ORIGINAL ARTICLE

Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia

Charlotte A. Bradbury, M.D., Ph.D., Julie Pell, Pg.C., Quentin Hill, M.D., Catherine Bagot, M.D., Nichola Cooper, M.D., Jenny Ingram, Ph.D., Katie Breheny, Ph.D., Rebecca Kandiyali, Ph.D., Rachel Rayment, M.D., Ph.D., Gillian Evans, M.D., Kate Talks, M.D., Ian Thomas, M.Sc., and Rosemary Greenwood, M.Sc.

ABSTRACT

BACKGROUND

Immune thrombocytopenia is a rare autoimmune disorder with associated bleeding risk and fatigue. Recommended first-line treatment for immune thrombocytopenia is high-dose glucocorticoids, but side effects, variable responses, and high relapse rates are serious drawbacks.

METHODS

In this multicenter, open-label, randomized, controlled trial conducted in the United Kingdom, we assigned adult patients with immune thrombocytopenia, in a 1:1 ratio, to first-line treatment with a glucocorticoid only (standard care) or combined glucocorticoid and mycophenolate mofetil. The primary efficacy outcome was treatment failure, defined as a platelet count of less than 30×10^9 per liter and initiation of a second-line treatment, assessed in a time-to-event analysis. Secondary outcomes were response rates, side effects, occurrence of bleeding, patient-reported quality-of-life measures, and serious adverse events.

RESULTS

A total of 120 patients with immune thrombocytopenia underwent randomization (52.4% male; mean age, 54 years [range 17 to 87]; mean platelet level, 7×10^9 per liter) and were followed for up to 2 years after beginning trial treatment. The mycophenolate mofetil group had fewer treatment failures than the glucocorticoid-only group (22% [13 of 59 patients] vs. 44% [27 of 61 patients]; hazard ratio, 0.41; range, 0.21 to 0.80; P=0.008) and greater response (91.5% of patients having platelet counts greater than 100×10^9 per liter vs. 63.9%; P<0.001). We found no evidence of a difference between the groups in the occurrence of bleeding, rescue treatments, or treatment side effects, including infection. However, patients in the mycophenolate mofetil group reported worse quality-of-life outcomes regarding physical function and fatigue than those in the glucocorticoid-only group.

CONCLUSIONS

The addition of mycophenolate mofetil to a glucocorticoid for first-line treatment of immune thrombocytopenia resulted in greater response and a lower risk of refractory or relapsed immune thrombocytopenia, but with somewhat decreased quality of life. (Funded by the U.K. National Institute for Health Research; FLIGHT ClinicalTrials.gov number, NCT03156452; EudraCT number, 2017-001171-23.)

From the Faculty of Translational Health Sciences (C.A.B.), University of Bristol (J.I., K.B., R.K.), and the Bristol Haematology and Oncology Centre (C.A.B.) and the Research Design Service (R.G.), University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, the Centre for Trials Research, Cardiff University (J.P., I.T.), and the Department of Haematology, Cardiff and Vale University Health Board (R.R.), Cardiff, Leeds Teaching Hospitals NHS Trust, Leeds (Q.H.), Glasgow Royal Infirmary, Glasgow (C.B.), the Department of Immunology and Inflammation, Imperial College London, London (N.C.), East Kent Hospitals University NHS Foundation Trust, Canterbury (G.E.), and Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne (K.T.) — all in the United Kingdom. Address reprint requests to Dr. Bradbury at Level 8, Bristol Haematology and Oncology Centre, Horfield Rd., Bristol, BS2 8ED, United Kingdom, or at c.bradbury@bristol.ac.uk.

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Immune thrombocytopenia is a rare condition, with an incidence in adults of 2.9 per 100,000 person-years.[1] It is an autoimmune condition that may manifest with bleeding and bruising owing to a low platelet count. Fatigue is also associated with disease activity and can be severe.[2,3] In immune thrombocytopenia, increased consumption of platelets and reduced production of platelets are due to antibody and cell-mediated autoimmune attacks on platelets and megakaryocytes that involve dysregulated autoreactive T and B lymphocytes.[4-7] Immune thrombocytopenia can be classified according to the duration of illness as newly diagnosed (<3 months), persistent (3 to 12 months), or chronic (>12 months).[8] Immune thrombocytopenia may also be classified as primary (when it manifests in isolation) or secondary (when it occurs in the context of an associated illness).[8]

