A real-world study of immune thrombocytopenia management during the COVID-19 pandemic in the UK

Alexandros Rampotas,[1,2] (iD)
Edmund Watson,[1] Kieran Burton,[1]
Quentin A. Hill[3] (iD) and
Sue Pavord[1] (iD)

[1]Oxford University Hospitals NHS Foundation Trust, [2]Oxford University Graduate Academic School, Oxford, and [3]Leeds Teaching Hospitals NHS Trust, Leeds, UK

Summary

The COVID-19 pandemic has created many challenges in the management of immune thrombocytopenic purpura (ITP). The recommendation for avoidance of steroids by WHO led to the off-licence use, supported by NHS England, of thrombopoietin mimetics (TPO-RA) for newly diagnosed or relapsed ITP. This is a real-world prospective study which investigated the treatment patterns and outcomes in this setting. Twenty-four hospitals across the UK submitted 343 cases. Corticosteroids remain the mainstay of ITP treatment, but TPO-RAs were more effective. Incidental COVID-19 infection was identified in a significant number of patients (9·5%), while 14 cases were thought to be secondary to COVID-19 vaccination.

Keywords: immune thrombocytopenia, COVID, coronavirus disease 2019, thrombocytopenia, platelets.

Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus has introduced new challenges for the management of patients with immune thrombocytopenia (ITP). Corticosteroids have been the mainstay of first-line treatment of ITP; however, the WHO has advised against use of corticosteroids, where possible, during this time, for concern they may increase risk of COVID-19 infection[1] and disease severity.[2] Steroids and immunosuppressants may also potentially reduce the immune response to COVID-19 vaccination.[3] Recent consensus guidance in the UK has recommended consideration of thrombopoietin receptor agonists (TPO-RA) as first-line treatment in patients presenting with new or relapsed ITP during this period[4] and National Health Service (NHS)-England has supported this off-label use in an interim rapid policy. ('C1258-Interim-Clinical-Comm-Policy-Thrombopoietin-Receptor-Agonists-as-First-Line-Therapy-Relapsed-v3. Pdf' n.d.). This study evaluated the real-life management of adults with new or relapsed ITP during the pandemic, auditing against the consensus guidance[4] and evaluating the efficacy of different first line treatments.

Methods

This was a national prospective observational study involving 24 NHS hospital trusts (21 tertiary centres and three district hospitals) across the UK. Data collectors submitted the cases into an online form with prespecified questions. Eligibility criteria included any patient over 18 years who was diagnosed with new or relapsed ITP during the study period (01/03/2020–01/03/2021).

Treatment was considered successful if there was no need for a further treatment line within 28 days. Treatment responses were also assessed by achieving a platelet count of $>30 \times 10^9$/l on day 7, 14 and 28. All patient data were anonymised at source and treated according to the principles of the Declaration of Helsinki and the UK Data Protection Act (1998). Each participating centre obtained a local service evaluation or audit approval.

Results

Of 343 submitted cases, 335 were eligible for inclusion in the analysis and eight were excluded for age <18 years. Table SI presents the baseline and disease characteristics of the cohort. The median age was 57 (range 18–98) and 48·1% were male. In 76 (22·3%) cases the ITP was secondary; most commonly autoimmune and connective tissue disorders (25; 32·9%), malignancy (17; 22·4%) and COVID vaccination (14; 18·4%) (full details in Table SIII). Among them, 213 (63·6%) were new diagnoses and 122 (36·4%) were relapses. Of relapses, 50 (41%) were on maintenance therapy at the time of relapse, most with a TPO-RA (29/44). The median platelet count at diagnosis was 7 (range 0–71) and treatment was commenced in 318 (94·9%) of the total cases.

Table I. Outcomes of patients who tested positive for COVID-19 during ITP diagnosis.

COVID-19	Overall (n = 343) (percent or range, IQR)	On maintenance therapy§ (n = 50) (percent or range, IQR)
Positive COVID-19 test	23/343 (6·7%)	4/50 (8%)
Day of COVID-19 symptoms when ITP was diagnosed	12·5 (−2–60, 2·75–26·25)	30 (14–60, 14–60)
Inpatient stay	13/23 (56·5%)	4/4 (100%)
Intubation for ventilation	5/23 (21·7%)	2/4 (50%)
Outpatient management	9/23 (39·1%)	0 (0%)
Corticosteroid treatment for ITP‡	15/23 (65·2%)	1/4 (25%)
Weaning started in <15 days*	10/12 (83·3%)	4/4 (100%)
Post COVID-19 vaccination	14/76 (18·4%)	0/3 (100%)
Days post COVID-19 vaccination†	24 (2–35, 13–28)	

IQR, interquartile range; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.

