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Safety of Plasmapheresis in Donors with Low IgG Levels: Results of a Prospective, Controlled Multicentre Study

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Keywords

Donor plasmapheresis · Donor vigilance · Immunoglobulin G level · Adverse events

Abstract

Background and Objectives: Although plasmapheresis is generally considered safe, there are still concerns about the long-term effects of plasma donation on immunoglobulin G (IgG) levels. The aim of the present study was to investigate if there is a need to permanently defer donors who donated three times with an IgG level below 6.0 g/L. ***Study Design and Methods:*** From September 2007 to December 2017, adverse events (AEs) including infections were analysed from data of a prospective, controlled multicentre study of healthy volunteer donors, participating in an individualized plasmapheresis programme stratified by initial IgG level and body weight (individualized arm) or in standard plasmapheresis according to national guidelines (control arm). IgG was monitored at every fifth donation, and donors with IgG levels below the threshold were identified and followed up for possible AEs. ***Results:*** In total, 97,540 donations in 1,462 donors in the control arm and 1,491,223 donations in 14,281 donors in the individualized arm were included. Donation-based incidences of at least severe AEs and any infections were 0.019% and 0.192% in the control arm, and 0.014% and 0.153% in the individualized arm. Three or more IgG-measurements below the threshold occurred in 38.2% of control arm donors and 20.9% of individualized arm donors. There were no increased incidence rates of at least severe AEs or any infections in donors with ≥3 IgG-measurements below the threshold in either donor's arm. ***Conclusions:*** Our data show no signs of compromised donor safety in donors with ≥3 IgG-measurements below the threshold, indicating that plasmapheresis is feasible and safe in these donors.

Introduction

The use of immunoglobulin G (IgG) in autoimmune disorders and immunodeficiencies is steadily expanding, and IgG has replaced human albumin and clotting factor concentrates as the leading products of the plasma fractionation industry in the past years. Thus, IgG has become the driving force for plasma fractionation, and the IgG content in plasma used for fractionation is of interest to plasma fractionation corporations. Plasma donation by plasmapheresis is the key source of plasma for fractionation [1]. Key donation parameters, such as the maximum plasma volume per donation, the maximum plasma volume that may be donated per year, the maximum frequency of plasma donations per year, or a combination of these parameters, are usually defined in country-specific guidelines. These documents typically also advise on qualitative or quantitative monitoring of IgG and total serum protein (TSP) levels in donor blood, as maintaining appropriate levels of these components is a key concern.

Current German guidelines require measurement of IgG levels prior to the first plasma donation and subsequently at every fifth plasma donation. Up to 60 donations per year are allowed [2]. Donors with serum IgG

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levels below 6.0 g/L must be deferred for at least 2 weeks and a sample must be drawn to ensure an IgG level above the lower limit prior to the next plasmapheresis. Donors with IgG levels below 6.0 g/L at three donations must be permanently deferred from plasmapheresis. This regulation came into force with the revision of the haemotherapy guidelines in 2017 and is a matter of controversial debate.

Several studies have investigated various approaches to intensify and/or individualize donation regimens in order to increase plasma supply and optimize self-sufficiency, such as the Study on Intensified PLAsmapheresis (SIPLA) in which individualized donation volumes based on donor body weight [3]. The study showed that IgG levels decreased in donors with a high IgG level at the study start but generally remained above the lower limit, and a high IgG level at the study start protected against drop-out due to low IgG, TSP, or haemoglobin. These results are in line with published studies that show donors falling below the lower IgG limit at least once during the study had significantly lower IgG levels before donation than donors who stayed above the limit [4]. Consequently, using baseline IgG levels to estimate individual regeneration rates after donation and to distinguish appropriate donation frequencies seems suitable, as donors who regenerate IgG more quickly could potentially donate plasma more often. This individualized approach could aid donation frequency optimization, while assuring the safety of donors.

The aim of the present study was to investigate safety in plasmapheresis donors with IgG levels below 6.0 g/L, as low IgG levels might result in adverse events (AEs) such as an increase of infections. Donation-related AEs were assessed in donors with less than three temporary deferrals due to low IgG levels and donors with ≥3 deferrals. Furthermore, the time to the third IgG-measurement below the threshold was studied.

