pathology of myeloproliferative disease, include *JAK-2* (43–57%), *CALR* (3%) and *MPL* (3%). Interestingly, it has been hypothesized that MDS with ring sideroblasts (MDS-RS) can transform into MDS/MPN-RS-T with acquisition of the JAK-2 mutation.[2] Poor prognostic factors in MDS/MPN-RS-T include older age (>80), low Hb (<8 g/dl), abnormal cytogenetics, the presence of SETBP-1 or ASXL-1 mutations and the absence of SF3B1 or JAK-2 mutations.[4]

It is interesting to compare outcomes and variables between MDS/MPN-RS-T and its sister conditions MDS-RS and essential thrombocythemia (ET). A recent study has shown that survival in MDS/MPN-RS-T significantly exceeds that of MDS-RS (76 months versus 63 months) and compares poorly with survival in ET (115 months).[2] Thrombotic events in MDS/MPN-RS-T and ET were shown to exceed those of MDS-RS, which may be expected considering the disease characteristics. Rates of transformation to AML were similar in the two MDS subtypes but lower in ET, the myeloproliferative counterpart.

This case is noteworthy as MDS/MPN-RS-T has a relatively low transformation rate to AML, with a leukemic transformation rate per 100 years of 1.8[2]. A recent paper described two cases; both were patients who were aged greater than 70 years and had been diagnosed with MDS/MPN-RS-T at least two years prior to transformation.[4] One patient had cytogenetics exhibiting clonal evolution, with 7q deletion detected in the marrow following transformation, and died from neutropenic sepsis with chemotherapy; the second did not have clonal evolution and was undergoing chemotherapy at the time of publication. Another case report involved a 70-year-old patient who died from AML transformed from MDS/MPN-RS-T; this case involved the development of a monosomy 7 clone in the leukemic marrow.[5] The refractoriness of the transformed AML in our case to multiple lines of chemotherapy also serves to highlight the aggressive nature of the disease.

In summary, we describe a case of MDS/MPN-RS-T with transformation to treatment-refractory AML highlighted by the presence of trisomy 13 and resistant thrombocytosis. Although transient, our patient's relative "response" to oral busulfan was unexpected but does suggest that this therapy may be clinically useful in similar cases.

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Impact of screening and exclusion of high anti-A titer donors on the risk of hemolytic anemia with intravenous immunoglobulin treatment: A hospital-based cohort study in the US

To the Editor:

Hemolytic anemia is a potential complication of administration of intravenous immunoglobulin preparations (IVIG).[1] The hypothesized predominant mechanism is the passive acquisition of A and B isoagglutinins (anti-A and anti-B antibodies) from the IVIG product,[2] related to the antibody quantity per body weight. Hemolytic anemia is more common in patients receiving high dose IVIG for immune modulation than for low dose immunoglobulin replacement therapy in immunodeficiency.

IVIG products are derived from large human plasma pools of many individual donations, containing immunoglobulin G class isoagglutinins that may co-purify with other antibodies in the IVIG production process. A isoagglutinins titers are higher than B isoagglutinin titers in the donor population and A patients are more frequent than B patients.[3]

TABLE 1 Incidence rates of hemolytic anemia in temporal association with Privigen use in period 1 and period 2, overall and stratified by Privigen indication and dose

