Bradbury, C. A., Ingram, J., Kandiyali, R., Breheny, K., & Greenwood, R. (2021). Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia. *New England Journal of Medicine*, 385(10), 885-895. <https://doi.org/10.1056/NEJMoa2100596>

Peer reviewed version

Link to published version (if available):
[10.1056/NEJMoa2100596](https://doi.org/10.1056/NEJMoa2100596)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Massachusetts Medical Society at <https://www.nejm.org/doi/full/10.1056/NEJMoa2100596> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Author: This file is the accepted version of your manuscript, and it shows any changes made by the Editor in Chief and the Deputy Editor since you submitted your last revision. This is the version that is being sent to Manuscript Editing for further editing in accordance with NEJM style. You will receive proofs of the edited manuscript, by e-mail. The proofs will contain queries from the manuscript editor, as well as any queries that may be present in this file. The proof stage will be your next opportunity to make changes; in the meantime, please do not make any changes or send any new material to us.

Mycophenolate Mofetil for First Line Treatment of Immune Thrombocytopenia.

Authors: Charlotte A. Bradbury₁ M.D., Ph.D.^{1,2}, Julie Pell₁ Pg.C.³, Quentin Hill₁ M.D.⁴, Catherine Bagot₁ M.D.⁵, Nichola Cooper₁ M.D.⁶, Jenny Ingram₁ B.Sc., Ph.D.⁸, Katie Breheny₁ M.Sc., Ph.D.⁸, Rebecca Kandiyali₁ M.Sc., Ph.D.⁸, Rachel Rayment₁ M.D., Ph.D.⁹, Gillian Evans₁ M.D.¹⁰, Kate Talks₁ M.D.¹¹, Ian Thomas₁ M.Sc.³, Rosemary Greenwood₁ M.Sc.¹²

¹Faculty of Translational Health Sciences, University of Bristol, Bristol, United Kingdom

²Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom

³Centre for Trials Research, Cardiff University, Cardiff, United Kingdom

⁴Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

⁵Glasgow Royal Infirmary, Glasgow, United Kingdom

⁶Dept Immunology and Inflammation, Imperial College, London, United Kingdom

⁸University of Bristol, United Kingdom

⁹Department of Haematology, Cardiff and Vale University Health Board, United Kingdom

¹⁰East Kent Hospitals University Foundation Trust, United Kingdom

¹¹Newcastle upon Tyne Hospitals NHS trust, United Kingdom

¹²Research Design Service, University Hospitals Bristol and Weston NHS Foundation Trust

KEYWORDS

Immune Thrombocytopenia, Prednisolone, Mycophenolate, Glucocorticoid

Word count excluding tables and references= 3189

Corresponding author: Dr Charlotte Bradbury, Level 8, Bristol Haematology & Oncology Centre,
Horfield Road, Bristol, BS2 8ED c.bradbury@bristol.ac.uk

Abstract

BACKGROUND

Immune thrombocytopenia (ITP) is a rare autoimmune thrombocytopenia with associated bleeding risk and fatigue. Recommended first line ITP treatment is with high dose glucocorticoids but side effects, heterogeneous responses and high relapse rates are significant problems.

METHODS

In this multicenter, UK based, open label, randomized controlled trial, we randomly assigned adult patients with ITP requiring first line treatment to glucocorticoid alone (standard care) versus combined glucocorticoid and mycophenolate (1:1 ratio). The primary efficacy outcome was time from randomization to treatment failure, defined as platelets $<30 \times 10^9/L$ with initiation of 2nd line treatment. Secondary outcomes included response rates, side effects, bleeding events, patient reported outcome measures and serious adverse events.

RESULTS

Of the 120 ITP patients recruited and randomized (52.4% male, mean age 54 years, range 17-87, mean platelets = $7 \times 10^9/L$), patients were followed up for up to 2 years. Fewer treatment failures were seen in patients randomized to mycophenolate (22%, $n=13/59$ vs 44%, $n=27/61$, aHR=0.41 [0.21, 0.80], $p=0.0064$), with higher response rates (91.5% achieving platelets $>100 \times 10^9/L$ vs 63.9%, $p<0.001$). We found no evidence of difference between groups in bleeding events, rescue treatments or treatment side effects including infection. However, quality of life measures of physical function and fatigue were worse in the mycophenolate group.

CONCLUSIONS

Addition of mycophenolate to glucocorticoid for first line ITP treatment results in higher response rates and reduces the risk of refractory or relapsed ITP but with somewhat decreased quality of life.

(Funded by the NIHR, ClinicalTrials.gov number: NCT03156452).

