A Randomized Multicenter Trial Comparing Low-Dose Prednisolone Versus Observation for Prevention of Recurrences in Adult Immune Thrombocytopenia

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Abstract
Adult immune thrombocytopenia (ITP) commonly relapses after stopping treatments. This may be preventable by low-dose steroids. In this multicenter study, adult patients with ITP who had been responding to corticosteroids were randomized with the 2 strata of newly diagnosed and relapsed ITP to prednisolone 7.5 mg/d or observation for 6 months. Relapses were defined by a platelet count below 30 × 10^9/L and/or clinical bleeding. There were 75 patients evaluable for the efficacy and 77 for safety. The recurrent ITP comprised 57.3%. During the median follow-up of 42 weeks, there were 20.5% (8/39) and 25% (9/36) of recurrences in the prednisolone and control groups (P = .643), with the hazard ratio (HR) of 0.75 (P = .549). The significant factor that could predict recurrences was relapsed ITP with the HR of 2.79 (95% confidence interval, 1.02-7.64, P = .037). Prednisolone showed a trend toward a benefit in the relapsed subgroup (P = .070). Adverse events were not different (P = .540) and mostly mild. In conclusion, prednisolone maintenance could not prolong relapse-free survival. Relapsed patients deserve further investigations for preventive measures.

Keywords
immune thrombocytopenia, recurrence, prednisolone, randomized trial

Introduction
Immune thrombocytopenia (ITP) is a common bleeding disorder caused by production of autoantibodies targeting platelet glycoproteins. These opsonized platelets are then destroyed in the spleen and/or liver. In addition, a platelet production defect also plays an important role in the disease pathogenesis.1 Severe thrombocytopenia may result in massive or vital organ hemorrhages that are potentially fatal. On the other hand, immunosuppressive therapy, especially high-dose corticosteroids, predisposes patients to infections which may also be lethal. In addition, there are other steroid adverse events, such as diabetes mellitus, peptic ulcer, osteoporosis, bone avascular necrosis, glaucoma, and cataract. Therefore, physicians managing ITP must weigh the benefits against the risks of the administered treatments and the disease itself.

International consensus guidelines suggest starting treatment for adult ITP only when platelet counts fall below 30 × 10^9/L and/or there is clinically relevant bleeding.2,3 Corticosteroids, either prednisolone (1 mg/kg/d) or high-dose dexamethasone (40 mg/d for 4 days), have been the recommended first-line therapy yielding a very good response rate of 70% to 90%.4 Due to adverse effects of long-term steroids, the treatment needs to be tapered and finally stopped. A guideline suggests a gradual reduction in steroid dosages rather than abrupt termination5, but the most appropriate steroid tapering schedule is still undefined as randomized trials are lacking. After stopping medications, the majority of ITP recurs,4-7 with

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an estimated disease-free rate of only 15% at 10 years.4 A strategy to prevent ITP relapses is, therefore, required. Nevertheless, long-term side effects and costs of the preventive measures are to be concerned.

Currently, the approved long-term extended therapy for chronic ITP is thrombopoietin receptor agonists as the medications are relatively safe.3,8,9 However, the drugs are approved only for steroid-refractory ITP and the costs of drugs are very high especially for potentially lifelong uses. Additionally, there may be an increased risk for thromboembolism10 and theoretical hazards of myelofibrosis and leukemic transformation as there is a long-standing MPL/JAK/STAT pathway hyperactivation similar to myeloproliferative neoplasm.

As the toxicity of high-dose steroid is well known, lower doses of prednisolone may be more tolerable. Regarding the efficacy, one randomized trial demonstrated that prednisolone at 0.25 mg/kg/d was as effective as the standard dose prednisolone for the treatment of acute ITP.11 The efficacy of lower doses of steroid is unknown. Because some patients have ITP relapses when prednisolone is discontinued, it is a common practice in our country to maintain a very low dose (≤10 mg/d) of prednisolone for a long period of time. There has been no previous randomized trial studying steroid maintenance therapy. Therefore, we aimed to determine the efficacy and safety of a physiological dose of prednisolone in preventing ITP recurrences in patients who had been responding to steroids.

