Potential Conflicts of Interest

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

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