Introduction

Immune thrombocytopenia (ITP) is rare with an incidence in adults of 2.9/100,000 person-years.¹ It is an autoimmune condition that may present with bleeding and bruising due to a low platelet count. Fatigue is also associated with disease activity and can be severe.^{2,3} In ITP, increased consumption and reduced production of platelets are due to both antibody and cell-mediated autoimmune attack on platelets and megakaryocytes involving dysregulated autoreactive T and B lymphocytes.⁴⁻⁷ ITP can be classified according to the duration of illness into newly diagnosed (<3 months), persistent (3-12 months) and chronic (>12 months).⁸ ITP may also be classified as either primary when it presents in isolation or secondary when ITP occurs in the context of an associated illness.⁸

First line ITP treatment for adults is with high dose glucocorticoids but this has several downsides.

Most patients suffer significant side effects including mood swings, difficulty sleeping, weight gain, high blood pressure, diabetes, gastric irritation, skin thinning and osteoporosis. A published survey of ITP patients reported 98% had at least one side effect and 38% stopped or reduced dosage due to intolerable side effects.⁹ Another problem is the heterogeneity of responses with approximately 20-30% having no response (refractory), and the majority of others relapsing at some point after glucocorticoid doses have been reduced or stopped with only about 20% remaining in long term remission with this approach.¹⁰⁻¹⁴ Patients in whom first line glucocorticoids fail remain at risk of bleeding/bruising until alternative therapies succeed and some may require hospital admission and expensive rescue therapies (e.g. IVIG).¹⁴

First line ITP treatment is unsatisfactory but remains 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 demonstrated. Therefore, high dose glucocorticoids continue to be recommended.^{12,14}

Mycophenolate (MMF) is a widely used second line agent for ITP in the UK and is less expensive than many alternative treatments. Although no randomized controlled trial data are published, evidence from retrospective data indicate that it is effective (response rates of 50-80%), although platelet response typically takes 4-6 weeks.^{10, 15-22} MMF has activity against both autoreactive T and B cells and has also shown efficacy in refractory ITP, including patients whose disease is glucocorticoid resistant, suggesting a complimentary mechanism of action.²⁰

The FLIGHT trial aimed to test the hypothesis that MMF combined with a glucocorticoid is a more effective first line ITP treatment pathway than a glucocorticoid alone.

Methods

Design

The FLIGHT trial is a multicenter, open label randomized controlled trial of first line treatment for ITP comparing MMF plus a glucocorticoid versus a glucocorticoid alone. The full trial methods have been previously published.²³

The FLIGHT trial received ethical approval from NRES Committee South West (IRAS number 225959) and is registered (EudraCT Number: 2017-001171-23. ClinicalTrials.gov number: NCT03156452).

Patients

Patients >16 years old were eligible for recruitment if they had a diagnosis of ITP (primary or secondary), a platelet count $<30 \times 10^9/L$ and a clinical need for first line treatment. Exclusion criteria were pregnancy, breastfeeding, HIV, Hepatitis B or C, Common Variable Immunodeficiency (CVID), contraindications to MMF or glucocorticoids, patients not capable of giving informed consent and patients unwilling to follow contraceptive advice if allocated to MMF. Because MMF increases the risk of miscarriage and birth defects, women of childbearing potential had to use two reliable forms of contraception simultaneously before starting MMF, during therapy and six weeks after stopping MMF (hormonal or barrier method of birth control; abstinence). Sexually active men with potentially child-bearing female partners were recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men. In addition, female partners of male patients treated with MMF were recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MMF. The eligibility criteria required that HIV and hepatitis serology testing had been done (along with immunoglobulins). Patients could be recruited pending results with a commitment to subsequently exclude patients if the HIV or hepatitis serology was positive or the patient had common variable immune deficiency. Patients were recruited and followed up in hematology departments of hospitals (secondary care) across the UK.

Trial Procedures

Patients who provided written informed consent were randomized to MMF with a glucocorticoid or a glucocorticoid alone in a 1:1 ratio using a secure web-based randomization system based at Cardiff Clinical Trials Unit. To ensure an even spread of patients across time, randomization was blocked using random block sizes of 6 and 8 to retain concealment.

Glucocorticoid dosing in the protocol followed international consensus recommendations and patients in both groups could receive either oral prednisolone or dexamethasone. Prednisolone dose was 1mg/kg for 4 days then 40mg daily for 2 weeks then 20 mg daily for 2 weeks then 10mg daily for 2 weeks then 5 mg daily for 2 weeks then 5mg alternate days for 2 weeks then stop. This dosing algorithm was followed regardless of platelet count although a more rapid taper was permitted for refractory patients and dose reduction was permitted for patients with side effects. Alternatively, patients could receive up to three dexamethasone pulses (for each pulse, 40mg daily for 4 days) with the number of pulses according to clinician discretion. Patients randomised to MMF commenced at 500mg twice daily (alongside a glucocorticoid) then increased to 750mg twice daily after 2 weeks if no side effects and 1g twice daily after another 2 weeks if no side effects (4 weeks after starting). This MMF dosing algorithm was followed regardless of platelet count. After 6 months of MMF therapy, all patients in complete response (platelet count $> 100 \times 10^9/L$) reduced the dose by 250mg each month, aiming to continue on the lowest dose that achieves a hemostatic (safe) platelet count ($>30 \times 10^9/L$) and to ensure that patients who have gone into a spontaneous remission do not continue to take the drug indefinitely.²³