Materials and Methods

Study Design

Data were retrieved from a prospective, multicentre, stratified, controlled study to assess donor safety in an individualized donor plasmapheresis programme. This intensified plasmapheresis study (IPS) consisted of an individualized arm and a control arm. For the IPS study, a number of 3,000 donors per donation programme were considered as sufficient to detect an AE with a probability of 0.95 at least once. Therefore, it was intended to recruit 30,000 donors for the whole study, including the control arm. Due to the limitation of the observed time period from 2007 to 2017 with no permanent deferral with ≥3 IgG levels below the threshold, data from 15,743 donors were analysed in the present evaluation. The aim of the present evaluation was to analyse the possible causal relationship of IgG levels below the threshold of 6.0 g/L and infections of the donor. We hypothesized that there was no causal relationship between IgG level and incidence of infections. The study was conducted at 13 plasma donation centres in Germany and started in September 2007; it was performed according to the standards of the Declaration of Helsinki and ethics approval was granted by regional Human Research Ethics Committees. A safety committee consisting of independent experts in the field of plasmapheresis monitored the data throughout the study.

Study Participants

Donors fulfilling current German eligibility criteria [2] were asked to participate in the study if they had donated plasma at least once and were expected to be available as donors for at least 1 year. The minimum time interval between plasmaphereses was 2 days. All donors were informed about the investigational character of the study, and informed consent was required for enrolment. Exclusion criteria were deferrals according to haemotherapy guidelines, IgG level >20 g/L, and participation in another study. Control and verum arm donors received an identical monetary allowance as well as non-study donors.

Plasmapheresis Regimens and Arm Allocation

Participants could choose between plasmapheresis according to previous German guidelines (control arm) and participation in an individualized plasmapheresis programme (individualized arm). Individualized arm donors were assigned to a donation programme according to their body weight, which determines the maximum volume per donation, and their serum IgG levels prior to the first plasma donation, which determines the maximum number of donations per year (Table 1). Throughout the study, data were collected in the same way for both the control and the individualized arm.

Deferrals and Study Termination

Participants were deferred from donation for any of the reasons listed in the German guidelines [2]. Donors presenting with low IgG (<5.8 g/L until 2010 and <6.0 g/L after that) were deferred for 2 weeks if IgG was ≥5.0 g/L and <5.8 g/L (until 2010) or <6.0 g/L (after 2010), 3 weeks if IgG was ≥4.0 g/L and <5.0 g/L and 5 weeks if IgG is <4.0 g/L. These deferral periods could be increased at the investigator's discretion.

Plasmapheresis Procedure and Routine Monitoring

Body weight, body temperature, and vital signs such as blood pressure and heart rate were measured prior to each plasmapheresis. At every plasmapheresis, donors were required to complete a standardized questionnaire, including questions about infections that might be due to low IgG levels.

All plasma donations were performed using the PCS2 Plasma Collection System (Haemonetics, Braintree, Chicago, MA, USA) using software version G until 2016 and subsequently Express software. Sodium citrate anticoagulant (4% w/v, Haemonetics) was used at an anticoagulant-to-blood ratio of 1:16. Serum IgG levels were determined at the study start and at least at every fifth donation by immunoturbidimetry using the OSR61172 IgG reagent (IgG) on AU640/680 analysers (Beckman Coulter, Krefeld, Germany).

Monitoring of AEs

To assess donor safety, all AEs were documented, including technical AEs, such as machine failures, repeat venepunctures, and symptoms affecting donor health. All local and systemic infections were recorded, e.g., fever, flu, etc. Information about infections were obtained by the donor questionnaire and interview as well as physical examination and laboratory results. If the donor visited a family doctor or stayed in a hospital the diagnosis and paraclinical test results were requested. The study physician reviewed all avail-