First-line treatment for adults with immune thrombocytopenia is high-dose glucocorticoids, but this treatment has several downsides. Most patients have side effects, including mood swings, difficulty sleeping, weight gain, high blood pressure, diabetes, gastric irritation, thinning of the skin, and osteoporosis. A published survey of patients with immune thrombocytopenia showed that 98% had at least one side effect and 38% stopped the medication or reduced the dose owing to unacceptable side effects.[9] Another problem with high-dose glucocorticoid treatment is the heterogeneity of responses, with approximately 20 to 30% of patients having no response (refractory disease), and the majority of patients who have a response having a relapse at some point after glucocorticoid doses have been reduced or stopped. Long-term remission occurs in only about 20% of patients treated with glucocorticoids only.[10-14] Patients in whom first-line glucocorticoids fail remain at risk for bleeding and bruising until alternative therapies succeed, and some patients may be hospitalized and receive expensive rescue therapies (e.g., immune globulin).[14]

First-line immune thrombocytopenia treatment is unsatisfactory but has remained unchanged for decades. Although a small number of studies have tested alternative approaches, a safe, effective, and durable first-line strategy has not been conclusively identified. Therefore, high-dose glucocorticoids continue to be the recommended treatment.[12,14]

Mycophenolate mofetil is widely used in the United Kingdom as a second-line treatment for immune thrombocytopenia and is less expensive than many alternative treatments. Although no data from randomized, controlled trials have been published, evidence from retrospective data indicates that mycophenolate mofetil is effective (with response rates of 50 to 80%), although platelet response typically takes 4 to 6 weeks.[10,15-22] Mycophenolate mofetil has activity against autoreactive T and B cells and has also shown efficacy in refractory immune thrombocytopenia, including in patients whose disease is resistant to glucocorticoids, which suggests a complementary mechanism of action.[20] The FLIGHT trial aimed to test the hypothesis that mycophenolate mofetil combined with a glucocorticoid is a more effective first-line treatment pathway than a glucocorticoid-only regimen in patients with immune thrombocytopenia.

Methods

Trial Design

The FLIGHT trial was a multicenter, open-label, randomized, controlled trial of mycophenolate mofetil plus a glucocorticoid, as compared with glucocorticoids only, as first-line treatment for immune thrombocytopenia. The full trial methods have been published previously.[23] The FLIGHT trial received ethics approval from the National Research Ethics Service.

The FLIGHT trial was designed by the first author with input from all the coauthors. The trial was sponsored and overseen by University Hospitals Bristol. The authors vouch for the fidelity of the trial to the protocol and for the accuracy and completeness of the data. The first author wrote the first draft of the paper with subsequent input from the coauthors. No one who is not an author contributed to writing the manuscript.

Patients

Patients older than 16 years of age were eligible for recruitment if they had received a diagnosis of immune thrombocytopenia (primary or secondary) and if they had a platelet count of less than 30×10^9 per liter and a clinical need for first-line treatment. Exclusion criteria were pregnancy, breast-feeding, human immunodeficiency virus (HIV) infection, hepatitis B or C infection,

common variable immunodeficiency, contraindications to mycophenolate mofetil or glucocorticoids, inability to give informed consent, and unwillingness to adhere to contraceptive advice if randomly assigned to receive mycophenolate mofetil. Because mycophenolate mofetil increases the risk of miscarriage and birth defects, women of childbearing potential were required to use two reliable forms of contraception (from among the choices of hormonal birth control, barrier method of birth control, and abstinence) simultaneously before starting treatment with mycophenolate mofetil, during therapy, and for 6 weeks after stopping treatment with mycophenolate mofetil. Sexually active male patients with female partners of childbearing potential were recommended to use condoms during treatment and for at least 90 days after cessation of treatment, regardless of whether they had undergone vasectomies. In addition, female partners of male patients treated with mycophenolate mofetil were recommended to use highly effective contraception while their partners were receiving treatment and for a total of 90 days after the last dose of mycophenolate mofetil. The eligibility criteria required serologic testing for the presence of HIV and hepatitis and to establish immunoglobulin levels. Patients could be recruited pending serologic results and later excluded if the result for HIV infection or hepatitis was positive or if the patient had common variable immune deficiency. Patients were recruited and followed up in hematology departments of hospitals (secondary care) across the United Kingdom.

TRIAL PROCEDURES

Patients who provided written informed consent were randomly assigned in a 1:1 ratio to receive either mycophenolate mofetil with a glucocorticoid or a glucocorticoid alone. Randomization was performed with the use of a secure, Web-based randomization system at the Cardiff Clinical Trials Unit. To ensure an even distribution of patients across time, randomization was performed in block sizes of 6 and 8 to maintain concealment.