Patients were followed up until the end of the trial and for a minimum of 12 months. Laboratory and clinical data were collected from routine appointments. Additional data and patient-reported outcome measures were recorded at diagnosis, 2, 4, 6, and 12 months using the following validated patient questionnaires:²⁴⁻²⁶ SF36v2-Quality of life; FACIT-Fatigue (version 4)-Fatigue; FACT-Th6 (version 4)-Patient concern for bleeding and ICECAP-A v2-Quality of life.

Outcomes

The FLIGHT trial primary outcome was time from randomization to treatment failure defined as a platelet count $<30 \times 10^9/L$ with the initiation of second line treatment. Secondary outcomes included medication side effects, bleeding events, need for rescue therapies, response rates (complete response: platelets $>100 \times 10^9/L$ and response: platelets $>30 \times 10^9/L$ and at least 2-fold increase from baseline)⁷ and patient related outcome measures.

Statistical methods

Patients excluded at primary or secondary screening (within 7 days of initial 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 trial. Length of follow-up time used in the analysis of treatment failure was from the date of randomization to either the date the trial closed, or the date the patient withdrew from the study or died, whichever was the sooner. In some cases, the patient withdrew from receiving questionnaires or the treatment allocation but continued to be followed up to allow the collection of the primary end point of treatment failure. In addition, patients were followed up past the point of treatment failure with quality-of-life questionnaires.

The sample size of 120 (60 per 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. This was calculated using the software PASS. The analysis of the primary outcome measure of treatment failure was carried out using Kaplan Meier plots and statistical significance using the log rank test. However, we were unable to produce median time to treatment failure statistics as less than 50% had reached the primary outcome in both treatment groups. Instead, we have reported hazard ratios for time to treatment failure in the MMF arm compared with the glucocorticoid only arm by using cox proportional hazards modelling. Hazard ratios were also computed controlling for whether ITP was primary or secondary as a confirmatory sensitivity analysis, as well as controlling for age over 65, sex and obesity due to observed differences in the groups following randomization. Adjustments to the significance level have not been made for the multiplicity of testing in this sensitivity analysis and so the possibility remains that the results in the sensitivity analyses are not reproducible.

Questionnaire data on quality of life was analyzed using area under the curve calculated using the trapezium rule (a method of calculating the area under the curve by breaking up the curve into segments or trapezoid shapes and adding the area of the shapes) for all those who completed both baseline and at least 2 further follow-up data points and using last observation carried forward for those who did not complete the final data points. Area under the curve was then analysed using

linear regression with normal error structure controlling for baseline and further controlling for age over 65, sex, obesity and whether primary or secondary ITP.

Author contributions

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

Results

Of the 123 patients recruited and randomized, three patients were excluded before receiving their allocated trial treatment due to the presence of exclusion factors at secondary screening (positive HIV test, diagnosis of cancer not ITP, and decision to opt for private medical care). The primary analysis therefore contained all 120 remaining subjects (Figure 1). One hundred and thirteen patients were included in the quality-of-life analysis with 7 patients omitted as 2 had not completed baseline questionnaires and 5 further subjects did not complete more than 1 follow-up time point.

Demographic and baseline variables including comorbidities are described in table 1. The overall mean age was 54 years (range 17-87), 54% male and mean pre-treatment baseline platelet count was $7 \times 10^9/L$. A proportion of elderly patients were recruited to the trial (27.5% were >70 years, 15.8% >75 years). Slight differences between the groups were noted in the proportions of patients 65+ years (MMF group 44.1% vs 31.2%), non-white ethnicity (MMF group 13.6% vs 3.3%), male sex (MMF group 47.5% vs 60.7%), obesity (MMF group 22% vs 8.2%) and secondary ITP (MMF group 5.1% vs 16.4%). The majority of patients in each group received prednisolone as the first line glucocorticoid, the others received dexamethasone (In the MMF group: 50 patients received prednisolone and 5 dexamethasone. In the glucocorticoid only group 50 patients received prednisolone and 10 received dexamethasone. Data are missing for glucocorticoid type in 4 in the MMF group and one in the glucocorticoid only group). Baseline results of quality-of-life questionnaires from patients who went on to complete questionnaires at a minimum of 2 follow up visits are presented in the supplementary appendix, table S1 (n=113).