Materials and Methods

Clinical Settings

This is a randomized multicenter open-label trial. The 4 actively contributing centers were 3 medical school-affiliated hospitals (King Chulalongkorn Memorial Hospital, Hospital for Tropical Diseases, and HRH Princess Maha Chakri Sirindhorn Medical Center) and 1 provincial hospital (Buddhasothorn Hospital). This study was approved by each hospital’s ethics committee. The study was registered in the Thai Clinical Trial Registry: TCTR20140213002

Patients

The inclusion criteria were the adult patients with primary ITP (age ≥18 years) who had been treated with corticosteroids, either prednisolone at 1 mg/kg/d or 4-day high-dose dexamethasone followed by lower doses of prednisolone,12 and showed responses according to the international working group criteria (platelet count ≥30 × 10^9/L at least twice and no clinical bleeding).13 The prednisolone doses were subsequently tapered according to the primary physicians. When prednisolone doses were reduced to 10 mg/d, or less, for at least 2 weeks and platelet counts were still ≥30 × 10^9/L, the patients were asked to participate in the trial. There must have been no other concomitant ITP treatment for at least 4 weeks before enrollment.

The exclusion criteria were the diagnosis of secondary ITP and causes of which were HIV infection, hepatitis C infection, malignancy, or other autoimmune diseases. Patients with steroid contraindications, which were an active infection, uncontrolled diabetes mellitus, uncontrolled hypertension, active peptic ulcer, glaucoma, cataract, osteoporosis, psychosis, or avascular osteonecrosis, were not included. Finally, postsplenectomized patients were also excluded. Informed consent was received from all enrolled patients.

Interventions

The enrolled patients were stratified into newly diagnosed and relapsed ITP before randomized by opening one of the 2 sets of randomly arranged concealed envelopes indicating either steroid or observation. One of the investigators (A.P.) was responsible for the randomization process.

The treatment group received 7.5 mg/d prednisolone for 6 months. Subsequently, steroids were reduced until stopped in 2 months and patients were followed for 2 more months to the total of 10 months. In the control group, prednisolone doses were immediately tapered to stop within 2 months and they were followed up to the total of 10 months. After the study completion, patients at King Chulalongkorn Memorial Hospital were followed for complete blood count (CBC) and bleeding symptoms every 3 to 6 months as long as they were willing to.

Baseline data included bleeding symptoms, CBC, blood smear, serum creatinine, liver function test, fasting plasma glucose, serum lipid profile, stool examination for parasites, and chest X-ray. The patients were evaluated at least every 2 months for signs and symptoms of bleeding by the clinical hemorrhagic score,14 CBC, and any adverse events. Blood chemistry was tested again at month 4 of follow-up. The primary end point was the ITP relapses as defined by platelet counts <30 × 10^9/L or bleeding symptoms with the clinical hemorrhagic score ≥2.

Sample Size Calculation

The reported ITP relapse rates are greatly variable among series.5-7,15-17 For the sample size calculation, a recurrent rate without treatment was estimated as two-thirds (66%) of the patients. There has been no previous report on the effects of low-dose corticosteroid maintenance. However, we thought that the treatment should be able to decrease relapses by half (to 33%) to be clinically significant. With the α and β errors of 0.05 and 0.20, respectively, the yielded sample size was 70. Approximately 15% more patients were enrolled for possible cases of loss to follow-up.

Statistical Analysis

The continuous data were expressed as means (standard deviations, SD) or medians with interquartile ranges (IQR) as appropriate. The unpaired t test was used to compare means, and the χ^2 test was used for proportions for univariate analysis. The factors that showed P values of .1 or lower were subjected to a multivariate analysis. Survival curves were generated by the
Kaplan-Meier method for depictions, and hazard ratios (HRs) were calculated using Cox regression analysis. All analyses were performed using SPSS software for Windows (version 16.0). A $P$ value <.05 was considered as statistical significance.

