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Clinical Study Protocol

High-dose Dexamethasone Therapy as the Initial Treatment for Idiopathic Thrombocytopenic Purpura: Protocol for a Multicenter, Open-label, Single Arm Trial

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Standard therapy for idiopathic thrombocytopenic purpura (ITP) has not been established. We are conducting a multicenter, prospective trial to determine the efficacy and safety of short-term, high-dose dexamethasone therapy in ITP patients aged 18-80 years with platelet counts of < 20, 000 /μL, or with < 50, 000/ μL and bleeding symptoms. The primary endpoints of this trial are the proportion of responses (complete plus partial response) on day 180 (day 46 + 180) after the completion of the 46-day high-dose dexamethasone therapy. The results of this investigation of the effectiveness and safety of this regimen will be essential for the establishment of standard therapy for ITP.

Key words: idiopathic thrombocytopenic purpura, short-term, high-dose dexamethasone therapy, open-label, single-arm trial

The first-line therapy for idiopathic thrombocytopenic purpura (ITP) is prednisolone at 1 mg/kg/day

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continuously for 2-4 weeks, followed by tapering (standard-dose prednisolone therapy). This regimen is widely used worldwide and is recommended in the clinical guidelines [1, 2] of several countries. However, the regimen is not based on the results of high-quality, randomized controlled trials (RCTs); it is ultimately empiric therapy. Approximately 80% of ITP patients show some improvement from prednisolone treatment, and the platelet count recovers to > 100,000 /μL in 50% of the patients [1, 6]. Nevertheless, thrombocytopenia often recurs during prednisolone therapy weaning. It is considered that only 10-20% of patients will be able to discontinue prednisolone due to a relapse-free state [3, 4], but long-term therapy with a steroid such as prednisolone can reduce an individual's quality of life and lead to side effects, including susceptibility to infections and osteoporosis.

Short-term, high-dose dexamethasone therapy has been administered to patients who are resistant to standard-dose prednisolone therapy, and in Japan this approach was confirmed to have achieved some therapeutic effects. Chen *et al.* [5] and Mazzucconi *et al.* [6] reported the effects of high-dose dexamethasone for treating the initial manifestations of ITP. In a multicenter, prospective trial, Mazzucconi *et al.* administered 40-mg dexamethasone for 4 days to 95 patients with newly diagnosed ITP, repeated every 2 weeks for a total of 4 courses [6]. Those authors reported some therapeutic effect in 85.6% of the patients, and a progression-free survival rate of 81% after 15 months. There were no particular safety issues associated with the treatment. Since the number of patients who experienced a therapeutic effect did not significantly increase from the third to the fourth course, the subjects in that RCT will now receive 3 courses of standard-dose prednisolone and high-dose dexamethasone.

Mashhadi *et al.* [7] reported the results of a prospective RCT that examined the effect of one course of either standard-dose prednisolone or high-dose dexamethasone, with 30 patients in each group. Significantly better results were observed in the high-dose dexamethasone group in terms of both the 3-month complete response (CR) rate (80% vs. 23.3%; $p < 0.0001$) and the 6-month CR rate (73.3% vs. 16.7%; $p < 0.0001$). The authors did not observe any differences between the groups with respect to treatment-related side effects.

In Japan, Sakamoto *et al.* [8] retrospectively compared 31 patients who received high-dose dexamethasone with 69 patients who received standard-dose prednisolone. They reported a significantly better treatment response (42.7% vs. 28.4%) and a significantly better steroid withdrawal rate after 6 months (64.5% vs. 37.7%) in the high-dose dexamethasone group compared to the standard-dose prednisolone group; no differences in toxicity were observed. In contrast, Nakazaki *et al.* [9] conducted a retrospective study comparing 8 patients who received standard-dose prednisolone, 12 patients who received one course of high-dose dexamethasone, and 5 patients who received three courses of high-dose dexamethasone; they observed a better long-term therapeutic effect in the prednisolone group.

No prospective investigation of high-dose dexamethasone therapy for ITP has been reported in Japan. Thus, a multicenter, prospective investigation of the effectiveness and safety of this regimen is essential for the establishment of a standard therapy for ITP. After the verification of the effectiveness of high-dose dexamethasone therapy, the confirmation of its early-, mid-, and long-term effects could help prevent the adverse events associated with long-term steroid therapy. With this in mind, and based on the results of clinical trials already reported and in progress, we chose as our primary endpoint the efficacy on day 180 after the completion of the 46-day high-dose dexamethasone therapy (day 46 + 180).

Japan is unique in that *Helicobacter pylori* eradication is emphasized in the treatment of ITP. A clinical reference guide [1] published in 2012 by a team studying coagulopathies as part of the Japanese Ministry of Health, Labour and Welfare's research initiative for treating intractable diseases states that the initial approach to treatment should involve testing for *H. pylori,* with the provision of eradication therapy in positive cases. This recommendation was put forward because clinical trials and other studies had shown that platelet levels rise in approx. 50% of ITP patients who still test positive for *H. pylori* infection after receiving *H. pylori* eradication therapy.