Participants were recruited between 25 Oct 2017 and 15 Feb 2019 and were followed for a total of 181 life years (89 life years in the MMF group, 92 life years in the glucocorticoid only group). The follow up time used in the treatment failure analysis was truncated to two years and further truncated by the date of treatment failure where that was present, giving a median follow-up time of 1.30 years and 1.10 years in the MMF group and glucocorticoid only group, respectively.

Forty treatment failure events were recorded from randomization to the end of follow-up, 13 in the MMF treatment arm (22%) and 27 in the glucocorticoid only arm (44%), the Kaplan-Meier graph in figure 2 shows the two time-to-event curves. The hazard ratio, estimated from a Cox proportional hazards model, is 0.41, (95% CI 0.21 to 0.80, $p=0.008$ (p value also from Cox model)). In the subsample that omits those with secondary ITP, in line with the pre-existing statistical analysis plan, and controlling for age, sex and obesity which were observed to be different between the two groups, the (adjusted) hazard ratio is 0.44 (95% CI 0.22, to 0.86). Sensitivity analysis using entire sample controlling for age, sex, obesity and ITP (primary/secondary) gave aHR 0.40 (95% CI 0.20, 0.78).

Patients assigned to MMF were also more likely to respond to first line treatment (table 2), with 91.5% achieving platelets $>100 \times 10^9/L$ (vs 63.9% with glucocorticoid only) and 93.2% achieving platelets $>30 \times 10^9/L$ (vs 75.4%). Only 6.8% of patients assigned to MMF were refractory to treatment (vs 24.6% for glucocorticoid only). Response rates at 2 weeks were similar between the 2 groups.

Treatment side effects, bleeding episodes, and need for rescue therapy or hospital admission were similar between the groups of (table 2).

Patient reported outcomes data over follow up are shown in table 3. Controlling for baseline, only small differences were noted between the groups in FACT-Th6 (patients concern about bleeding), ICECAP (broad QoL measure) or SF36 mental health summary. However, patients assigned to MMF appeared to have worse fatigue (FACIT Fatigue) and SF36 physical health summary. Although, after adjusting for multiple testing none of these comparisons excludes the possibility of this being a chance finding.

Discussion

ITP is a rare autoimmune disease in which few randomized controlled trials have been conducted, particularly for commonly prescribed “older” generic treatments such as MMF, azathioprine, splenectomy, dapsone and danazol. Of the randomized trials done, the majority have focussed on patients later in the course of illness (chronic ITP) and often excluded elderly patients that make up a greater proportion of “real life” ITP patients. In addition, only the clinical trials assessing thrombopoietin-like agents (Romiplostim and Eltrombopag) for chronic ITP have systematically included assessment of patient reported outcomes.^{27,28}

Although high dose glucocorticoids continue to be the recommended first line treatment for ITP,^{12,14} side effects, heterogeneous responses and high relapse rates are a clinical challenge, with only approximately 20% of patients remaining in long term remission with this approach. We present here a randomized trial testing MMF plus glucocorticoids in ITP. These data demonstrate that, compared to a glucocorticoid alone, addition of MMF approximately halved the risk of refractory or relapsed ITP. This significant reduction in treatment failure with MMF was in spite of very favorable responses in the glucocorticoid only arm, with 56% not requiring 2nd line treatment over a mean of 18 months follow up, which is higher than previously reported in most studies. For example, one randomized trial demonstrated sustained response at 6 months of 41% with prednisolone and 40% with dexamethasone.²⁹ The international consensus guideline reports 23% sustained response to a glucocorticoid at 39 months and long term follow up data suggest only a small proportion of adult patients remain in remission without further therapy.^{30,31} The addition of MMF plus a glucocorticoid also resulted in a higher proportion of patients responding to first line therapy (table 2). Responses at 2 weeks were very similar between the groups. Rates of bleeding were similar in both groups and relatively infrequent, with no fatal bleeds (table 2). No patient went on to have a splenectomy during follow up, consistent with the declining use of this treatment approach, particularly early in the course of ITP.³²

When we evaluated the treatment side effects experienced by patients during follow up (table 2b), those related to glucocorticoids are most common including mood change, difficulty sleeping and weight gain. In contrast, the side effects expected with MMF were comparable between the 2 groups, with similar numbers of infections (n=14 in each group), GI side effects and no patient receiving MMF developed neutropenia (neutropenia occurred in 4 patients receiving a

glucocorticoid only). These results compare favorably with a previous trial for first line ITP treatment assessing rituximab combined with dexamethasone (up to 6 cycles) versus dexamethasone alone. Although addition of rituximab increased sustained responses (platelets $>50 \times 10^9/L$) at 6 months (58% vs 37%, $p=0.02$), the incidence of grade 3-4 adverse events were higher in the group assigned to rituximab ($p=0.04$).³³ Because of the adverse event rate, the cost, and the lack of predictability of responses, recent guidelines have not advocated early rituximab treatment.^{12,14}

