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A single 1 g/kg dose of intravenous immunoglobulin is a safe and effective treatment for immune thrombocytopenia; results of the first HaemSTAR "Flash-Mob" retrospective study incorporating 961 patients

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Key Messages

1. A one off 1 g/kg infusion of IVIg may be as effective as two consecutive 1 g/kg doses.
2. This is the largest ever study of the efficacy of IVIg for ITP.
3. There is poor adherence to the 2016 NHS England guidelines on IVIg dosing.

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Immune thrombocytopenia (ITP) is an autoimmune condition characterised by an isolated thrombocytopenia[1]. Intravenous immunoglobulin (IVIg) is a commonly used rescue treatment, alone or alongside other treatments such as corticosteroids, when a rapid increase in platelet count is required. Most patients (80%) respond to IVIg, some within 24 hours and the majority by 2-4 days[2]. IVIg is expensive[3] and can have significant side effects[4] as well as the associated infective risks of being a pooled plasma product[5]. Studies in the 1990s suggested optimal dosing using 1 g/kg/day for 1-2 days[6-8] but supply constraints have resulted in increasingly restrictive dosing recommendations[3,9-11]. NHS England (NHSE) Specialised Commissioning Circulars (SCC1676.25.11.16 and SCC1804.1.11.17) recommend 1 g/kg on a single day, with a second dose at seven days only if there is failure to achieve a haemostatically adequate platelet count (≥30 x10^9/l)[12]. We aimed to audit UK haematologists' IVIg prescribing as well as examine response rates and time to response (TTR). Here we report the results of this project, the first to be entirely conceived and performed by HaemSTAR[13] and the world's largest study of IVIg treatments for ITP to date.

Details of the audit standards, study population, procedures, statistical analyses and study protocol are included in the Supplementary Material.

Data was obtained from 961 patients receiving a total of 961 initial and 416 subsequent IVIg treatments (see Supplementary Figure 1). Basic demographics, type of ITP, baseline clinical characteristics, details of IVIg treatments and previous and concomitant therapies can be found in the Supplementary Material. Of note, 52.6% of IVIg treatments were given alongside concurrent ITP-directed therapy.

35.8% of treatment episodes were dosed according to NHSE guidelines. The most

common dosing strategies were 1 g/kg on a single day (32.7%) or 1 g/kg on two consecutive days (31.2%) (Table 1 and Supplementary Results). The platelet count was <30 x10^9/l at the time of IVIg infusion for 75.5% of treatments (Table 1). 92.9% of treatments were given for indications consistent with a requirement for a rapid increase in platelet count (Table 1 and Supplementary Table 1).

Following IVIg, 915 (88%) of the 1040 treatments where baseline platelet count was <30 x10^9/l achieved a platelet count above this threshold. The median TTR was 4 days (interquartile range [IQR] 2-10 days), and the median response duration was 15 days (IQR 7-25 days). 810 (60%) of the 1349 treatments where baseline platelet count was <100 x10^9/l achieved a platelet count of ≥100 x10^9/l. The median TTR was 9 days (IQR 4-22 days), the median response duration was 11 days (IQR 5-20 days). To examine how response rates varied by type of ITP see Supplementary Results and Supplementary Table 2.

Multivariate analysis was used to explore if any patient-, disease- or treatment-related variables had an effect on the platelet response. For full description of these results see Supplementary Material. Of particular note, whether patients were dosed with 1 g/kg on one or two consecutive days, did not affect the attainment of platelet counts of ≥30 x10^9/l or ≥100 x10^9/l or duration of time for which the platelet count was above these thresholds (Figure 1). These outcomes were also not influenced by concurrent or prior treatment with any other disease modifying agent. We also found evidence of dose capping in those patients ≥100 kg (see Supplementary Discussion anad Supplementary Figure 2).