	Period 1 Jan 2008 to Dec 2012			Period 2 Oct 2013 to Dec 2015			Comparison[a]		
	HA cases	Person-days at risk	Crude IR[b] (95% CI)	HA cases	Person-days at risk	Crude IR[b] (95% CI)	Crude IRR[c] (95% CI)	Adjusted IRR[c,d] (95% CI)	*P*-value[c,e]
Total	68	644756	1.05 (0.82-1.34)	39	476931	0.82 (0.58-1.12)	0.78 (0.52-1.15)	0.82 (0.55-1.23)	.17
Privigen indication[f]									
Immune thrombocytopenia	33	84083	3.92 (2.70-5.51)	10	56129	1.78 (0.85-3.28)	0.45 (0.22-0.92)	0.46 (0.22-0.93)	.02
Immunodeficiency	15	380985	0.39 (0.22-0.65)	8	266318	0.30 (0.13-0.59)	0.76 (0.32-1.80)	0.69 (0.29-1.66)	.21
Malignant neoplasm	16	117912	1.36 (0.78-2.20)	7	77042	0.91 (0.37-1.87)	0.67 (0.28-1.63)	0.69 (0.28-1.70)	.21
GBS	5	20292	2.46 (0.80-5.75)	1	18863	0.53 (0.01–2.95)	0.22 (0.03-1.84)	0.25 (0.03-2.25)	.11
Kawasaki disease	4	7373	5.43 (1.48-13.9)	0	6135	0.00 (0.00–6.01)	-	-	-
Myasthenia gravis	1	36352	0.28 (0.01-1.53)	4	34941	1.14 (0.31-2.93)	4.16 (0.47-37.3)	4.99 (0.55-45.5)	.92
CIDP	1	53534	0.19 (0.00–1.04)	1	53020	0.19 (0.00–1.05)	1.01 (0.06–16.2)	1.12 (0.07–18.7)	.53
Other or unknown indication	9	70141	1.28 (0.59-2.44)	14	50857	2.75 (1.50-4.62)	2.15 (0.93-4.96)	2.32 (1.00–5.40)	.98
Privigen dose (g/kg body weight)									
<0.75	20	410763	0.49 (0.30-0.75)	15	285409	0.53 (0.29-0.87)	1.08 (0.55-2.11)	1.07 (0.54-2.11)	.58
≥0.75 to <1.75	19	111137	1.71 (1.03-2.67)	13	110991	1.17 (0.62-2.00)	0.69 (0.34-1.39)	0.90 (0.44-1.84)	.39
≥1.75	24	70467	3.41 (2.18-5.07)	9	62565	1.44 (0.66-2.73)	0.42 (0.20-0.91)	0.48 (0.22-1.04)	.03
Unknown dose	5	52389	0.95 (0.31-2.23)	2	17966	1.11 (0.13-4.02)	1.17 (0.23-6.01)	1.09 (0.20-5.88)	.54

CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; GBS: Guillain-Barré Syndrome; HA: Hemolytic anemia; IR: Incidence rate; IRR: Incidence rate ratio.

[a]Using period 1 as reference.

[b]IR per 10 000 person-days at risk.

[c]Omitted when no case detected in period 1 or 2.

[d]Adjusting for treatment setting, sex, age, Privigen indication and Privigen dose using Poisson regression. Overall adjusted IRR estimate was adjusted for all covariates (i.e., treatment setting, sex, age, Privigen indication and total Privigen dose). All other IRR estimates were adjusted for all covariates except for the respective stratifying covariate.

[e]Using one-sided Wald test for multivariate Poisson regression.

[f]More than one indication per Privigen episode possible.

Recent reports of increased hemolytic anemia rates relate to the change in the IVIG production from Cohn's method (cold-ethanol fractionation), that reduced isoagglutinins, to chromatographic processes with higher purity and functional integrity.[4] One available IVIG product is Privigen (CSL Behring, Bern, Switzerland) that until 2013 was produced with a chromatographic process lacking dedicated steps to reduce isoagglutinins. To reduce the isoagglutinin titers and the risk of hemolytic anemia with Privigen, a two- step approach was implemented: exclusion of donors with high anti-A titer donors introduced in mid-2013,[4] followed by an immunoaffinity chromatography step which started in Oct-2015.[5]

We conducted a study to describe the risk of hemolytic anemia before and after the first step of exclusion of high anti-A titers donors from pooled plasma in the manufacturing of the IVIG Privigen.

Data were obtained from the United States (US) Premier Perspective database. We analyzed data from 862 US hospitals of patients treated with Privigen intravenously. Two study cohorts were formed of patients with use of Privigen before and after excluding high titer anti-A donors: Jan-2008 through Dec-2012 (period 1, Privigen produced without isoagglutinin reduction) and Oct-2013 through Dec-2015 (period 2, Privigen produced mainly from anti-A screened donors).