**Results**

**Baseline Data**

There were 86 patients screened for the study, and 81 cases were included. The CONSORT (Consolidated Standards of Reporting Trials) diagram is shown in Figure 1. There were 41 patients randomized to the prednisolone group and 40 to the control group. Three cases (1 in the prednisolone group and 2 cases in the control group) were lost to follow-up just after the first visits, and therefore, efficacy and safety outcomes could not be evaluated. In addition, 2 patients in the control group withdrew consent. One of these patients could not come for further follow-up after month 2 visit. The other patient in the control group developed fatigue and weight loss after discontinuing prednisolone and requested to resume prednisolone at month 6. One patient in the treatment group developed tuberculosis of the spine 2 months before the scheduled termination and the physician decided to discontinue prednisolone. None of these patients had ITP relapse at their last follow-up visits. The latter 2 patients who were switched the treatment arms due to adverse events (1 from each group) were also included in the safety study with the total number of 77 patients.

There were a total of 75 patients who received the interventions as planned and were evaluable for the efficacy. Fifty-eight (77.3%) of them were female, and the average age was 40.5 (14.9) years. The recurrent cases comprised 57.3% and the remaining was at the first diagnosis. Thirty-six and 39 patients were randomized to the control and prednisolone groups, respectively. The median platelet count at the onset was $7 \times 10^9/L$ (IQR: $4 \times 10^9/L$ to $17 \times 10^9/L$). The sites of bleeding at ITP presentations were the skin ($n = 61$), mouth ($n = 32$), heavy menstruation ($n = 11$), urinary tract ($n = 4$), gastrointestinal tract ($n = 2$), nose ($n = 2$), and central nervous system ($n = 1$). There were 38 patients who had multiple sites of bleeding and 2 cases without bleeding symptoms despite severe thrombocytopenia. They were initially treated with either high-dose dexamethasone followed by prednisolone (38.7%) or...
prednisolone from the beginning (61.3%). The median duration of corticosteroid before entering the study was 132 days, with the IQR of 90 to 187 days. The mean cumulative prednisolone-equivalent dose received was 2997 (1368) mg. There were 29 (38.7%) patients who were treated at the provincial hospital.

Upon entering the study, 85.3% achieved complete response (CR; platelet count ≥100 × 10⁹/L) to corticosteroids. The mean (SD) platelet count at entering the study was 199 × 10⁹/L (92 × 10⁹/L), ranging from 30 to 455 × 10⁹/L. The baseline characteristics of patients were comparable between groups, as shown in Table 1. The observation group tended to be older than the prednisolone group. No other ITP treatment was allowed at least 4 weeks before entering the study.

**Efficacy Analysis**

During the study period of 10 months, there was no statistical difference in ITP relapses between the 2 groups. There were 9 (25.0%) and 8 (20.5%) recurrences in the control and prednisolone groups, respectively (P = .643). There was also no difference in platelet counts at any time points between the 2 groups (data not shown). The Kaplan-Meier curve is shown in Figure 2, and the HR revealed no statistical difference in relapse-free survival. The prednisolone group showed no apparent different relapse rates among the 6 months of prednisolone, 2 months of steroid tapering, and final 2 months of no prednisolone (Figure 2). In cases that achieved CR, the losses of CR occurred in 43.3% versus 47.1% in observation versus prednisolone groups, respectively.

Twenty-seven patients (10 and 17 in observation and prednisolone groups, respectively) were followed further without corticosteroids beyond the study period of 10 months. The whole group was re-analyzed at a mean follow-up period of 90.5 weeks. There were 12 (33.3%) and 14 (35.9%) relapses in the control and prednisolone groups, respectively (P = .816), with the HR of 1.00 (95% confidence interval [CI], 0.46-2.19, P = .993).