Previous studies have demonstrated that chronic ITP is associated with fatigue and impaired quality of life, which can be greater concerns from the patient's perspective than platelet counts.^{3,34,35} The FLIGHT trial incorporated the use of validated questionnaires to assess overall quality of life (SF36, ICECAP), patient concern about bleeding (FACT Th6) and fatigue (FACIT Fatigue). Nearly all patients managed to complete these questionnaires at baseline and at least 2 follow up points ($n=113$ of 120, 94.2%). Over 12 months follow up, patients who received MMF had lower levels of patient reported physical health (SF36) and greater fatigue (FACIT Fatigue). We found no evidence of differences between groups in bleeding concern or mental health. These results are important as they demonstrate that disease response and patient experience may not necessarily correlate. This is an extremely important methodological consideration for future trials in ITP, highlighting the need to focus on the broader context of patient health rather than just the disease. It is unclear why these aspects of quality of life appeared less favorable for patients receiving MMF. The quality-of-life differences do not seem to be explained by specific MMF drug side effects such as infection or diarrhea. Other possible reasons include the longer duration of ITP-directed treatment with the more successful MMF regimen with potential psychological impact related to treatment duration. The open label design of the FLIGHT trial is another potential limitation.

In summary, compared to a glucocorticoid alone, MMF combined with a glucocorticoid was an effective first line treatment option, increasing response rates and reducing the risk of treatment failure with durable responses over an average of 18 months follow up. As over half of patients receiving a glucocorticoid alone had not required second line treatment during follow up and MMF use may be associated with more fatigue, further research is needed to clarify the role of MMF in ITP treatment pathways. For example, MMF could be used in a subset of patients expected to fail a glucocorticoid alone based on laboratory or clinical features.³⁶ Early use of MMF 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 severe bleeding or

additional bleeding risk factors such as the presence of anticoagulation or antiplatelet therapy. A systematic assessment of MMF plus a glucocorticoid as second line therapy after demonstrated resistance to a glucocorticoid alone should also be undertaken.

[Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.](#)

Funding

This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number **PB-PG-0815-20016**). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Other non-financial support

We are grateful for the support received for the FLIGHT trial from the ITP support association (patient and public group), the UK ITP forum, and the HaemSTARS.

Formatted: Space After: 5 pt, Don't add space between paragraphs of the same style, Font Alignment: Baseline, Pattern: Clear (White)

References

1. Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailer L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. *Blood* 2014;124:3308-15.
2. Hill QA, Newland AC. Fatigue in immune thrombocytopenia. *Br J Haematol* 2015;170:141-9.
3. Newton JL, Reese JA, Watson SI, Vesely SK, Bolton-Maggs PHB, George JN, Terrell DR. Fatigue in adult patients with primary immune thrombocytopenia. *Eur J Haematol* 2011;86(5):420-9.
4. McKenzie CG, Guo L, Freedman J, Semple JW. Cellular immune dysfunction in immune thrombocytopenia (ITP). *Br J Haematol* 2013;163:10-23.
5. Iraqi M, Perdomo J, Yan F, Choi PY, Chong BH. Immune thrombocytopenia: antiplatelet autoantibodies inhibit proplatelet formation by megakaryocytes and impair platelet production in vitro. *Haematologica* 2015;100:623-32.
6. Ji X, Zhang L, Peng J, Hou M. T cell immune abnormalities in immune thrombocytopenia. *Journal of hematology & oncology* 2014;7:72.
7. Audia S, Rossato M, Santegoets K, et al. Splenic TFH expansion participates in B-cell differentiation and antiplatelet-antibody production during immune thrombocytopenia. *Blood* 2014;124:2858-66.
8. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009;113:2386-93.
9. Brown TM, Horblyuk RV, Grotzinger KM, Matzdorff AC, Pashos CL. Patient-reported treatment burden of chronic immune thrombocytopenia therapies. *BMC blood disorders* 2012;12:2.
10. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168-86.
11. Neunert CE. Management of newly diagnosed immune thrombocytopenia: can we change outcomes? *Hematology Am Soc Hematol Educ Program* 2017;2017:400-5.
12. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood advances* 2019;3:3829-66.
13. Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190-207.
14. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood advances* 2019;3:3780-817.
15. Miano M, Ramenghi U, Russo G, et al. Mycophenolate mofetil for the treatment of children with immune thrombocytopenia and Evans syndrome. A retrospective data review from the Italian association of paediatric haematology/oncology. *Br J Haematol* 2016;175:490-5.
16. Taylor A, Neave L, Solanki S, et al. Mycophenolate mofetil therapy for severe immune thrombocytopenia. *Br J Haematol* 2015;171:625-30.
17. Kotb R, Pinganaud C, Trichet C, et al. Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: a single center preliminary study. *Eur J Haematol* 2005;75:60-4.
18. Provan D, Moss AJ, Newland AC, Bussel JB. Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol* 2006;81:19-25.
19. Hou M, Peng J, Shi Y, et al. Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003;70:353-7.
20. Colović M, Suvajdzic N, Colović N, Tomin D, Vidović A, Palibrk V. Mycophenolate mofetil therapy for chronic immune thrombocytopenic purpura resistant to steroids, immunosuppressants, and/or splenectomy in adults. *Platelets* 2011;22:153-6.
21. Zhang WG, Ji L, Cao XM, et al. Mycophenolate mofetil as a treatment for refractory idiopathic thrombocytopenic purpura. *Acta pharmacologica Sinica* 2005;26:598-602.

