

Isoagglutinin Reduction in IVIg by Specific Immunoaffinity Chromatography Reduces Spontaneous Reporting Rates of Hemolytic Reactions

Amgad Shebl,¹ Susie Gabriel,² Kristy Van Dinther,² Alphonse Hubsch,³ Liane Hoeffler³ and Susan Welsh⁴

¹CSL Behring GmbH, Marburg, Germany; ²CSL Limited, Parkville, Melbourne, Australia; ³CSL Behring AG, Bern, Switzerland; ⁴CSL Behring, King of Prussia, PA, USA

Introduction

- Intravenous immunoglobulin (IVIg) is used as replacement or immunomodulatory therapy in a wide range of disorders, including immune thrombocytopenia (ITP), and neurological conditions such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP)
- Clinically significant hemolysis is an infrequent, but known effect of high-dose IVIg and can result in severe complications^{1,2}
- Hemolytic reactions in non-O blood group patients receiving high-dose IVIg have been linked to anti-blood group A and B antibodies (isoagglutinins) in the product²
- Chromatography-based IVIg production processes do not reduce isoagglutinins, unlike cold ethanol fractionation
- Isoagglutinins can be efficiently reduced by a specific immunoaffinity chromatography (IAC) step³, or with anti-A donor screening⁴
- IgPro10 is produced using a chromatography-based process (Table 1)⁵

Table 1: IgPro10 production time periods compared*

	Chromatography, no isoagglutinin reduction (n=260)	Chromatography, IAC (n=142)
	Baseline	After IAC step
IgPro10 production years	2007–2013	2016–ongoing
Median isoagglutinin titer [†]		
Anti-A	32	8
Anti-B	16	4

*Direct method (Chapter 2.6.20: Anti-A and Anti-B Haemagglutinins, Method A and B, European Pharmacopoeia (PhEur) 2016; 8th edition (88): 203–4) [†]Specific for IgPro10. IAC, immunoaffinity chromatography; IgPro10, 10% intravenous immunoglobulin preparation

Objective

- To assess the impact of the IAC manufacturing step on the spontaneous reporting rates of hemolysis with an IVIg product (IgPro10) versus the risk minimization measure (RMM) of anti-A donor screening and versus baseline (no RMMs implemented)

Methods

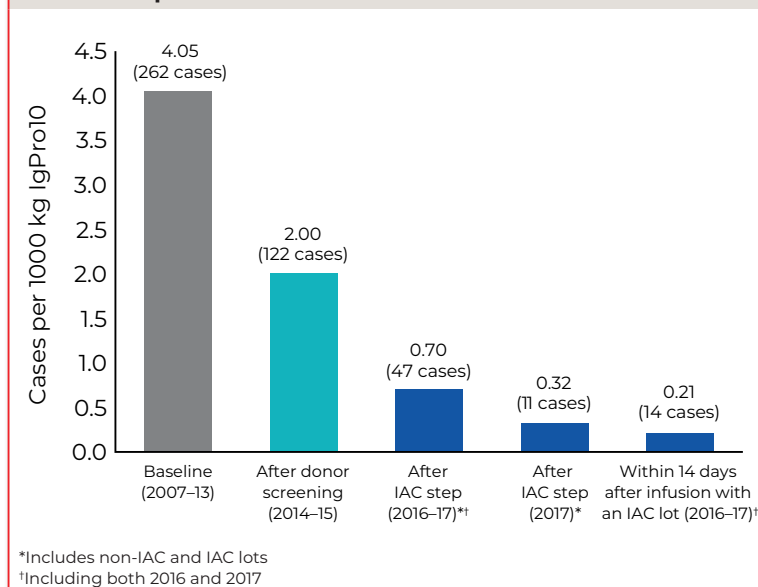
- We compared the reporting rates of spontaneous cases of hemolysis across three time periods
- Reports of hemolytic reactions in patients receiving IgPro10 were obtained from the CSL Global Safety Database for the period of February 2008 to December 2017
 - The standard MedDRA Query (SMQ) “Hemolytic disorders Broad” was used to calculate the hemolytic reporting rates
 - Reports from clinical trials or those involving unbranded cases were excluded (i.e., no brand name, but only international non-proprietary name reported)
 - To account for the number of patients exposed, hemolysis rates are shown as number of cases per 1000 kg IgPro10 used