**Safety Analysis**

There were 77 patients who were evaluated for safety. There was no mortality or a grade 4 adverse event in this study. The frequencies of adverse events were not different (Table 2). However, 2 serious adverse events occurred in the prednisolone group. One patient had acute kidney injury on top underlying chronic renal disease requiring admission. The kidney function finally recovered to the baseline without a change in prednisolone dosage. The other patient had tuberculous spondylitis requiring hospitalization, and prednisolone was discontinued. In the control group, there was 1 serious adverse event from avascular necrosis of hip that required decompression surgery. In addition, 1 patient in the control needed an emergency department visit for dyspepsia and recovered after treatment for peptic ulcer without hospital admission.
Predictors of Relapses

Factors possibly associated with ITP relapses were explored by univariate analysis. Age, sex, presence of comorbidity, platelet count at the ITP onset, initial treatment (dexamethasone vs prednisolone), treatment centers (provincial vs university hospitals), duration of corticosteroids before entering the study, total cumulative doses of steroids at entry, platelet count on enrollment, CR upon entry, and prednisolone maintenance were not significantly associated with recurrences.

Notably, the relapsed ITP was more likely to relapse with the HR of 2.79 (95% CI: 1.02-7.64). The relapsed versus newly diagnosed cases had the recurrent rates of 34.4% versus 14.0% at 10 months (P = .037) and 56.2% versus 18.6% (P = .001) at the mean follow-up of 90.5 weeks, respectively. The probability of recurrences in newly diagnosed versus relapsed cases is shown in Figure 3.

There were 45 patients who still had response at the median follow-up time of 90.5 months. The mean age was 40.9 years and 73.5% were female. The mean baseline platelet count was $11.3 \times 10^9/L$. Dexamethasone was used in 40.8% with 89.8% CR, and the mean cumulative steroid dose was 3112 (1346) mg prednisolone. These characteristics were similar to the whole group of patients.

Table 2. Adverse Events During the Study Period.

| Cases With Any Adverse Event(s) | Observation (n = 37) | Prednisolone (n = 40) |
|---------------------------------|----------------------|----------------------|
|                                 | 16 (43.2%)           | 20 (50%)             |
| Grade                           |                      |                      |
|                                 | 1                    | 2                    | 3     | 1     | 2     | 3     |
| Elevated transaminases          | 3 (8.1%)             | 1 (2.7%)             | 0     | 3 (7.5%) | 0    | 0    |
| Hyperglycemia                   | 5 (13.5%)            | 0                    | 0     | 7* (17.5%) | 0   | 0    |
| Bone avascular necrosis         | 0                    | 1 (2.7%)             | 0     | 0       | 1 (2.7%) | 0   |
| Acute on top chronic renal failure | 0                | 0                    | 0     | 0       | 0    | 1 (2.5%) |
| Tuberculous spondylitis         | 0                    | 0                    | 0     | 0       | 0    | 1 (2.5%) |
| Fatigue                         | 0                    | 1 (2.7%)             | 0     | 0       | 0    | 0    |
| Hypercholesterolemia            | 1 (2.7%)             | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Dizziness/vertigo               | 1 (2.7%)             | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Weight gain                     | 1 (2.7%)             | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Dyspepsia/vertigo               | 1 (2.7%)             | 1 (2.7%)             | 0     | 1 (2.5%) | 0   | 0    |
| Constipation                    | 0                    | 1 (2.7%)             | 0     | 0       | 0    | 0    |
| Knee pain                       | 0                    | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Skin rash                       | 0                    | 0                    | 0     | 0       | 1 (2.5%) | 0   |
| Postherpetic neuralgia          | 0                    | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Upper respiratory tract infection| 0                | 0                    | 0     | 1 (2.5%) | 0   | 0    |
| Blastocystis hominis infection  | 0                    | 0                    | 0     | 1 (2.5%) | 0   | 0    |

*a n = 77.
bWorkup studies revealed fatty liver.
cOne of them had elevated liver enzymes at baseline.
dThree of them had hyperglycemia before entering the study.
eFour of them had hyperglycemia before entering the study.
fThe patient needed decompression surgery.
gSerious adverse events required admissions.
hThe patient received conservative treatments.
iThe patient wanted to resume prednisolone.
jThey had a history of dyslipidemia.
kOne patient needed to come to the emergency department.

Figure 3. The relapse-free survival comparing the newly diagnosed versus relapsed immune thrombocytopenia (ITP).
Subgroup Analysis

In a subgroup analysis of the newly diagnosed ITP, there was no significant difference in the relapse rate between the prednisolone and control groups (Figure 4A). However, the relapsed ITP subgroup (N = 32) showed a trend toward reduction in ITP recurrences in the prednisolone arm (Figure 4B).