22. Howard J, Hoffbrand AV, Prentice HG, Mehta A. Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. *Br J Haematol* 2002;117:712-5.
23. Pell J, Greenwood R, Ingram J, et al. Trial protocol: a multicentre randomised trial of first-line treatment pathways for newly diagnosed immune thrombocytopenia: standard steroid treatment versus combined steroid and mycophenolate. The FLIGHT trial. *BMJ open* 2018;8:e024427.
24. Signorovitch J, Brainsky A, Grotzinger KM. Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011;20:1737-44.
25. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *Journal of epidemiology and community health* 1999;53:46-50.
26. Al-Janabi H, Flynn TN, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012;21:167-76.
27. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med* 2010;363:1889-99.
28. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011;377:393-402.
29. Wei Y, Ji XB, Wang YW, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. *Blood* 2016;127:296-302; quiz 70.
30. Stasi R, Stipa E, Masi M, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. *Am J Med* 1995;98(5):436-42.
31. Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric Trial of the Cooperative Latin American group on Hemostasis and Thrombosis. *Blood* 1984;64(6):1179-83.
32. Doobaree IU, Newland A, McDonald V, et al. Primary immune thrombocytopenia (ITP) treated with romiplostim in routine clinical practice: retrospective study from the United Kingdom ITP Registry. *Eur J Haematol* 2019;102:416-23.
33. Gudbrandsdottir S, Birgens HS, Frederiksen H, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood* 2013;121:1976-81.
34. Kirsch M, Klaassen RJ, De Geest S, Matzdorff A, Ionova T, Dobbels F. Understanding the importance of using patient-reported outcome measures in patients with immune thrombocytopenia. *Seminars in hematology* 2013;50 Suppl 1:S39-42.
35. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) World Impact Survey (iWISH): Patient and physician perceptions of diagnosis, signs and symptoms, and treatment. *Am J Hematol* 2020.
36. Stimpson ML, Lait PJP, Schewitz-Bowers LP, et al. IL-10 and IL-17 expression by CD4(+) T cells is altered in corticosteroid refractory immune thrombocytopenia (ITP). *J Thromb Haemost* 2020;18:2712-20.

FIGURE LEGENDS

Figure 1. CONSORT Flow Diagram for the Flight trial

Figure 2. Kaplan Meier graph showing the proportion of patients without treatment failure