Clinical trials conducted outside of Japan regarding the use of high-dose dexamethasone therapy in the context of ITP do not address *H. pylori* eradication. In clinical practice, patients similar to the subjects in the present trial (platelet count < 20,000 /μL or with bleeding symptoms) would first have steroids administered. Then, after the demonstration of some therapeutic effect, eradication therapy would be initiated based on

testing for *H. pylori* infection. The reference guide published in Japan [1] also recommends eradication therapy in patients with markedly low platelet levels and bleeding symptoms, but only after some therapeutic effect from the treatment has been observed. In the present trial, eradication therapy was administered to patients who tested positive for *H. pylori* after the initiation of treatment, and the safety of this therapeutic approach was investigated.

Diagnosis by exclusion is the basic method for diagnosing ITP, as no useful diagnostic markers of ITP have been identified. It can thus be difficult to differentiate ITP from other diseases that also involve thrombocytopenia. Plasma thrombopoietin levels and other markers have been found to be useful in differentiating ITP from other diseases [10]. In the present trial, the measurements performed at the start of therapy could offer new insights related to the therapeutic responsiveness or other factors.

Endpoints

The primary endpoints of this trial are the proportion of responses (complete + partial responses) on day 180 (day 46 + 180) after the patients complete the high-dose dexamethasone therapy (which will be completed 46 days after starting treatment). The secondary endpoints are the platelet count on day 46 + 180 (by response, complete response, and partial response), relapse-free survival, the frequency of adverse events, the frequency of *H. pylori* infection, the bacterial eradication effect, the proportion of complete responses on day 46 + 180 among the patients without *H. pylori* infection, the proportion of complete responses on day 46 + 180 among the patients with *H. pylori* infection with eradication/no eradication effect, the relapse-free survival for the patients without *H. pylori* infection, the relapse-free survival for patients with *H. pylori* infection with eradication/no eradication effect, and the adverse events with eradication/no eradication effect.

Eligibility Criteria

Inclusion criteria. (1) Patients ≥ 18 years old and ≤ 80 years old at registration. (2) Patients newly diagnosed with ITP and assessed as requiring treatment. (3) Platelet count of < 20,000 /μL, or < 50,000 /μL with bleeding symptoms. (4) Performance status of 0-2 at registration. (5) Patients who receive a full explanation of the trial from an investigator or sub-investigator at an institution participating in the trial with the use of an informed consent form, and who themselves (or their guardians for minors) voluntarily give written consent to participate in the trial.

Exclusion criteria. (1) Active malignant disease at registration. (2) Administration of antiplatelet or anticoagulant drugs. (3) Mental illness. (4) Pregnant or breast-feeding women. (5) Cardiovascular disease that requires treatment. (6) Treatment-resistant hypertension or diabetes. (7) Liver or kidney dysfunction (creatinine, aspartate transaminase [AST], or alanine transaminase [ALT] levels ≥ 2 times the upper limit of normal). (8) Positive test result for hepatitis C virus (HCV) antibodies, human immunodeficiency virus (HIV) antibodies, or hepatitis B surface protein (HBs) antigen. (9) Chronic liver disease. (10) History of a viral infection, positivity for immunoglobulin M (IgM), or vaccination within the last month. (11) Initiation of a new drug within 1 week of diagnosis. (12) Active gastrointestinal ulcer disease. (13) Serious intracerebral or gastrointestinal hemorrhage. (14) Continuous administration of a steroid hormone or immunosuppressant for another disease. (15) Otherwise deemed unsuitable for the trial by a sub-investigator.

Methods

Study design. This study is a multicenter, open-label, single-arm trial. The study was approved by the central review board of Japan's National Hospital Organization for clinical trials (H28-0810001). The registration of trial participants began in March 2016. We are currently recruiting participants. The study was registered in the University Hospital Medical Information Network Center (UMIN)-Clinical Trials Registry (CTR) on May 23, 2016 (UMIN 000022415). The trial's design is shown in Fig.1.