Glucocorticoid dosing described in the protocol (available with the full text of this article at NEJM.org) adhered to international consensus recommendations, and patients in both groups could receive either oral prednisolone or dexamethasone. The dose of prednisolone was 1 mg per kilogram of body weight for 4 days followed by 40 mg daily for 2 weeks, 20 mg daily for 2 weeks, 10 mg daily for 2 weeks, 5 mg daily for 2 weeks, and 5 mg every other day for the final 2 weeks. This dosing algorithm was followed regardless of the patient's platelet count, although a more rapid taper was permitted for patients with immune thrombocytopenia that was refractory to treatment, and dose reduction was permitted for patients who had side effects. Alternatively, patients could receive up to three dexamethasone pulses (each pulse consisting of 40 mg daily for 4 days), with the number of pulses at the discretion of the clinician. Patients assigned to receive mycophenolate mofetil began treatment at a dose of 500 mg twice daily (along with a glucocorticoid) for 2 weeks, at which time the dose was increased to 750 mg twice daily if the patient had no side effects; after 2 more weeks (4 weeks after initiation of treatment with mycophenolate mofetil), the dose was increased to 1 g twice daily if the patient had no side effects. The mycophenolate mofetil dosing algorithm was followed regardless of the patient's platelet count. After 6 months of mycophenolate mofetil therapy, the dose for all patients who had a complete response to mycophenolate mofetil (platelet count $>100\times10^9$ per liter) was reduced by 250 mg each month, with the goal of continuing the lowest dose that achieved a hemostatic (safe) platelet count ($>30\times10^9$ per liter) and ensuring that patients whose disease had gone into spontaneous remission did not continue to take the drug indefinitely.[23]

Patients were followed for a minimum of 12 months and until the end of the trial. Laboratory and clinical data were obtained during routine appointments. Additional data and patient-reported quality-of-life outcome measures were recorded at diagnosis and at 2, 4, 6, and 12 months by means of four validated patient questionnaires[24-26]: quality of life as measured with the use of the 36-Item Short-Form Health Survey (SF-36), version 2, and the Investigating Choice Experiments Capability Measure–Adults (ICECAP-A) questionnaire, version 2; fatigue as measured on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, version 4; and patient's level of concern regarding bleeding as measured with the use of the Functional Assessment of Cancer Therapy–Thrombocytopenia (FACT-Th6) questionnaire.

OUTCOMES

The primary outcome of the FLIGHT trial was treatment failure, defined as a platelet count of less than 30×10^9 per liter and initiation of a second-line treatment, assessed in a time-to-event analysis. Secondary outcomes were medication side effects, bleeding events, need for rescue therapies, response (with response defined as a platelet count that was $>30\times10^9$ per liter and that was at least twice as high as the baseline count, and complete response as a platelet count of $>100\times10^9$ per liter),[7] and patient-reported quality-of-life measures.

STATISTICAL ANALYSIS

Patients excluded at the primary screening or the secondary screening (conducted within 7 days after the primary screening) were not included in the follow-up or analysis. All remaining patients were followed through routine clinical appointments for a minimum of 12 months and until the end of the trial. The length of follow-up used in the analysis of treatment failure was the time from randomization to either the date the trial closed or the date the patient withdrew from the study or died, whichever was first. In some cases, the patient withdrew from receiving questionnaires or the assigned treatment but continued to be followed up to allow collection of data regarding the primary outcome. In addition, patients were followed past the point of treatment failure by means of quality-of-life questionnaires.

The sample size of 120 patients (60 in each group) with less than 5% loss to follow-up was calculated to achieve 91.5% power to detect a doubling of the median time to treatment failure from 5 months to 10 months, with accrual over 12 months of recruitment and 12 months' minimum follow-up. The sample size was calculated with the use of PASS software. The analysis of the primary outcome was performed with the use of Kaplan–Meier plots, and we calculated statistical significance using the log-rank test. However, we were unable to produce statistics regarding the median time to treatment failure, since less than 50% of patients in each group had reached the primary outcome. Instead, we have reported hazard ratios for the time to treatment failure in the mycophenolate mofetil group as compared with the glucocorticoid-only group by using Cox proportional hazards modeling. As a confirmatory sensitivity analysis, hazard ratios were also computed with adjustment for whether immune thrombocytopenia was primary or secondary, as well as with adjustment for age over 65 years, sex, and obesity, because of observed differences in the groups after randomization. Adjustments to the significance level have not been made for the multiplicity of testing in this sensitivity analysis, so the possibility remains that the results in the sensitivity analysis are not reproducible.

We analyzed questionnaire data on quality of life by calculating the area under the curve with the use of the trapezium rule (a method of calculating the area under the curve by breaking the curve into segments or trapezoid shapes and calculating the total area of the shapes) for all patients with data for both baseline and at least two additional follow-up points and with the use of the last-observation-forward method for patients who did not complete the final data points. The area under the curve was then analyzed by means of linear regression with normal error structure with adjustment for baseline variables and further adjustment for age over 65 years, sex, obesity, and primary or secondary immune thrombocytopenia.