Results

REPORTS OF HEMOLYSIS

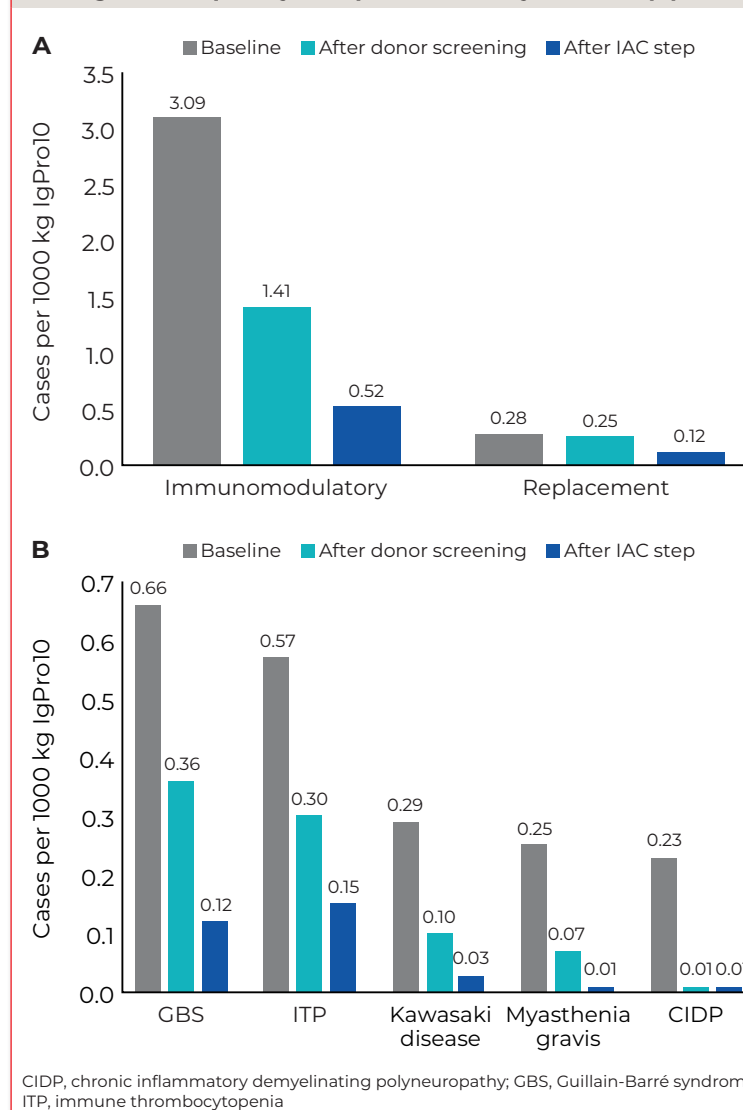
- The overall rate of hemolysis decreased after donor screening and IAC compared with baseline
- The worldwide reporting rates and total number of cases of reported hemolysis are shown in Figure 1
 - Anti-A donor screening showed a 51% decrease in worldwide reporting rates from baseline
 - After IAC incorporation, a substantial decrease (83%) in hemolysis reporting rate from baseline was observed (4.05 to 0.70 cases per 1000 kg IgPro10)
 - In 2017 (when a higher proportion of IAC lots were in the market than 2016), a further reduction from baseline after IAC incorporation was observed (92% reduction)
 - In 2016 and 2017 both IAC and non-IAC lots were available in the market. Of the 47 hemolysis events reported, 37 had lot number data
 - In total, 20 cases were associated with only non-IAC lots (18+2), 10 with both IAC and non-IAC lots (9+1) and 7 with only IAC lots (3+4); in 2016 and 2017, respectively
 - For cases associated with both IAC and non-IAC lots, the hemolysis case was considered associated with an IAC lot if the reaction occurred within 14 days after the infusion of an IAC lot
 - From the hemolysis cases with known lot information, 14 of these events occurred within 14 days of an IAC lot, 6 of which (42.86%) were from only IAC lots