Table 1. Plasmapheresis regimens of the study

Initial IgG levels	Body weight		
	≥50 and <60, kg	≥60 and <70, kg	≥70, kg
≥6 and <8, g/L	≤26 donations per year 760 mL* per donation Maximum 19.76 L per year	≤26 donations per year 820 mL* per donation Maximum 21.32 L per year	≤26 donations per year 860 mL* per donation Maximum 22.36 L per year
≥8 and <10, g/L	≤52 donations per year 760 mL* per donation Maximum 39.52 L per year	≤52 donations per year 820 mL* per donation Maximum 42.64 L per year	≤52 donations per year 860 mL* per donation Maximum 44.72 L per year
≥10, g/L	≤104 donations per year 760 mL* per donation Maximum 79.04 L per year	≤104 donations per year 820 mL* per donation Maximum 85.28 L per year	≤104 donations per year 860 mL* per donation Maximum 89.44 L per year
Control group	≤45** donations per year 660 mL* per donation Maximum 29.7 L per year	≤45** donations per year 760 mL* per donation Maximum 34.2 L per year	≤45** donations per year 860 mL* per donation Maximum 38.7 L per year

* Including anticoagulant and sample for analysis (approx. 10 mL). ** According to previous German haemotherapy guidelines during the study period.

Table 2. Grades of severity of AEs

Severity	Description
Mild	Transient or mild physical impairment, no medical intervention required
Moderate	Limits daily activities, medical monitoring, or minimal intervention or hospitalization required
Severe	Disrupts daily activities, medical intervention, and hospitalization required
Life-threatening	Severely impairs health, is life-threatening, and requires immediate medical intervention and hospitalization or results in disability
Fatal	Results in death

Table 3. Categories of causal relationships of AEs to plasmapheresis

Causal relationship	Definition
Unrelated	No temporal relationship and AE does not follow any known pattern
No temporal relationship	No temporal relationship
Possibly related	Temporally related or a causal relationship cannot be excluded
Probably related	Probably or definitely related

able information and the severity and causal relationship of all AEs to plasmapheresis were rated (Tables 2, 3). In the present evaluation only severe, life-threatening, and fatal AEs and infections of all severities were analysed. Non-infectious mild and moderate AEs were most often technical errors and failed venipunctures and had no impact on donor safety and the results will be presented elsewhere. The time at risk of infection was defined as at least 6 weeks with at least 3 IgG measurements at 3 different time points and the donors had to donate at least 4 times.

Data Analysis

AE incidence was determined based on a data cut from December 31, 2017, as from August 2017 onwards, donors with three IgG-measurements below the threshold were permanently deferred as required by the new German haemotherapy guidelines. To be eligible for analysis, donors had to have ≥3 IgG-measurements, ≥4 donations of ≥120-mL plasma, and a time at risk of ≥6 weeks during the study. Donors were divided into groups with 0, 1, 2, or ≥3 IgG-measurements below the threshold; control and individualized arms were analysed separately. Frequencies of AEs were calculated both as donation-based incidence (number of events per 100 donations) and as the number of events per year at risk.

Descriptive statistics (frequency and incidence for categorical parameters; arithmetic mean and standard deviation for continuous variables) were primarily used such as statistical hypothesis testing and confidence intervals to determine differences between donor groups or to detect associations that are exploratory in nature. Due to the relatively large sample size, exclusively parametric

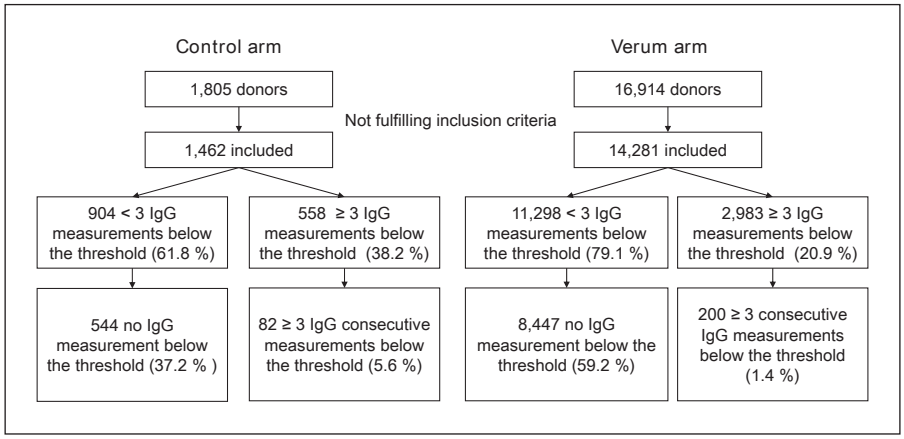

Fig. 1. IgG-measurements below the threshold in individualized and control arm donors.