RESULTS

PATIENTS

Of the 123 patients who were recruited and who underwent randomization, 3 were excluded before receiving their assigned trial treatment because they met exclusion criteria at the secondary screening (positive HIV test, diagnosis of cancer that was not immune thrombocytopenia, and a decision to seek private medical care). The primary analysis included all 120 remaining patients (Fig. 1). A total of 113 patients were included in the quality-of-life analysis, with 7 patients omitted (1 who had not completed the baseline questionnaire and 6 who did not complete more than one follow-up requirement).

Demographic and baseline variables, including coexisting conditions, are described in Table 1. The overall mean age was 54 years (range, 17 to 87), 54% of the patients were male, and the mean pretreatment platelet count at baseline was 7×10^9 per liter. A total of 27.5% of the patients were older than 70 years of age, and 15.8% were older than 75 years of age. Slight differences between the groups were noted in the percentages of patients 65 years of age or older (44.1%

in the mycophenolate mofetil group vs. 31.2% in the glucocorticoid-only group), non-White race (13.6% vs. 3.3%), male sex (47.5% vs. 60.7%), obesity (22% vs. 8.2%), and secondary immune thrombocytopenia (5.1% vs. 16.4%). The majority of patients in each group received prednisolone as the first-line glucocorticoid, and the remaining patients received dexamethasone. In the mycophenolate mofetil group, 50 patients received prednisolone and 5 received dexamethasone. In the glucocorticoid-only group, 50 patients received prednisolone and 10 received dexamethasone. Data regarding the type of glucocorticoid received are missing for four patients in the mycophenolate mofetil group and one patient in the glucocorticoid-only group. Baseline results of quality-of-life questionnaires from 113 patients who completed questionnaires at a minimum of two follow-up visits are shown in Table S1 in the Supplementary Appendix, available at NEJM.org.

Patients were recruited between October 25, 2017, and February 15, 2019, and were followed for a total of 181 life-years (89 life-years in the mycophenolate mofetil group and 92 life-years in the glucocorticoid-only group). The follow-up time used for analysis of treatment failure was truncated to 2 years and further truncated by the date of treatment failure, if applicable, resulting in a median follow-up time of 1.30 years in the mycophenolate mofetil group and 1.10 years in the glucocorticoid-only group.

PRIMARY OUTCOME

A total of 40 treatment failure events were recorded from randomization to the end of follow-up — 13 in the mycophenolate mofetil group (22%) and 27 in the glucocorticoid-only group (44%). Time-to-event curves plotted on a Kaplan–Meier graph are shown in Figure 2. The hazard ratio, estimated with the use of a Cox proportional hazards model, is 0.41 (95% confidence interval [CI], 0.21 to 0.80; P=0.008 [P value derived from the Cox model]). In a subsample that excluded patients with secondary immune thrombocytopenia (in line with the preexisting statistical analysis plan) and controlled for age, sex, and obesity (variables that were observed to be different in the two groups), the adjusted hazard ratio was 0.44 (95% CI, 0.22 to 0.86). A sensitivity analysis involving the entire sample and controlling for age, sex, obesity, and immune thrombocytopenia (primary or sec-