There was no significant difference in the speed or duration of platelet response whether IVIg was given as a single dose of 1 g/kg or as two 1 g/kg infusions on consecutive days. Despite NHSE (SCC1676.25.11.16) advocating a single 1 g/kg infusion, adherence to this dosing strategy was poor. The reluctance of clinicians to change practice may reflect alternate guidelines permissive for the use of 1-2 g/kg IVIg[14] and the paucity of data upon which NHSE recommendations were made. The two randomised studies that consider IVIg dose in adults are of 55 patients in total and do not directly compare 1 g/kg on one vs two days15. We hope our data will reassure clinicians that the single 1 g/kg dosing regimen is effective, less expensive, rations a scarce resource and reduces side effect risks. There are approximately 1250 IVIg treatments across England each year costing approximately £3150 for each 1 g/kg infusion issued to a 70 kg adult[3]. It follows that if the 40% of UK haematologists currently using 2 g/kg IVIg for ITP switched to one 1 g/kg dose, this would reduce costs from £5.5 million to £4.3 million per annum in the NHS in England alone.

The strengths of this study are that it was large and analysed real-world data (with a heterogenous but representative cross-section of the UK ITP patient population). It had similar overall response rates to already published data[2,7] but collected more detail on platelet counts over time such that the kinetics as well as the degree of response could be analysed. It showed evidence of dose-capping in those ≥100 kg and importantly indicated that this did not result in a worse outcome. The main limitation is that it was retrospective and non-randomised. Patients given a second IVIg treatment may have had reasons for this, not captured by our data. Overall, 53% of treatment episodes were associated with concurrent ITP-directed treatment, reflecting real world practice. While expected to influence long-term treatment response, concurrent treatment was not a predictor of response or response duration within the 35 day follow-up period. We accounted for potential bias introduced from collection of first and subsequent treatments by ensuring that all included patients had data from their first treatment in addition to any subsequent treatments. We felt it reasonable to include data from all episodes in the descriptive outcomes but to eliminate bias we have only included first treatments for the multivariate and Kaplan-Meier analyses,

although we did compare the efficacy of first and second treatment episodes. Additional strengths and limitations are detailed in the Supplementary Material.

Acknowledgements

PLRN conceived the study, coordinated data collection, analysed results and wrote the manuscript. RB collected data and analysed results. PLRN, RP, AF, GS, LM, GCL and QAH formed the study management committee and designed the study. RP also coordinated data collection and generated data queries. KO analysed results. RB, RP, LM, GCL and QAH critically appraised the manuscript. All other contributors collected data.

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References

1. Stasi R, Newland AC. ITP: a historical perspective. *Br J Haematol* 2011; **153**: 437–50.
2. Godeau B, Chevret S, Varet B, *et al.* Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe

autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *The Lancet* 2002; **359**: 23–9.
3. Misbah SA, Murphy MF, Pavord S, *et al.* Outcome of national oversight of intravenous immunoglobulin prescribing in immune thrombocytopenia. *J Clin Pathol* 2020; **337**: 1–2.
4. Debes A, Bauer M, Kremer S. Tolerability and safety of the intravenous immunoglobulin Octagam®: a 10-year prospective observational study. *Pharmacoepidem Drug Safe* 2007; **16**: 1038–47.
5. Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. *Front Immunol* 2018; **9**: 15–13.
6. Imbach P, dApuzzo, Hirt A, Rossi E, Vest M. High-dose intravenous gammaglobulin for Idiopathic Thrombocytopenic Purpura in Childhood. *The Lancet* 1981; **1**: 1228–31.
7. Bussel J. Intravenous Immune Serum Globulin in Immune Thrombocytopenia: Clinical Results and Biochemical Evaluation. *Vox Sanguis* 1985; **49**: 44–50.
8. Godeau B, Caulier MT, Decuypere L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0.5 and 1 g/kg b.w. *Br J Haematol* 1999; **107**: 716–9.
9. Provan D, Chapel HM, Sewell WAC, O'Shaughnessy D, on behalf of the UK Immunoglobulin Expert Working Group. Prescribing intravenous immunoglobulin: summary of Department of Health guidelines. *BMJ* 2008; **337**: 990–2.
10. Robert P. Global plasma demand in 2015. *Pharmaceuticals, Policy and Law* 2009; **11**: 359–67.
11. Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; **117**: 4190–207.
12. Groom M. Specialised Commissioning Circular 1804. Guidance on the timing of a repeat dose of intravenous immunoglobulin. 2017.
13. Nicolson PLR, Desborough MJR, Hart D, Biss TT, Lowe GC, Toh CH. A HaemSTAR is born; a trainee-led, UK-wide research network in haematology. *Clinical Medicine* 2019; **19**: 532–3.
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. Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. *Blood* 1993; **82**: 1415–21.