Exposure of interest was treatment with Privigen, determined for each patient and study cohort. Treatment episodes were defined as units of continuous duration of IVIG. Patients in each cohort were observed from the first Privigen administration until the earliest of: 30 days after the last Privigen administration, the occurrence of first hemolytic anemia, end of the respective period, or death. The cumulative IVIG dose per kilogram (kg) body weight and treatment episode was estimated from the daily quantity of Privigen administered and the corresponding median age- and sex specific body weight from the US population.[6]

The primary outcome was hemolytic anemia within 30 days of IVIG administration assessed from manual review of patient summaries by a hematologist (TLS) for the assessment of all potential hemolytic anemia events, the date of hemolytic anemia and the indication for IVIG use.

Indications for Privigen use were history of immunodeficiency, malignant neoplasm of lymphatic and hematopoietic tissue, immune thrombocytopenia, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, and myasthenia gravis.

Crude incidence rates of hemolytic anemia temporally related to Privigen use were calculated for each period and stratified by treatment setting (inpatient or outpatient), age, sex, Privigen indication, and Privigen dose per kg body weight. Incidence rates of hemolytic anemia in period 2 were compared with respective rates in period 1 by calculating incidence rate ratios (IRR) from Poisson regression, using the incidence rate in period 1 as reference and adjusted for treatment setting, sex, age, Privigen indication and dose per body weight. The study protocol was approved by the European Medicines Agency, protocol number ENCePP/SDPP/6040.

The cohorts in period 1 and 2 consisted of 9099 and 7431 Privigen users; mean age, 50.7 and 46.5 years respectively. Common indications were immune thrombocytopenia, immunodeficiency and malignant neoplasm.

The hemolytic anemia rate was 1.05/10 000 person-days (95% CI, 0.82-1.34) in period 1 and 0.82 (0.58-1.12) in period 2, adjusted IRR 0.82 (0.55-1.23) for period 2 vs. period 1 ($P = .17$).

The incidence rate of hemolytic anemia per 10 000 person-days was higher in period 1 compared with period 2 in patients with immune thrombocytopenia [3.92 (2.70-5.51) versus 1.78 (0.85-3.28)], in patients with Kawasaki disease [5.43 (1.48-13.89) versus 0.0 (0.00–6.01)], and in patients with a total Privigen dose $\geq$1.75 g/kg body weight per episode [3.41 (2.18-5.07) versus 1.44 (0.66-2.73)] (Table 1). A marked increase in the rate of hemolytic anemia with Privigen dose seen in period 1 (0.49 at low dose to 3.41 at high dose, $P < .01$), was attenuated in period 2 (0.53 to 1.44, $P = .21$).

With Privigen administered for immune thrombocytopenia and period 1 as the reference, the adjusted IRR was 0.46 ($P = .02$), and when given at high dose ($\geq$1.75 g/kg body weight) it was 0.48 ($P = .03$, Table 1). The relative risk reduction of 52% resulted in an absolute reduction of 1.55 hemolytic anemia cases avoided per 10 000 person-days of high-dose IVIG treatment in period 2 vs 1.

In summary, using a large hospital-based cohort of over 16 000 patients treated with Privigen we found a decrease in the risk of hemolytic anemia in association with exclusion of donors with high anti-A titers from plasma pools used in manufacturing IVIG. This association was dose-dependent and observed in indications requiring higher IVIG doses. In indications requiring $\geq$1.75 g IVIG/kg body weight there was a significant risk reduction of 52% associated with exclusion of high titer anti-A donors ($P = .03$).

This study supports an association between dose of IVIG treatment and risk of hemolytic anemia and indicates that the exclusion of donors with high titers of anti-A from plasma pools was associated with a reduction of risk with high dose therapy.

AUTHORS CONTRIBUTION

All authors made substantial contributions to the conception and design, analysis and interpretation of data. TLS was adjudicator for all study outcomes. CM and CW conducted the data analysis and drafted the manuscript. All authors revised the manuscript critically for important intellectual content.