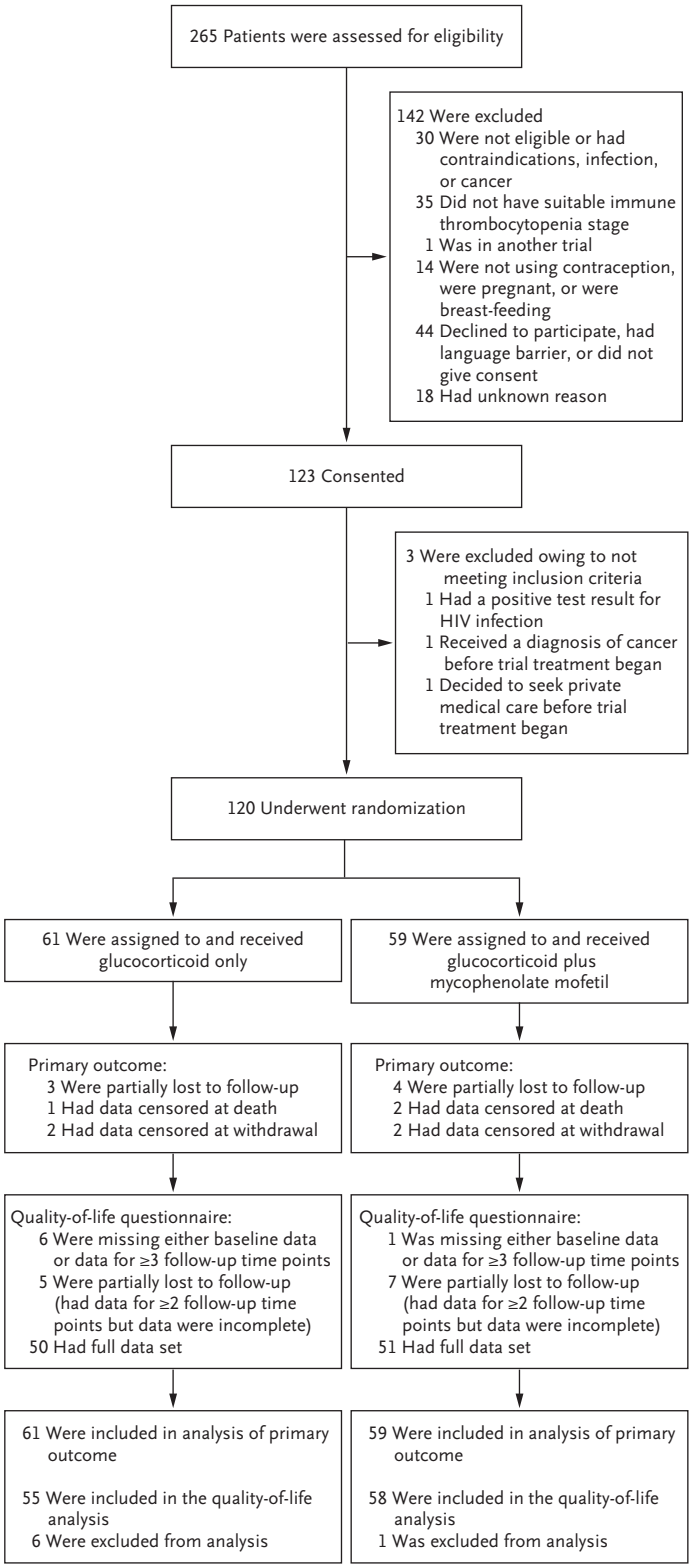

Figure 1. Enrollment, Treatment, and Analysis.

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Mycophenolate Mofetil plus Glucocorticoid (N=59)	Glucocorticoid Only (N=61)
Age		
Mean (range) — yr	56.9 (18–86)	53.1 (17–87)
Distribution — no. (%)		
<18 yr	0	1 (1.6)
18 to 64 yr	33 (55.9)	41 (67.2)
≥65 yr	26 (44.1)	19 (31.1)
Sex — no. (%)		
Male	28 (47.5)	37 (60.7)
Female	31 (52.5)	24 (39.3)
Race or ethnic group — no. (%)*		
White	51 (86.4)	59 (96.7)
Asian (Indian)	0	1 (1.6)
Asian (non-Indian)	2 (3.4)	1 (1.6)
Black or African	3 (5.1)	0
Other	3 (5.1)	0
Secondary immune thrombocytopenia — no. (%)	3 (5.1)	10 (16.4)
Blood pressure — mm Hg		
Systolic	133.0±19.4	131.7±19.2
Diastolic	78.0±11.7	76.7±10.3
Body-mass index†	29.7±6.4	27.8±5.8
Hemoglobin — g/liter	134.9±19.1	140.3±18.0
Platelet count — $\times 10^{-9}$/liter	7.9±7.6	6.5±6.7
Total white-cell count — $\times 10^{-9}$/liter	7.2±3.3	7.4±2.3
Neutrophils — $\times 10^{-9}$/liter	4.6±2.2	4.8±2.4
Mean corpuscular volume — fl	85.9±13.3	87.5±9.1
Other conditions — no. (%)		
Arrhythmia	3 (5.1)	4 (6.6)
Heart-valve disease	2 (3.4)	4 (6.6)
Other cardiac disorder	2 (3.4)	3 (4.9)
Inflammatory bowel disease	2 (3.4)	1 (1.6)
Diabetes	6 (10.2)	8 (13.1)
Cerebrovascular disease	3 (5.1)	2 (3.3)
Psychiatric disorder	6 (10.2)	3 (4.9)
Obesity	13 (22.0)	5 (8.2)
Active infection	2 (3.4)	2 (3.3)
Rheumatologic disease	5 (8.5)	6 (9.8)
Peptic ulcer	0	1 (1.6)
Moderate or severe renal disease	2 (3.4)	1 (1.6)
Moderate pulmonary disorder	0	1 (1.6)
Severe pulmonary disorder	0	1 (1.6)
Previous solid tumor	7 (11.9)	6 (9.8)
Mild hepatic disease	2 (3.4)	1 (1.6)
Moderate or severe hepatic disease	3 (5.1)	1 (1.6)

* Information on race and ethnic group was obtained from patient medical records.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.

ondary) resulted in an adjusted hazard ratio of 0.40 (95% CI, 0.20 to 0.78).