Table 4. Donor characteristics by number of IgG-measurements below the threshold

IgG-measurements below the threshold, *n* (%)	Age at study start, years	Donations per year, *n**	Time at risk, years
Control arm (*n*= 1,462)			
0 (*n* = 544; 37.2)	37.7±13.6	31.7±16.6	1.9±1.5
	36.0 (18–71)	30.2 (2.0–102.3)	1.5 (0.1–10.0)
1 (*n* = 226; 15.5)	36.2±12.9	35.5±16.9	1.7±1.4
	32.0 (18–65)	35.1 (2.1–93.3)	1.4 (0.1–8.2)
2 (*n* = 134; 9.1)	35.3±12.4	35.7±15.8	1.7±1.4
	31.0 (19–61)	36.8 (5.3–82.1)	1.3 (0.2–8.9)
≥3 (*n* = 558; 38.2)	37.1±12.9	35.2±12.5	2.6±1.8
	35.0 (18–70)	35.5 (2.7–79.8)	2.3 (0.2–9.2)
Individualized arm (*n* = 14,281)			
0 (*n* = 8,447; 59.1)	32.8±11.8	40.1±22.6	2.3±2.0
	29.0 (18–70)	36.8 (1.0–113.6)	1.7 (0.1–10.1)
1 (*n* = 1,851; 13.0)	31.7±11.5	40.5±21.1	2.3±2.0
	28.0 (18–67)	38.1 (0.9–101.3)	1.6 (0.1–10.1)
2 (*n* = 1,000; 7.0)	31.7±11.6	41.8±19.9	2.4±2.1
	28.0 (18–67)	39.5 (2.8–96.5)	1.9 (0.1–10.0)
≥3 (*n* = 2,983; 20.9)	33.7±12.3	45.0±18.2	3.8±2.5
	30.0 (18–74)	43.5 (2.6–95.7)	3.2 (0.2–10.1)

Data are presented as mean ± standard deviation and median (range). * For donors with less than a year on the study, the number of donations per year was inferred, which for some donors led to a theoretically higher number of donations per year than allowed for their donation regime.

statistical tests were used. The χ^2 test was used to compare relative frequencies between donor groups and Student's *t* test was used to compare mean values. Statistical significance was set at 0.05.

Results

In the control arm, 1,462 (870 male and 592 female) of 1,805 donors were included. Median age of control arm donors was 35 years (range 18–71 years) and they spent a median time of 1.7 years at risk during the study. Median weight of control arm donors was 82.0 kg (range 51–166 kg). In the individualized arm, 14,281 (8,450 male, 5,831 female) of 16,914 donors fulfilled the inclusion criteria of the analysis. Median donor age was 29 years (range 18–74 years), and the median time at risk was 1.9 years.

38.2% of the control arm donors showed ≥3 IgG-measurements below the threshold during the study period, while 37.2% of the control group donors never presented with an IgG value below the threshold (Fig. 1). In the individualized arm, IgG-measurements below the threshold occurred in 20.9% of the donors. No IgG-measurements below the threshold were seen in 59.2% of individualized arm donors (Fig. 1).

Detailed characteristics of donors with IgG-measurements below the threshold are shown in Table 4. Median time until the third measurement below the threshold

Table 5. Severe, life-threatening, and fatal AEs in donors by number of IgG-measurements below the threshold

IgG-measurements below the threshold, *n*	Severe		Life-threatening		Fatal	
	n	incidence, %*	*n*	incidence, %*	*n*	incidence, %*
Control arm (n = 1,462)						
0 (*n* = 544)	6	0.020	0	0.000	0	0.000
1 (*n* = 226)	3	0.025	0	0.000	0	0.000
2 (*n* = 134)	5	0.068	0	0.000	0	0.000
≥3 (*n* = 558)	5	0.010	0	0.000	0	0.000
Individualized arm (n = 14,281)						
0 (*n* = 8,447)	126	0.017	0	0.000	0	0.000
1 (*n* = 1,851)	10	0.006	1	0.001	1	0.001
2 (*n* = 1,000)	19	0.020	0	0.000	0	0.000
≥3 (*n* = 2,983)	56	0.011	0	0.000	2	0.001

* The donation-based incidence rate was calculated as 100 × number of AEs/number of donations.