Table 1: Patient demographics and baseline values

	MMF and Glucocorticoid N=59	Glucocorticoid only N=61
Mean age, years (range)	56.9 (18 – 86)	53.1 (17 – 87)
Aged <18, n= (%)	0 (0%)	1 (1.6%)
Aged 18 -64, n= (%)	33 (59.5%)	41 (67.2%)
Aged 65+, n= (%)	26 (44.1%)	19 (31.2%)
Male:Female (% male)	28:31 (47.5%)	37:24 (60.7%)
Ethnic origin:		
White, n= (%)	51 (86.4%)	59 (96.7%)
Asian (Indian), n= (%)	0 (0%)	1 (1.6%)
Asian (other), n= (%)	2 (3.4%)	1 (1.6%)
Black (African), n= (%)	3 (5.1%)	0 (0%)
Other n= (%)	3 (5.1%)	0 (0%)
Ethnic origin:	-	-
White, n= (%)	51 (86.4%)	59 (96.7%)
Asian (Indian), n= (%)	0 (0%)	1 (1.6%)
Asian (other), n= (%)	2 (3.4%)	1 (1.6%)
Black (African), n= (%)	3 (5.1%)	0 (0%)
Other n= (%)	3 (5.1%)	0 (0%)
Secondary ITP, n= (%)	3 (5.1%)	10 (16.4%)
Mean Systolic, mmHg (SD)	133.0 (19.4)	131.7 (19.2)
Mean diastolic, mmHg (SD)	78.0 (11.7)	76.7 (10.3)
Mean BMI, kg/m ² (SD)	29.7 (6.4)	27.8 (5.8)
Hb, g/L (SD)	134.9 (19.1)	140.3 (18.0)
Platelet count, x10 ⁹ /L (SD)	7.9 (7.6)	6.5 (6.7)
Total White Blood count, x10 ⁹ /L (SD)	7.2 (3.3)	7.4 (2.3)
Neutrophils, x10 ⁹ /L (SD)	4.6 (2.2)	4.8 (2.4)
MCV, fL (SD)	85.9 (13.3)	87.5 (9.1))
Comorbidities at baseline:	-	-
Arrhythmia, n= (%)	3 (5.1%)	4 (6.6%)
Cardiac, n= (%)	2 (3.4%)	3 (4.9%)
Heart valve disease, n= (%)	2 (3.4%)	4 (6.6%)
Inflammatory bowel disease, n= (%)	2 (3.4%)	1 (1.6%)
Diabetes, n= (%)	6 (10.2%)	8 (13.1%)
Cerebrovascular disease, n= (%)	3 (5.1%)	2 (3.3%)
Psychiatric disturbance, n= (%)	6 (10.2%)	3 (4.9%)
Obesity, n= (%)	13 (22.0%)	5 (8.2%)
Active Infection	2 (3.4%)	2 (3.3%)
Rheumatologic, n= (%)	5 (8.5%)	6 (9.8%)
Peptic ulcer, n= (%)	0	1 (1.6%)
Moderate/severe renal, n= (%)	2 (3.4%)	1 (1.6%)
Moderate pulmonary, n= (%)	0	1 (1.6%)

Formatted Table

Formatted Table

Severe pulmonary, n= (%)	<u>0</u>	<u>1 (1.6%)</u>
Prior solid tumour, n= (%)	<u>7 (11.9%)</u>	<u>6 (9.8%)</u>
Hepatic, mild, n= (%)	<u>2 (3.4%)</u>	<u>1 (1.6%)</u>
Moderate/severe hepatic, n= (%)	<u>3 (5.1%)</u>	<u>1 (1.6%)</u>
Comorbidities at baseline:		
Arrhythmia, n= (%)	<u>3 (5.1%)</u>	<u>4 (6.6%)</u>
Cardiac, n= (%)	<u>2 (3.4%)</u>	<u>3 (4.9%)</u>
Heart valve disease, n= (%)	<u>2 (3.4%)</u>	<u>4 (6.6%)</u>
Inflammatory bowel disease, n= (%)	<u>2 (3.4%)</u>	<u>1 (1.6%)</u>
Diabetes, n= (%)	<u>6 (10.2%)</u>	<u>8 (13.1%)</u>
Cerebrovascular disease, n= (%)	<u>3 (5.1%)</u>	<u>2 (3.3%)</u>
Psychiatric disturbance, n= (%)	<u>6 (10.2%)</u>	<u>3 (4.9%)</u>
Obesity, n= (%)	<u>13 (22.0%)</u>	<u>5 (8.2%)</u>
Active Infection	<u>2 (3.4%)</u>	<u>2 (3.3%)</u>
Rheumatologic, n= (%)	<u>5 (8.5%)</u>	<u>6 (9.8%)</u>
Peptic ulcer, n= (%)	<u>0</u>	<u>1 (1.6%)</u>
Moderate/severe renal, n= (%)	<u>2 (3.4%)</u>	<u>1 (1.6%)</u>
Moderate/severe renal, n= (%)	<u>0</u>	<u>1 (1.6%)</u>
Moderate pulmonary, n= (%)	<u>0</u>	<u>1 (1.6%)</u>
Severe pulmonary, n= (%)	<u>0</u>	<u>1 (1.6%)</u>
Prior solid tumour, n= (%)	<u>7 (11.9%)</u>	<u>6 (9.8%)</u>
Hepatic, mild, n= (%)	<u>2 (3.4%)</u>	<u>1 (1.6%)</u>
Moderate/severe hepatic, n= (%)	<u>3 (5.1%)</u>	<u>1 (1.6%)</u>

Table 2. Platelet count responses to first line ITP treatment, treatment side effects, bleeding episodes and rescue treatment. Side effects, bleeding episodes and rescue treatments were recorded on the clinical report forms at 2, 4, 6 and 12 months and presence recorded at any one of those time points is presented.