SECONDARY OUTCOMES

Patients assigned to the mycophenolate mofetil group were also more likely to have a response to first-line treatment than patients in the glucocorticoid-only group (Table 2). In the mycophenolate mofetil group, 91.5% of patients had platelet counts greater than 100×10^9 per liter, as compared with 63.9% in the glucocorticoid-only group, and 93.2% had platelet counts greater than 30×10^9 per liter, as compared with 75.4% in the glucocorticoid-only group. Only 6.8% of patients assigned to the mycophenolate mofetil group had immune thrombocytopenia that was refractory to treatment, as compared with 24.6% of patients in the glucocorticoid-only group. Response to treatment at 2 weeks was similar in the two groups, as were the incidences of treatment side effects, bleeding episodes, and rescue therapy or hospital admission (Table 2).

Data regarding patient-reported outcomes over the 12-month follow-up period are shown in Table 3. After adjustment for baseline variables, only small differences were noted between the groups regarding FACT-Th6 (patient level of concern about bleeding), ICECAP-A (a broad quality-of-life measure), or the SF-36 mental health summary. Patients assigned to the mycophenolate mofetil group appeared to have worse fatigue (as measured by the FACIT-F survey) and lower scores on the SF-36 physical health summary. However, after adjustment for multiple testing, none of these comparisons excluded the possibility of these being chance findings.

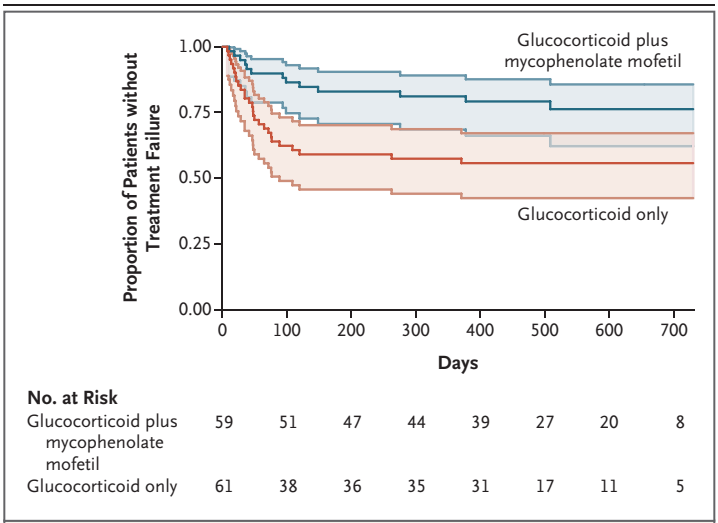

Figure 2. Primary Outcome (Treatment Failure).

DISCUSSION

Immune thrombocytopenia is a rare autoimmune disease, and few randomized, controlled trials have been conducted to evaluate treatments, particularly involving commonly prescribed "older" generic treatments such as mycophenolate mofetil, azathioprine, splenectomy, dapsone, and danazol. Of the randomized trials that have been conducted, the majority have focused on patients later in the course of illness (chronic immune thrombocytopenia) and often excluded elderly patients, who make up the majority of persons with immune thrombocytopenia. In addition, only the clinical trials assessing thrombopoietin-like agents (romiplostim and eltrombopag) for chronic immune thrombocytopenia have systematically included assessment of patient-reported quality-of-life outcomes.[27,28]

Although high-dose glucocorticoids continue to be the recommended first-line treatment for immune thrombocytopenia,[12,14] side effects, heterogeneous responses, and high rates of relapse are a clinical challenge, with only approximately 20% of patients remaining in long-term remission with glucocorticoid treatment. Here, we report the results of a randomized trial testing mycophenolate mofetil plus glucocorticoids in patients with immune thrombocytopenia. These data show that, as compared with treatment with a glucocorticoid only, the addition of mycophenolate mofetil resulted in approximately half the risk of refractory or relapsed immune thrombocytopenia. This significant difference in treatment failure with mycophenolate mofetil was observed despite very favorable responses in the glucocorticoid-only group, with 56% of patients in the glucocorticoid-only group not requiring second-line treatment over a mean of 18 months of follow-up, which is a higher percentage than that reported in most previous studies. For example, one randomized trial showed a sustained response at 6 months in 41% of patients treated with prednisolone and in 40% treated with dexamethasone.[29] The international consensus guideline reports that 23% of patients have a sustained response with a glucocorticoid at 39 months, and long-term follow-up data suggest that the disease remains in remission without further therapy in only a small proportion of

Table 2. Platelet-Count Responses to First-line Treatment, Side Effects, Bleeding Events, and Rescue Treatments.*