High-dose dexamethasone therapy. Three courses of high-dose dexamethasone therapy will be administered every 2 weeks. One course consists of dexamethasone 40 mg orally, administered daily for 4 days, or dexamethasone 30.2 mg intravenously, administered daily for 4 days. The attending physician can decide between oral or intravenous administration. If the patient's platelet count is < 20,000 /μL after 4 days of the investigational drug, up to 2 mg of dexamethasone may

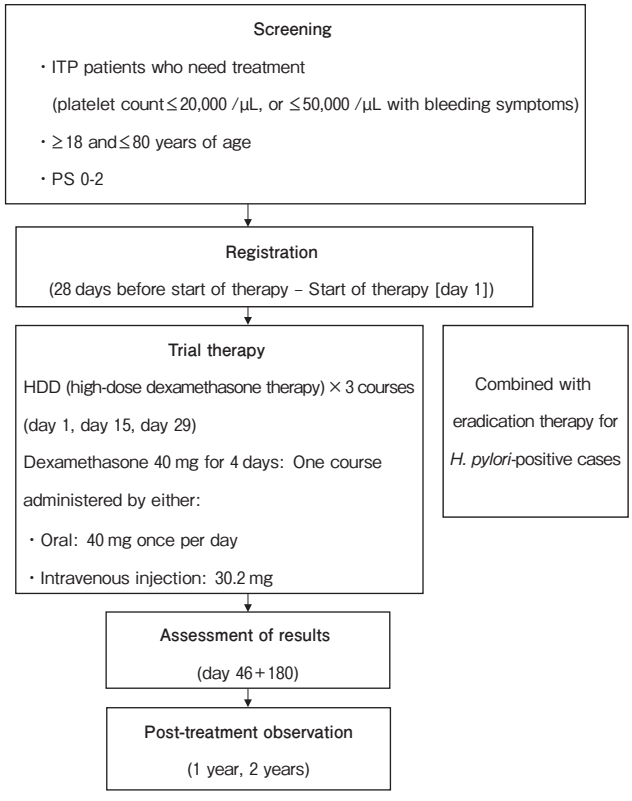

Fig. 1 The design of the present multicenter, open-label, single-arm trial.

be administered. Patients who exhibit steroid withdrawal symptoms or are deemed to be at high risk for these symptoms may have up to 2 mg of dexamethasone administered. Regardless of the platelet count or other symptoms, weaning should be performed so that dexamethasone administration ends by day 14 after the end of the third course.

Helicobacter pylori eradication therapy. Patients are tested for *H. pylori* at the time of diagnosis. A stool test for *H. pylori* antigen is recommended, but the test selection is left to the discretion of the attending physician. After the beginning of the trial, eradication therapy may be given at any point if a patient is found to be positive for *H. pylori*. This therapy consists of a 7-day course of 3 drugs (amoxicillin 1,500 mg, clarithromycin 400 mg, and a proton pump inhibitor [PPI]) given in 2 divided doses per day (after breakfast and after dinner). Following this treatment course, the success of the eradication is assessed over the next 4-8 weeks via stool tests for *H. pylori* antigen or the urea breath test. If eradication is unsuccessful, a second round of therapy is administered, replacing clarithromycin with metronidazole (amoxicillin 1,550 mg, metronidazole 500 mg, and PPI), and the effects are again assessed over the next 4-8 weeks.

Antiviral therapy. Patients who test positive for HBs antibodies or hepatitis B core (HBc) antibodies will not be excluded from the trial, but the trial therapy carries a risk of hepatitis B virus (HBV) reactivation. These patients should be monitored for HBV DNA with polymerase chain reaction (PCR) every 1 or 2 months for ≥6 months after completing treatment. Patients who test positive should receive aggressive antiviral therapy.

Preventing gastrointestinal ulcers and infections. A gastrointestinal ulcer drug (PPI or H2-blocker) will be administered during oral dexamethasone therapy. Antituberculosis drugs, trimethoprim-sulfamethoxazole, antifungal drugs, and antiviral drugs will be used to prevent infections at the discretion of the attending physician.

Statistical Considerations

Sample size. In a retrospective study performed in Japan, the complete response (CR) rate after 1 year of prednisolone administration was 28.4% [8]. In a registry in Japan, the proportion of responses (CR + partial response [PR]) at 2 years after diagnosis was 75.0% (114/152) [11]. In a prospective interventional study from Iran, the CR + PR rate of the group that received standard steroid treatment was 53.3% (16/30) and 46.7% (14/30) after 6 months and 1 year, respectively [7]. Based on these results, we chose 50% as the threshold proportion of response.

The response rate at ≥2 months after the completion of therapy according to the GIMEMA (Gruppo Italiano per le Malattie Ematologiche dell'Adulto) protocol was 83.8% (31/37) in a single-center study and 84.4% (76/90) in a multicenter study [6]. Based on these results, we chose 80% as the expected proportion of response. The number of patients needed was calculated to be 21 based on binomial proportion with a significance level of 0.05 (one-tailed) and detection power of 0.90. To account for dropouts, we set the sample size as 25.

Interim analysis and monitoring. An interim analysis will not be conducted. Monitoring will be performed regularly once per year. Data collected from the internet will be subject to central monitoring, but institutions will not be monitored by means of site visits.

Discussion

A standard therapy for ITP has not yet been established. It is hoped that this trial will assist in the establishment of a standard therapeutic regimen. This trial cannot reach any further than an explanatory study, and the trial's results should thus be verified in a randomized controlled trial.

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