Table 6. Severe, life-threatening, and fatal AEs with a possible or probable causal relationship in donors by number of IgG-measurements below the threshold

IgG-measurements below the threshold, *n*	Severe		Life-threatening		Fatal	
	n	incidence, %*	*n*	incidence, %*	*n*	incidence, %*
Control arm (n = 1,462)						
0 (*n* = 544)	0	0.000	0	0.000	0	0.000
1 (*n* = 226)	0	0.000	0	0.000	0	0.000
2 (*n* = 134)	0	0.000	0	0.000	0	0.000
≥3 (*n* = 558)	1	0.002	0	0.000	0	0.000
Individualized arm (n = 14,281)						
0 (*n* = 8,447)	8	0.001	0	0.000	0	0.000
1 (*n* = 1,851)	0	0.000	1	0.001	0	0.000
2 (*n* = 1,000)	1	0.001	0	0.000	0	0.000
≥3 (*n* = 2,983)	4	0.001	0	0.000	0	0.000

* The donation-based incidence rate was calculated as 100 × number of AEs/number of donations.

was 0.4 years in the control arm and 0.7 years in the individualized arm.

Adverse Events

Overall, 19 severe AEs occurred in the control arm, which corresponds to 0.006 AEs per year at risk and a donation-based incidence of 0.019% (97,540 donations in total). In the individualized arm, 212 severe or life-threatening AEs were observed, also corresponding to 0.006 AEs per year at risk and a donation-based incidence rate of 0.014% (1,491,223 donations in total). In donors with ≥3 IgG-measurements below the threshold, the incidence of severe AEs was almost identical in the individualized and control arms (Table 5). In donors with ≥3 IgG-measurements below the threshold, the incidence of severe AEs was almost identical in the individualized and control arms (Table 5). Only one out of 19 (5.3%) AEs of the control arm was categorized as probably related to the donation while 14 AEs (6.6%) in the individualized arm were deemed possibly or probably related to donation (Table 6).

During the study period, 187 infections were observed in control arm donors. Of these, 63 (33.7%) were categorized as mild and 124 (66.3%) as moderate. No severe, life-threatening or fatal infections were reported. The donation-based incidence rate was 0.192% and 0.060 infections occurred per year at risk. Incidence rates for mild and moderate infections were comparable for all control arm donors, regardless of the number of IgG-measurements below the threshold. A possible causal relationship to donation was reported for 2 infections (1 mild and 1 moderate; Table 7). Both infections occurred in donors with ≥3 IgG-measurements below the threshold who continued plasmapheresis. No significant statistical differences were found for donation-based incidences and causal relationships in donors with 0, 1, and 2 IgG levels below 6.0 g/L.

Table 7. Overall reported infections by number of IgG-measurements below the threshold

IgG-measurements below the threshold, *n*	Mild		Moderate		Severe		Life-threatening		Fatal		Total	
	n	incidence, %	*n*	incidence, %	*n*	incidence, %	*n*	incidence, %	*n*	incidence, %	*n*	incidence, %
Control arm (*n* = 1,462)												
0 (*n* = 544)	20	0.068	42	0.142	0	0.000	0	0.000	0	0.000	62	0.210
1 (*n* = 226)	7	0.058	15	0.125	0	0.000	0	0.000	0	0.000	22	0.183
2 (*n* = 134)	5	0.068	7	0.095	0	0.000	0	0.000	0	0.000	12	0.164
≥3 (*n* = 558)	31	0.064	60	0.123	0	0.000	0	0.000	0	0.000	91	0.187
Individualized arm (*n* = 14,281)												
0 (*n* = 8,447)	510	0.071	752	0.104	6	0.001	0	0.000	0	0.000	1,268	0.175
1 (*n* = 1,851)	98	0.061	152	0.095	1	0.001	0	0.000	0	0.000	251	0.157
2 (*n* = 1,000)	69	0.073	96	0.101	0	0.000	0	0.000	0	0.000	165	0.174
≥3 (*n* = 2,983)	240	0.047	362	0.070	3	0.001	0	0.000	0	0.000	605	0.118

The donation-based incidence rate was calculated as 100 × number of infections/number of donations.