Variable	Mycophenolate Mofetil plus Glucocorticoid (N=59)	Glucocorticoid Only (N=61)	Relative Risk Ratio (95% CI)
Platelet level >30×10^9/liter and twice the level at baseline within 2 weeks after randomization — no. (%)	30 (50.8)	29 (47.5)	1.06 (0.74–1.54)
Platelet level >100×10^9/liter within 2 weeks after randomization — no. (%)	21 (35.6)	21 (34.4)	1.04 (0.63–1.68)
Platelet level >30×10^9/liter and twice the level at baseline in response to first-line treatment — no. (%)	55 (93.2)	46 (75.4)	1.23 (1.05–1.45)
Platelets >100×10^9/liter in response to first-line treatment — no. (%)	54 (91.5)	39 (63.9)	1.43 (1.17–1.76)
Patients with disease refractory to first-line treatment — no. (%)	4 (6.8)	15 (24.6)	
Median time to platelet level of >30×10^9/liter and twice the level at baseline (IQR) — days†‡	14 (6–57)	18 (5–55)	
Median time to platelet level of >100×10^9/liter (IQR) — days†§	38 (6–65)	46 (6–58)	
Treatment side effects — no. (%)			
Infection	14 (23.7)	14 (23.0)	
Weight gain	17 (28.8)	21 (34.4)	
Neutropenia	0	4 (6.6)	
Difficulty sleeping	12 (20.3)	17 (27.9)	
Mood change or psychiatric disorder	18 (30.5)	21 (34.4)	
Steroid-induced diabetes	1 (1.7)	2 (3.3)	
Steroid-induced hypertension	2 (3.4)	2 (3.3)	
Diarrhea or other gastrointestinal symptom	20 (33.9)	15 (24.6)	
Patients with bleeding episode — no. (%)	14 (23.7)	15 (24.6)	
Type of bleeding — no. (%)			
Cutaneous	5 (8.5)	1 (1.6)	
Gastrointestinal	2 (3.4)	4 (6.6)	
Epistaxis	1 (1.7)	3 (4.9)	
Urinary	1 (1.7)	0	
Other mucosal	2 (3.4)	2 (3.3)	
Intracranial	1 (1.7)	0	
Rescue treatments — no. (%)			
Red-cell transfusion	3 (5.1)	1 (1.6)	
Platelet transfusion	2 (3.4)	0	
Tranexamic acid	5 (8.5)	6 (9.8)	
Immune globulin	8 (13.6)	10 (16.4)	
Hospital admission	11 (18.6)	9 (14.8)	
Splenectomy	0	0	

* Side effects, bleeding episodes, and rescue treatments were recorded on the clinical report forms at 2, 4, 6, and 12 months, and the presence of any of these recorded at any one of those times is reported. IQR denotes interquartile ratio.
† Data on treatment failures were censored if failure occurred before platelet levels reached >30×10^{9}per liter.
‡ Statistical significance for the comparison between groups cannot be estimated owing to bias caused by excluding patients who started second-line therapy before going into remission. Data reflecting a median time that could be used for analysis was not available for those patients, although their median times would have been longer than the medians shown.
§ Data on treatment failures were censored if failure occurred before platelet levels reached >100×10^9/liter.

adult patients.[30,31] The addition of mycophenolate mofetil to a glucocorticoid also resulted in a higher proportion of patients who had a response to first-line therapy (Table 2). Responses at 2 weeks were similar in the groups. The incidence of bleeding was similar in the two groups and relatively infrequent, with no fatal bleeding events (Table 2). No patient underwent a splenectomy during follow-up, a finding consistent with the declining use of this treatment ap-

Table 3. Quality-of-Life Assessments.*

Assessment	Mycophenolate Mofetil plus Glucocorticoid	Glucocorticoid Only	Mean Difference in AUC at 12-month Follow-up (95% CI)†
	No. of Patients Assessed		
SF-36‡			
Physical functioning	56	54	−5.9 (−11.8 to −0.1)
Role — physical	55	54	−8.7 (−16.9 to −0.5)
Body pain	56	53	−6.6 (−13.5 to 0.3)
General health	57	54	−5.1 (−11.0 to 0.8)
Vitality	55	53	−4.1 (−10.4 to 2.3)
Social functioning	57	53	−7.0 (−14.4 to 0.5)
Role — emotional	54	54	−4.6 (−12.7 to 3.6)
Mental	56	53	−2.2 (−7.3 to 3.0)
Physical health summary score	54	53	−3.0 (−5.5 to −0.6)
Mental health summary score	54	53	−1.2 (−4.0 to 1.7)
FACIT-F§	57	54	−3.3 (−6.60 to −0.04)
FACT-Th6¶	56	55	−0.4 (−1.8 to 1.1)
ICECAP-A‖	53	50	−0.017 (−0.06 to 0.03)
SF-6D**	—	—	−0.029 (−0.07 to 0.01)

* Results are shown as mean difference in area under the curve over 12 months of follow-up with 95% confidence intervals. Analysis was adjusted for whether the diagnosis was primary or secondary immune thrombocytopenia, age, and sex. Confidence intervals are not adjusted for multiple reporting and so results may not be reproducible.