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Program expansion of a day hospital dedicated to manage sickle cell pain

To the Editor:

Vaso-occlusive crisis (VOC) is the hallmark complication of sickle cell disease (SCD), and the majority of SCD-related healthcare costs in the United States, estimated at $2.4 billion annually, is attributed to frequent emergency department (ED) visits and hospitalizations due to recurrent VOC.[1–3] A day hospital (DH) dedicated to manage uncomplicated VOC has been shown to reduce admission rates, decrease inpatient length of stay (LOS), and save health care costs.[4,5] The majority of DH programs have hours of operation from 9 am to 5 pm, and programs with extended hours beyond this are limited by a lack of sufficient resources. The impact of extended hours of DH programs on patient care is less clear.

The Comprehensive Sickle Cell Center at the University of Illinois at Chicago (UIC) instituted a DH program to manage uncomplicated VOC in 2009 that was open from 8 am to 5 pm Monday through Friday, modeled upon previous DH.[4] Patients who presented with uncomplicated VOC were assessed, and then treated based on previous pain treatment history and current assessment. After treatment in DH, patients were either discharged home or admitted to the hospital if adequate pain relief was not achieved. To improve patient access and decrease the burden on ED, the hours of operation were expanded to 8 am-11 pm in February, 2014. To evaluate the impact of extended hours on patient care, data on VOC-related patient visits from the two years before the expansion to two years after the expansion (2012–2016) were collected from the electronic medical record and evaluated. Descriptive statistics, the Cochrane trend test, the ANOVA test, and a multivariate linear regression were used for data analysis. The study was approved by the UIC Institutional Review Board prior to the initiation of chart review.

The number of DH visits increased from 205 visits in 2012 to 1057 visits in 2016, and the program expansion in 2014 alone increased the number of visits by more than 2-fold (292 visits in 2013 vs 691 visits in 2014). The proportion of the DH visit numbers relative to 2012 showed a trend of significant increase during the five-year period compared to the number of ED visits (516% in DH to 93% in ED, $P < .0001$; Figure 1A). The number of unique patients served in the DH (81 in 2012 to 177 in 2016) also had a greater increase compared to that in ED (269 in 2012 to 282 in 2016), and the proportion relative to 2012 was significantly higher (219% in DH vs. 105% in ED, $P < .0001$; Figure 1B). The most substantial increase in unique patients treated in the DH occurred in 2014, the year the program hours were expanded (107 patients in 2013 vs. 174 patients in 2014). With increasing utilization of the DH, the inpatient admission rate from the DH over the 5-year span showed a significant decrease (24% in 2012 to 14% in 2016; $P < .0001$), especially after program expansion in 2014 (Figure 1C). In contrast, the average admission rate for uncomplicated VOC from the ED was 69% during the same 5-year span. To evaluate

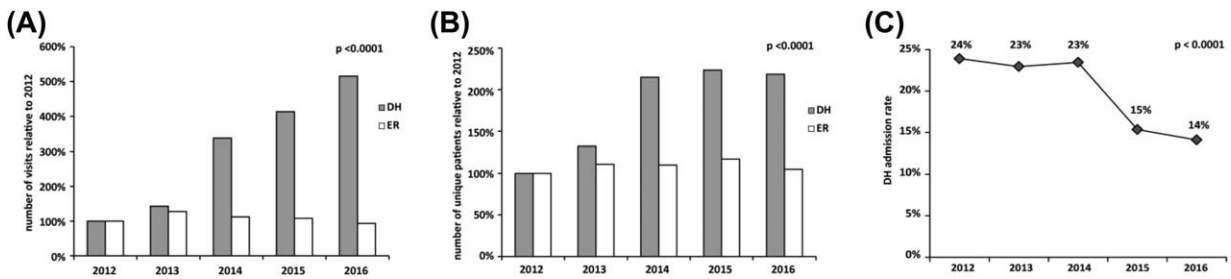

FIGURE 1 DH and ED utilization and admission rates through DH. A and B. The number of visits and unique patients relative to 2012 in DH were compared to ED during 2012–2016. Both showed significantly increasing trend ($P < .0001$). **C.** The admission rates in DH showed a significantly decreasing trend during 2012–2016 ($P < .0001$). The Cochrane trend test was used