Tables / Figures

	All		1st		2nd		3rd and beyond	
Dosing strategies	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total dosed	1377		961		230		186	
Insufficient info	53	3.8%	29	3.0%	14	6.1%	10	5.4%
Dosed as per guidelines	493	35.8%	331	34.4%	88	38.3%	74	39.8%
0.8-1.2 g/kg on 1 day	450	32.7%	299	31.1%	82	35.7%	69	37.1%
0.8-1.2 g/kg over 2 days (split to allow response assessment)	43	3.1%	32	3.3%	6	2.6%	5	2.7%
Other dosing								
Not according to guidelines	831	60.3%	601	62.5%	128	55.7%	102	54.8%
0.32-0.48 g/kg over 5 days	59	4.3%	45	4.7%	9	3.9%	5	2.7%
<0.8 g/kg other	291	21.1%	197	20.5%	48	20.9%	46	24.7%
0.8-1.2 g/kg over two consecutive days	429	31.2%	323	33.6%	62	27.0%	44	23.7%
0.8-1.2 g/kg (>2 doses)	23	1.7%	17	1.8%	4	1.7%	2	1.1%
>1.2 g/kg	29	2.1%	19	2.0%	5	2.2%	5	2.7%
Indication for IVIg								
Indication according to guidelines	1268	92.1%	902	93.9%	202	87.8%	164	88.2%
Indication not according to guidelines	109	7.9%	59	6.1%	28	12.2%	22	11.8%
Platelet count at time of IVIg infusion								
Number of patients with Platelet count adhering to guidelines	1040	75.5%	729	75.9%	170	73.9%	141	75.8%
< 10	643	46.7%	480	49.9%	95	41.3%	68	36.6%
10 to 29	397	28.8%	249	25.9%	75	32.6%	73	39.2%
Number of patients with Platelet count not adhering to guidelines	322	23.4%	227	23.6%	51	22.2%	44	23.7%
30 to 49	171	12.4%	118	12.3%	28	12.2%	25	13.4%
50 to 99	138	10.0%	105	10.9%	18	7.8%	15	8.1%
≥ 100	13	0.9%	4	0.4%	5	2.2%	4	2.2%
Unknown	15	1.1%	5	0.5%	9	3.9%	1	0.5%
Platelet responses								
Number of patients achieving platelets ≥ 30	915	88.0%	639	87.7%	145	85.3%	131	92.9%
Number of patients achieving platelets ≥ 100	810	60.0%	606	63.7%	108	50.0%	96	53.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Platelet count on day of IVIg infusion	10	4 - 28	9	3 - 27	13	5 - 28	13	5 - 28
Median time to Platelets count ≥ 30	4	2 - 10	3	2 - 8	6	2 - 18	6	2 - 18
Median time to platelet count ≥ 100	9	4 - 22	8	4 - 22	11	3 - 24	11	4 - 25
Median duration of platelets ≥ 30	15	7 - 25	17	7 - 25	14	8 - 24	14	7 - 23
Median duration of platelets ≥ 100	11	5 - 20	12	5 - 21	9	6 - 17	9	6 - 17

Table 1: Main study outcomes. Audit outcomes of IVIg dosing strategy, indication and platelet count at time of

infusion are shown. Platelet counts on the day of infusion and on any of the 35 days following dose were also recorded. Any counts that were supported by a platelet transfusion in the 24 hours prior to the test were discounted. These counts were used to calculate exploratory outcome measures of platelet responses, time to response and duration of response for platelet counts. Median and interquartile ranges (IQR) for these are shown.