Discussion

This study cannot demonstrate a clinical benefit of low-dose prednisolone maintenance in preventing relapses of steroid-responsive ITP. Additionally, an analysis including the patients who were followed up for longer durations showed that both arms had similar relapse rates.

The recurrent rate of 22.7% (17/75) during our study period was relatively lower than those of previous reports.5,6,13,15 This may be because approximately 40% of patients were newly diagnosed ITP, which had a lower risk of relapses compared with chronic or persistent ITP.13 In addition, our patients had been followed for a relatively short time, while previous studies that showed the sustained response rates of only 15% to 30% observed their patients for 4 to 10 years.6,13,15 The survival curve of our patients (Figure 2) does not show a plateau suggesting that future relapses are probable. Hence, 34.7% (26/75) of our patients had recurrences at the median follow-up time of 90.5 weeks. Furthermore, participants in this study were selected because they all responded well to corticosteroids, not general ITP cases. Our data are consistent with a recent registry study that showed a 1-year relapse rate of 16.3%, as 92% of their patients initially responded to first-line therapy.16

Our data suggest also that after the first episode of ITP, steroid can be safely discontinued. The durations of corticosteroid treatment were relatively long in this study mainly because platelet counts dropped during steroid tapering and the physicians decided to increase or maintain the steroid doses. The data suggest that this dose and duration of steroid (cumulative prednisolone dose of 3 g in approximately 4 months) is sufficient. Further extension of the steroid course is unlikely to be much helpful.

The treatment with a physiological dose of prednisolone for 6 months was relatively well tolerated and the frequency of adverse events was not significantly different from the observation. These events might be related to high-dose steroids received before entering the trial, such as 1 patient who developed avascular necrosis of the hip in the control arm. Two serious adverse events were difficult to be ascertained if they were related to such a low dose of prednisolone. However, subclinical corticosteroid toxicities, such as a decrease in bone mineral density or hypothalamic–pituitary–adrenal suppression, were not investigated in this study. Patients in both groups were encouraged to take calcium and vitamin D supplement to preserve bone density. One patient who needed to resume prednisolone in the control group probably had adrenal suppression due to previous exposure to high-dose corticosteroids.

This clinical trial identified the presence of previous episodes of ITP as a strong predictor of recurrences. This characteristic was prespecified and, therefore, balanced between the 2 treatment arms. In approximately 2 years, the newly diagnosed ITP had a relapse rate of only 18.6% compared with over 50% in previously relapsed cases. The information may be useful as one of the factors decide whether or not to stop ITP therapy. This is consistent with the observations that the long remission is less likely for ITP duration of more than 1 year.13,18

![Figure 4. Subgroup analyses. A, The relapse-free survival comparing control (observation) versus prednisolone (7.5 mg/d) in cases with newly diagnosed ITP. B, The relapse-free survival comparing control (observation) versus prednisolone (7.5 mg/d) in cases with relapsed immune thrombocytopenia (ITP).](image-url)
However, the prognostic significance of a relapse after remission has not been previously reported. Future research is needed to find a better strategy in the relapse group. Low-dose prednisolone maintenance may be helpful in these cases (Figure 3), but a larger sample size is required to prove this hypothesis.

The sample size of this study was not large enough to detect a small effect, if there is any, of the intervention. However, long-term prednisolone is potentially harmful and high efficacy is necessary to offset the potential side effects. There were 4 patients (3 in the control group and 1 in the prednisolone group) who were not followed up completely and were excluded from the analysis. If we assume that all 3 controls relapsed and 1 prednisolone case did not recur, there is still no statistical difference in the recurrent rates ($P = .274$), suggesting that our conclusion is valid. Therefore, this study does not support the long-term prednisolone uses in ITP.

In conclusion, a physiological dose of prednisolone for 6 months could not significantly prevent ITP relapses. Notably, previous ITP episodes can predict ITP recurrences. This subgroup deserves further investigations for an appropriate measure to prevent relapses.

Declaration of Conflicting Interests

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