† Differences in area under the curve (AUC) are adjusted for baseline variables, immune thrombocytopenia (primary or secondary), age over 65 years, obesity, and sex.

‡ Scores on the 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life. A negative difference for SF-36 indicates that the mycophenolate mofetil group had worse quality of life.

§ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire range from 0 to 52, with higher scores indicating less fatigue. A negative difference for FACIT-F indicates that the mycophenolate mofetil group had more fatigue.

¶ Scores on the Functional Assessment of Cancer Therapy–Thrombocytopenia (FACT-Th6) questionnaire range from 0 to 24, with higher scores indicating better quality of life. A negative difference for FACT-Th6 indicates that patients in the mycophenolate mofetil group had greater concerns about bleeding risk.

‖ Scores on the Investigating Choice Experiments Capability Measure–Adult (ICECAP-A) questionnaire range from 1 (indicating best possible quality of life) to less than 0 (indicating a quality of life worse than death), with higher scores indicating greater capability for stability, attachment, autonomy, achievement, and enjoyment. A negative difference for ICECAP-A indicates that the mycophenolate mofetil group had a worse capability score.

** Scores on the Short-Form Six-Dimension survey (SF-6D) range from 1 (indicating best possible quality of life) to less than 0 (indicating a quality of life worse than death). A negative difference for SF-6D indicates that the mycophenolate mofetil group had a worse overall quality-of-life score.

proach, particularly early in the course of immune thrombocytopenia.[32]

When we evaluated the treatment side effects in patients during follow-up (Table 2), those related to glucocorticoids were the most common and included mood change, difficulty sleeping, and weight gain. In contrast, the side effects expected with mycophenolate mofetil were similar in the two groups, with both groups having the same number of infections (14) and similar numbers of gastrointestinal side effects. Neutropenia developed in no patients in the mycophenolate mofetil group and in 4 patients in the glucocorticoid-only group. These results compare favorably with a previous trial of first-line treatment for immune thrombocytopenia that assessed rituximab combined with dexamethasone (up to six cycles) as compared with a dexamethasone-only regimen. Although the addition of rituximab increased the sustained responses (platelets $>50\times10^9$ per liter) at 6 months (58% vs. 37%, $P=0.02$), the incidence of grade 3 or 4 adverse events was higher in the group assigned to rituximab ($P=0.04$).[33] Because of the rate of adverse events, the cost, and the lack of predictability of responses, recent guidelines

have not advocated early treatment with rituximab.[12,14]

Previous studies have shown that chronic immune thrombocytopenia is associated with fatigue and impaired quality of life, which from the patient's perspective can be of greater concern than platelet counts.[3,34,35] The FLIGHT trial incorporated the use of validated questionnaires to assess overall quality of life (SF-36 and ICECAP-A), patients' concerns about bleeding (FACT-Th6), and fatigue (FACIT-F). Nearly all patients (113 of 120 [94.2%]) completed the questionnaires at baseline and at a minimum of two follow-up points. Over 12 months of follow-up, patients who received mycophenolate mofetil reported lower levels of physical health (SF-36) and greater levels of fatigue (FACIT-F). We found no evidence of differences between the groups in bleeding concerns or mental health. These results are important because they show that disease response and patient experience may not necessarily correlate. This is a methodologic consideration for future trials related to immune thrombocytopenia, highlighting the need to focus on the broader context of patient health and not just on the disease. The reasons for patient-reported aspects of quality of life appearing less favorable among patients receiving mycophenolate mofetil are unclear. The quality-of-life differences do not seem to be explained by specific side effects of mycophenolate mofetil, such as infection or diarrhea. Possible reasons include the length of treatment with mycophenolate mofetil, with a potential psychological effect related to treatment duration. The open-label design of the FLIGHT trial is another potential limitation.

As compared with a glucocorticoid-only regimen, treatment with mycophenolate mofetil combined with a glucocorticoid was an effective first-line treatment option, with greater response and less risk of treatment failure and with durable responses over an average of 18 months of follow-up. Because more than half the patients receiving a glucocorticoid-only regimen had not required second-line treatment during follow-up and because mycophenolate mofetil use may be associated with more fatigue, further research is needed to clarify the role of mycophenolate mofetil in immune thrombocytopenia treatment pathways. For example, mycophenolate mofetil could be used in patients for whom laboratory and clinical markers suggest that a glucocorticoid-only regimen would be expected to fail.[36] Early use of mycophenolate mofetil may also be particularly valuable for patients in whom early disease control with avoidance of relapse is a priority, either from the patient's perspective or on clinical grounds, such as when severe bleeding or additional bleeding risk factors (e.g., the patient is receiving anticoagulation or antiplatelet therapy) are present. A systematic assessment of mycophenolate mofetil plus a glucocorticoid as second-line therapy after demonstrated resistance to a glucocorticoid-only regimen should also be undertaken.

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