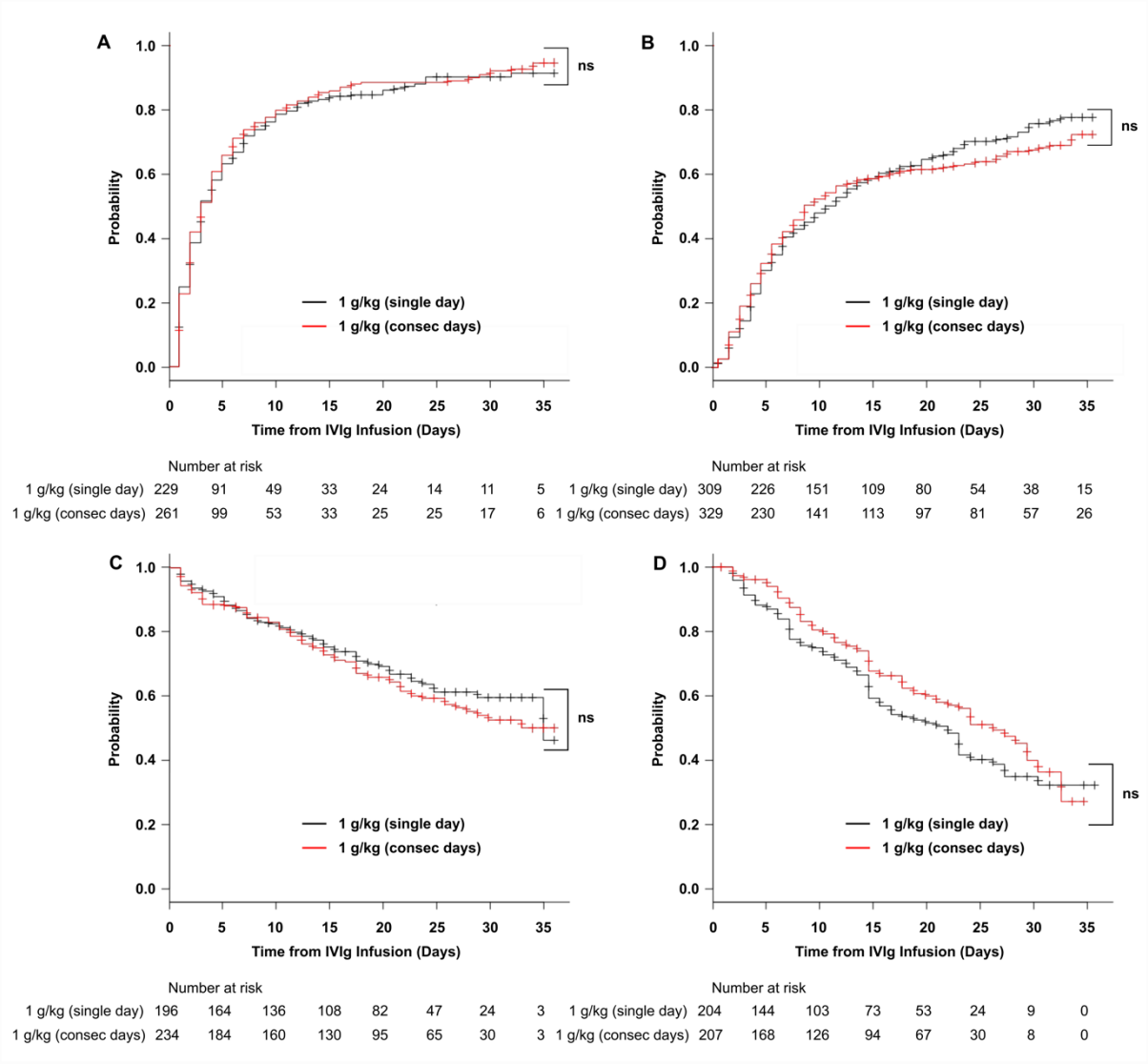

Figure 1: There is no difference in platelet count response, speed or duration whether patients are treated with one or two days of 1 g/kg IVIg. The response to the first treatment of IVIg for patients treated with a single dose or two consecutive doses of 1 g/kg had their platelet count responses compared in four domains. (A) The probability of those with an initial platelet count < 30 x10^9/l attaining a platelet count over this threshold, (B) the probability of those with an initial platelet count of < 100 x10^9/l attaining a platelet count over this threshold, (C) the probability of those achieving a platelet count of ≥ 30 x10^9/l maintaining a platelet count over this threshold and (D) the probability of those achieving a platelet count of ≥ 100 x10^9/l maintaining a platelet count over this threshold. * P<0.05, ns = non-significant.