Figure 1: Relative rate of reported cases of hemolysis per quantity of IgPro10 sold and number of hemolysis cases over three time periods



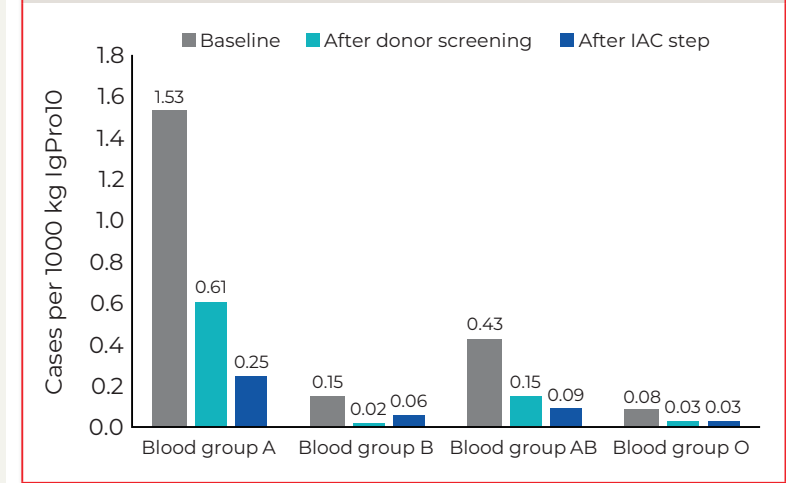
- Where indication was reported, the majority of reported cases of hemolysis were in patients receiving IVIg for immunomodulatory purposes (Figure 2A)
 - For these indications, the rate of hemolysis was reduced following donor screening and after IAC (Figure 2B)

Figure 2: IgPro10 used for immunomodulatory therapy and replacement therapy (A), broken down by indication with the highest frequency of reported hemolysis cases (B)



- Over the three time periods, ABO blood group data were collected in 220 cases; the majority of hemolysis cases occurred in patients with blood group A (Figure 3)
 - The reporting rates of hemolysis in the context of ABO blood groups are consistent with published literature
- Changes in the background adverse event reporting rates were ruled out as a contributing factor to the reduction of the hemolytic reaction reporting rates following the IAC step

Figure 3: Relative rate of reported cases of hemolysis per quantity of IgPro10 sold by ABO blood group



LIMITATIONS

- This research is limited due to the overlap of non-IAC lots in the assessment period, changes in IVIg prescribing practices and variability in spontaneous reporting behaviors and/or a lack of information

Conclusions

- Incorporating the immunoaffinity chromatography (IAC) step into the IgPro10 (IVIg) production process substantially reduced the anti-A and anti-B titers in IgPro10
- The IAC step was followed by a substantial reduction in the IgPro10 spontaneous reporting rates of hemolytic reactions reported worldwide; these effects are substantially more pronounced compared with anti-A donor screening
- The reduction of spontaneous reporting rates of hemolytic reactions worldwide through introduction of IAC shows evidence of the effectiveness of this measure in reducing the risk of these reactions and should be further investigated by immunoglobulin manufacturers

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Author Disclosures

All authors are employees of CSL Behring. Amgad Shebl, Susan Welsh, Kristy Van Dinther, Alphonse Hubsch and Liane Hoeffler hold stock in CSL Behring.

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