*Three missing data.

†Two missing data; 4/23 patients were on maintenance therapy.

‡All started with doses higher than 20 mg daily.

§All four patients on maintenance therapy were on MMF at the time of diagnosis, with one also receiving TPO-RA.

Of 243 patients who had a COVID-19 test at diagnosis, 23 tested positive (9·5%; Table I), 23/335 (6·9%) overall. The median time that ITP was diagnosed after the onset of COVID-19 symptoms was 12·5 days (range −2 to 60). Thirteen of the 23 COVID-19-positive patients required inpatient stay with five intubated for ventilatory support. Four of the 23 patients were on maintenance ITP therapy when diagnosed with COVID-19 infection and relapsed ITP. All four of these were on mycophenolate (MMF) with one also receiving TPO-RA and all four required inpatient stay with two needing intubation for ventilation support. 14 cases were secondary to COVID-19 vaccination, presenting at median 24 days (range 2–35) post vaccination.

Table SI divides the baseline and disease characteristics according to the treatment used. The largest group is those who received corticosteroid treatment (189/318), while there is a comparable split between TPO-RA (47), intravenous immunoglobulin (IVIG; 51) and other treatments (31). Median age was similar across all groups. There were far less secondary ITP cases in the group who received TPO-RA (6·4%) compared to those receiving corticosteroids (26·5%) and IVIG (60%). Corticosteroids and other treatments were mostly used in new diagnoses (76·2% and 71%), while TPO-RA was mainly used for relapsed disease (80·1%).

The main indication for starting treatment was the low platelet count (46·5%), while there were bleeding symptoms or risk of bleeding in 42·5% of the cases. 8·5% had to start treatment to bring their platelets above 50×10^9/l to allow anticoagulation. Table SII presents the indications and rationale for choice of treatment. The main determinants for choice of treatment were clinical experience (44·1%), the UK guidance on managing ITP during the COVID-19 pandemic (30·6%) and past response to treatment (11·8%).

Of 318 treated patients, treatment response was evaluable in 307 (Table II) with a median follow-up of 17 weeks. Here, 166 (54·1%) were successful with first-line treatment; this was highest in the TPO-RA group (38/46; 82·6%) compared to the corticosteroid group (92/181; 50·8%) and IVIG (17/51; 32·7%). When IVIG and steroids were used together as first-line treatment, success rate was 10/16 (62·5%). Other treatment strategies achieved 69·2% success rate (9/13). Across all treatment groups, a platelet count $>30 \times 10^9$/l was achieved after 28 days in >90% of the cases. In 45·9% of the cases this had required second-line treatment, 19·7% third-line and 6·8% fourth-line. A platelet count of $>100 \times 10^9$/l was achieved in 60–75% across all groups except for IVIG plus steroids where it was achieved in 87·5%. Bleeding complications across all treatment groups at diagnosis were observed in 45·4% of the cases with 4·4% having a thrombotic complication. Thrombosis occurred most in patients receiving steroids (11/189; 5·8%) as induction treatment, compared with TPO-RA (1/47; 2·1%), IVIG (1/51; 2·0%) and no treatment (1/31; 3·2%). Only one patient with thrombosis had concurrent COVID-19 infection.

Second- and third-line treatment strategies used in the corticosteroid group after treatment failure are shown in Figure S1. When TPO-RA were used as second line, there was no need for third-line treatment in 23/30 cases (76·1%).

Of 335 cases, 251 (74·9%) received corticosteroid treatment during the management of their ITP episode; 212/335 (63·3%) received it as single first-line therapy or in combination with other treatments. The weaning of steroids started within seven days in 99/251 (39·4%) cases, within 8 to 14 days in 74/251 (29·5%) cases and after more than 15 days in 49/251 (19·5%) cases. There were no weaning data in 29/251 (11·6%) cases. Treatment responses were similar regardless of the modality or dose of steroids used.

Discussion

This is the first nationwide study on the management of ITP showing real-time experience. That our cohort was

Table II. Outcomes of ITP treatments.