Variable	MMF and Glucocorticoid N=59	Glucocorticoid only N=61	Relative risk ratio with 95% CI
Platelets >30 x10 ⁹ /L* within 2 weeks of randomization, n= (%)	30 (50.9%)	29 (47.5%)	1.06 [0.74, 1.54]
Platelets >100 x10 ⁹ /L within 2 weeks of randomization, n= (%)	21 (35.6%)	21 (34.4%)	1.04 [0.63, 1.68]
Platelets >30 x10 ⁹ /L* response to first line treatment, n= (%)	55 (93.2%)	46 (75.4%)	1.23 [1.05, 1.45]
Platelets >100 x10 ⁹ /L response to first line treatment, n= (%)	54 (91.5%)	39 (63.9%)	1.43 [1.17, 1.76]
Patients refractory to first line treatment	4 (6.8%)	15 (24.6%)	
Median time to platelets >30 x10 ⁹ /L* with interquartile range (treatment failures censored if failed before platelets >30 x10 ⁹ /L)	14 days [6, 57]	18 days [5, 55]	^
Median time to Platelets >100 x10 ⁹ /L with interquartile range (treatment failures censored if failed before platelets >100 x10 ⁹ /L)	38 days [6, 65]	46 days [6, 58]	^
Presence of treatment side effects.			
Infection, n= (%)	14 (23.7%)	14 (23.0%)	
Weight gain, n= (%)	17 (28.8%)	21 (34.4%)	
Neutropenia, n= (%)	0 (0%)	4 (6.6%)	
Difficulty sleeping, n= (%)	12 (35.6%)	17 (27.9%)	
Mood change/Psychiatric disorders, n= (%)	18 (30.5%)	21 (34.4%)	
Steroid induced diabetes, n= (%)	1 (1.7%)	2 (3.3%)	
Steroid induced hypertension, n= (%)	2 (3.39%)	2 (3.3%)	
Diarrhea or other Gastrointestinal symptom, n= (%)	20 (33.9%)	15 (24.6%)	
Bleeding episodes and rescue treatment			
Bleeding episodes, n (%)	14 (23.7%)	15 (24.6%)	
Site of bleeding: cutaneous, n= (%)	5 (4.5%)	1 (1.6%)	
Site of bleeding: gastrointestinal, n= (%)	2 (3.4%)	4 (6.6%)	
Site of bleeding: epistaxis, n= (%)	1 (1.7%)	3 (4.9%)	
Site of bleeding: urinary, n= (%)	1 (1.7%)	0 (0%)	
Site of bleeding: other mucosal, n= (%)	2 (3.4)	2 (3.3)	
Site of bleeding: intracranial, n= (%)	1 (1.7%)	0 (0%)	
Number of patients given a red blood cell transfusion, n= (%)	3 (5.1%)	1 (1.6%)	
Number of patients given a platelet transfusion, n= (%)	2 (3.4%)	0 (0%)	
Number of patients given Tranexamic acid, n= (%)	5 (8.5%)	6 (9.8%)	
Number of patients given IVIG, n= (%)	8 (13.6%)	10 (16.4%)	
Number of patients admitted to Hospital, n= (%)	11 (18.6%)	9 (14.8%)	
Number of patients requiring splenectomy, n= (%)	0 (0%)	0 (0%)	

* and 2 fold higher than baseline, ^data cannot be compared using statistical significance due to bias caused by excluding those who started second line therapy before going into remission as they don't have a median time we can use in this analysis although their time would have been longer.

Table 3. Quality of life. Results are shown as mean difference in area under the curve over 12 months follow up with 95% confidence intervals. Analysis was controlled for whether the diagnosis was primary or secondary ITP, age and sex. Confidence intervals are not adjusted for multiple reporting and so results may not be reproducible.

Quality of life variable n=MMF: n= Glucocorticoid	Mean difference in area under the curve at 12 months follow up with 95% CI. Controlling for baseline, secondary ITP, over 65 years of age, obesity and sex
SF36: a negative difference means that the MMF arm has lower quality of life	
Physical functioning 56:54	-5.9 [-11.8, -0.1]
Role physical 55:54	-8.7 [-16.9, -0.5]
Bodily Pain 56:53	-6.6 [-13.5, 0.3]
General Health 57:54	-5.1 [-11.0, 0.8]
Vitality 55:53	-4.1 [-10.4, 2.3]
Social functioning 57:53	-7.0 [-14.4, 0.5]
Role emotional 54:54	-4.6 [-12.7, 3.6]
Mental 56:53	-2.2 [-7.3, 3.0]
Physical Health Summary score 54:53	-3.0 [-5.5, -0.6]
Mental health summary score 54:53	-1.2 [-4.0, 1.7]
A negative difference for FACIT fatigue means the MMF group have more fatigue	
FACIT fatigue 57:54	-3.3 [-6.6, -0.04]
A negative difference for FACT Th6 means the MMF group are more concerned about bleeding risk	
FACT Th6 56:55	-0.4 [-1.8, 1.1]
A negative difference for ICECAP means the MMF group have worse capability score	
ICECAP utility 53:50	-0.017 [-0.060, 0.027]
A negative difference for SF6D means the MMF group have worse overall quality of life score	
SF6D	-0.029 [-0.067, 0.0089]