Induction treatment used	Treatment success (no 2nd line treatment)	2nd line treatment used	3rd line treatment used	4th line treatment used	Tranexamic acid used	Platelets >100 x10⁹/l achieved	Platelet Response (Platelets >30 x10⁹/l)****					Bleeding complications	Thrombotic complications^
							Overall platelet response	Achieved in 0–7 days	Achieved in 8–14 days	Achieved in ≥15 days	Not achieved		
Overall (n = 318)	166/307 (54·1%)	141/307 (45·9%)	59/300 (19·7%)	20/295 (6·8%)	116/318 (36·5%)	211/293 (72%)	272/293 (92·8%)	167/293 (57%)	52/293 (17·7%)	53/293 (18·1%)	21/293 (7·2%)	143/318 (45%)	14/318 (4·4%)
Steroids (n = 189*)	92/181 (50·8%)	89/181 (49·2%)	37/176 (21%)	33/172 (19·2%)	74/189 (39·2%)	128/172 (74·4%)	165/172 (96%)	106/172 (61·6%)	30/172 (17·4%)	29/172 (16·9%)	7172 (4·1%)	86/189 (45·5%)	11/189 (5·8%)
Prednisolone (n = 160)	80/152 (52·6%)	72/152 (47·4%)	28/150 (18·7%)	7/148 (4·7%)	58/152 (38·2%)	110/147 (74·8%)	142/147 (96·6%)	87/147 (59·2%)	26/147 (17·7%)	29/147 (19·7%)	5/147 (3·4%)	74/160 (46·3%)	10/160 (6·3%)
dexamethasone (n = 29)	12/29 (41·4%)	17/29 (58·6%)	9/26 (34·6%)	3/24 (12·5%)	16/29 (55·2%)	18/25 (72%)	23/25 (92%)	19/25 (76%)	4/25 (16%)	0 (0%)	2/25 (8%)	12/29 (41·4%)	1/29 (3·4%)
TPO-RA – all cases (n = 47**)	38/46 (82·6%)	8/46 (17·4%)	5/46 (10·9%)	3/46 (6·5%)	13/47 (27·7%)	29/47 (61·7%)	41/45 (91·1%)	17/45 (37·8%)	9/45 (20%)	15/45 (33·3%)	4/45 (8·9%)	16/47 (34%)	1/47 (2·1%)
TPO-RA – new diagnosis (n = 9)	6/8 (75%)	2/8 (25%)	1/8 (12·5%)	0 (0%)	1/9 (11%)	5/9 (55·6%)	7/8 (87·5%)	4/8 (50%)	2/8 (25%)	1/8 (12·5%)	1/8 (12·5%)	1/9 (11·1%)	1/9 (11·1%)
IVIG (n = 51)	17/51 (32·7%)	34/51 (66·7%)	13/49 (26·5%)	4/48 (8·3%)	19/51 (37·3%)	32/47 (68·1%)	39/47 (83%)	25/47 (53·2%)	9/47 (19·1%)	5/47 (10·6%)	8/47 (17%)	25/51 (49%)	1/51 (2%)
Steroids plus IVIG (n = 16)	10/16 (62·5%)	6/16 (37·5%)	2/16 (12·5%)	2/16 (12·5%)	3/16 (18·6%)	14/16 (87·5%)	15/16 (93·6%)	12/16 (75%)	1/16 (6·3%)	2/16 (12·5%)	1/16 (6·3%)	8/16 (50%)	0/16 (0%)
Other treatment strategies (n = 17+***)	9/13 (69·2%)	4/13 (30·8%)	2/13 (15·4%)	1/13 (7·7%)	7/15 (46·7%)	10/13 (76·9%)	12/13 (92·3%)	7/13 (53·8%)	3/13 (23·1%)	2/13 (15·4%)	1/13 (7·7%)	8/15 (53·3%)	0/15 (0%)

+Other strategies include steroids plus TPO-RA (4), platelet transfusion (2), rituximab (2), azathioprine (1), MMF (1), MMF plus rituximab (1), steroids plus azathioprine (1), steroids plus IVIG plus rituximab (1), tranexamic acid (1).

*Eight missing data.

**One missing data.

***Four missing data.

****25 missing data.

^There were seven venous thromboses (three deep vein thromboses, four pulmonary embolisms, one portal vein thrombosis and on sinus venous thrombosis) and five arterial (three cerebrovascular events and two myocardial infarctions).

representative of the general ITP population is supported by a median age and the proportion of secondary cases similar to those in a previous French national study[5]

The rate of COVID-19 infection in this cohort was considerably higher than the community prevalence in England during the audit period, which ranged between 0·5 and 1·5% (*Office for National Statistics*). This supports an association between COVID-19 and ITP, as previously postulated.[6,7] More than half of these patients required inpatient stay and more than a fifth ventilation support. Of note is that all four patients on immunosuppressants as ITP maintenance therapy developed severe COVID-19 infection. COVID-19 vaccination was a common cause of secondary ITP despite vaccine only being available in the last three study months. A recent Scottish study estimated the incidence of vaccine-induced ITP following Oxford–AstraZeneca COVID-19 vaccine to be 1·13 per 100 000 doses.[8]

Our data indicate that despite concerns during the COVID-19 pandemic, corticosteroids remain the cornerstone of ITP treatment with 74·9% of all patients being exposed to them at some point in their treatment course. The success rate of 50·8% in newly diagnosed patients is comparable with published historical data and although numbers are small, it appears to be similar regardless of the type of steroids used. Low-dose corticosteroids (prednisolone 20 mg), appear equally effective as higher doses. Although there was generally good compliance with the consensus guidelines with regards to weaning off steroids, 19·5% remained on the maximum corticosteroid dose for more than 15 days.

This study also highlights the high efficacy of TPO-RAs when used as first-line therapy and as additional therapy, in keeping with studies using TPO-RAs in the chronic/relapsed setting.[9,10] Interestingly, the rate of thrombosis was lower in those on TPO-RAs than for those on steroids or on no treatment, with no difference in patient characteristics of these groups. Previous studies have shown thrombotic risk with steroids[11–13] and with ITP alone.[14,15]

Lack of need for second-line therapy was used as an outcome measure, in keeping with the real-life setting of this study. This outcome measure may have penalised the group which had IVIG alone as first-line treatment. Time to achieve a platelet count of over 30 x10^9/l is reported, which may have followed one or more lines of treatment. The advantages of a real-world study are reduced by potential biases; we minimised these by the prospective design of the study and use of a predefined collection form, and focussing our analysis on objective outcomes that are less prone to interpretation biases from data collectors.

This real-world prospective study on ITP management during the COVID-19 pandemic highlights the benefit of a collaborative approach using established professional networks to collect a representative and timely snapshot of clinical practice nationally. TPO-RA can be a safe and effective treatment choice for the management of newly diagnosed or relapsed ITP. Efficacy of corticosteroids appears to be inferior to TPO-RA, while poor weaning strategies mean that long-term steroid toxicity can adversely affect patients with ITP. Clinical trials are urgently needed to confirm the benefits of TPO-RA as first-line agents for the management of ITP and in the meantime, our study has supported the value of these as first-line therapy during the COVID-19 pandemic where steroids may be more problematic.

Conflicts of interest

The authors disclose no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Outcomes of patients who were treated with corticosteroids as first line treatment.

Fig S2. Cases of immune thrombocytopenia during the COVID pandemic.

Table SI. Baseline and disease characteristics.

Table SII. Indications for treatment.

Table SIII. Secondary immune thrombocytopenia diagnoses.

References

1. Santos CS, Férnandez XC, Moriano Morales C, Álvarez ED, Álvarez Castro C, López Robles A, et al. Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe? *RMD Open*. 2021;7:e001439.
2. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2020;79:859–66.
3. Nace DA, Kip KE, Mellors JW, Peck Palmer OM, Shurin MR, Mulvey K, et al. Antibody responses after mRNA-based COVID-19 vaccination in

residential older adults: implications for reopening. *J Am Med Dir Assoc.* 2021;**22**:1593–8.

4. Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffan M, et al. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. *Br J Haematol.* 2020;**189**:1038–43.

5. Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. *Blood.* 2014;**124**:3308–15.

6. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. *SN Compr Clin Med.* 2020;**2**:2048–58.

7. Mingot-Castellano ME, Alcalde-Mellado P, Pascual-Izquierdo C, Perez Rus G, Calo Pérez A, Martinez MP, et al. Incidence, characteristics and clinical profile of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with pre-existing primary immune thrombocytopenia (ITP) in Spain. *Br J Haematol.* 2021;**194**:537–41.

8. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med.* 2021;**27**:1290–7.

9. Kuter DJ, Rummel M, Ralph Boccia B, Macik G, Pabinger I, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med.* 2010;**363**:1889–99.

10. Gregory C, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet.* 2011;**377**:393–402.

11. Majoor CJ, Sneeboer MM, de Kievit A, Meijers JC, van der Poll T, Lutter R, et al. The influence of corticosteroids on hemostasis in healthy subjects. *J Thromb Haemost.* 2016;**14**:716–23.

12. Stuijver DJF, Majoor CJ, van Zaane B, Souverein PC, de Boer A, Dekkers OM, et al. Use of oral glucocorticoids and the risk of pulmonary embolism: a population-based case-control study. *Chest.* 2013;**143**:1337–42.

13. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, Cannegieter SC, Jørgensen JO, Ehrenstein V, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med.* 2013;**173**:743–52.

14. Severinsen MT, Engebjerg MC, Farkas DK, Jensen AØ, Nørgaard M, et al. Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *Br J Haematol.* 2011;**152**:360–2.

15. Sarpatwari A, Bennett D, Logie JW, Shukla A, Beach KJ, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematologica.* 2010;**95**:1167–75.