Table 8. Infections with a possible or probable causal relationship to plasmapheresis by number of IgG-measurements below the threshold

Number of IgG measurements below the threshold	Mild		Moderate		Severe	
	n	incidence, %	*n*	incidence, %	*n*	incidence, %
Control arm (n = 1,462)						
0 (*n* = 544)	0	0.000	0	0.000	0	0.000
1 (*n* = 226)	0	0.000	0	0.000	0	0.000
2 (*n* = 134)	0	0.000	0	0.000	0	0.000
≥3 (*n* = 558)	1	0.002	1	0.002	0	0.000
Individualized arm (n = 14,281)						
0 (*n* = 8,447)	18	0.002	6	0.001	0	0.000
1 (*n* = 1,851)	3	0.002	5	0.003	0	0.000
2 (*n* = 1,000)	2	0.002	0	0.000	0	0.000
≥3 (*n* = 2,983)	4	0.001	6	0.001	0	0.000

Number of IgG measurements below the threshold	Life-threatening		Fatal		Total	
	n	incidence, %	*n*	incidence, %	*n*	incidence, %
Control arm (n = 1,462)						
0 (*n* = 544)	0	0.000	0	0.000	0	0.000
1 (*n* = 226)	0	0.000	0	0.000	0	0.000
2 (*n* = 134)	0	0.000	0	0.000	0	0.000
≥3 (*n* = 558)	0	0.000	0	0.000	2	0.004
Individualized arm (n = 14,281)						
0 (*n* = 8,447)	0	0.000	0	0.000	24	0.003
1 (*n* = 1,851)	0	0.000	0	0.000	8	0.005
2 (*n* = 1,000)	0	0.000	0	0.000	2	0.002
≥3 (*n* = 2,983)	0	0.000	0	0.000	10	0.002

In individualized arm donors, 2,289 infections were reported; of these, 917 (40.1%) were mild, 1,362 (59.5%) moderate, and 10 (0.4%) severe. Severe infections were pneumonia (*n* = 2), high fever (*n* = 2), flu, Epstein-Barr-virus infection, infection of the mandibula, myocarditis, bronchitis, and gastrointestinal infection. There was no causal relationship to plasmapheresis for any of the severe infections and no life-threatening or fatal infections occurred. The donation-based incidence was 0.153%, i.e., lower than in the control arm, while the number of infections per year was 0.062, comparable to that in the control arm. Donors with ≥3 IgG-measurements below the threshold showed significantly lower donation-based incidences for infections than donors with 0, 1, or 2 IgG-

Table 9. Deaths in plasmapheresis donors

Gender, age, years*	First study donation	Last donation	IgG-measurements below the threshold, *n*	Date of death	Cause of death	Relationship
Control arm (*n* = 1,462)						
m, 48	Sept 28 ,2015	Oct 23, 2017	0	Oct 25, 2017	Cardiac arrest	No
Individualized arm (*N* = 14,281)						
m, 54	Dec 19, 2007	Apr 4, 2013	0	Apr 09, 2013	Accident	No
m, 41	Jan 31, 2008	Aug 18, 2008	≥3	Aug 26, 2008	Suspected suicide	No
m, 24	Nov 28, 2007	Aug 16, 2012	≥3	Aug 30, 2012	Suicide	No
m, 57	Nov 12, 2008	Feb 6, 2013	0	Feb 12, 2013	Sudden cardiac death	No
m, 28	Jan 16, 2009	Aug 5, 2010	0	Sept 24, 2010	Suspected suicide	No
m, 45	Aug 24, 2009	Oct 04, 2012	1	Oct 19, 2012	Sepsis after elective surgery (umbilical hernia)	No
m, 51	Jan 05, 2012	Mar 07, 2016	0	Mar 10, 2016	Work accident	No

m, male. * Age at time of death.

measurements below the threshold ($p < 0.0001$, $p = 0.0019$, and $p = 0.0013$, respectively) (Table 7). In 44 individualized arm donors, infections with possible or probable causal relationships were observed (Table 8). The highest incidence rate of infections with the possible or probable causal relationship was 0.005% in donors with one IgG measurement below the threshold. In donors with ≥3 IgG-measurements below the threshold, the incidence rate of mild infections with a possible or probable causal relationship was significantly lower than in donors without any measurements below the threshold ($p = 0.0357$).

One death was reported in the control arm and seven in the individualized arm (Table 9). None of the deaths were deemed related to plasmapheresis.

Discussion

Treatment with IgG is the standard of care for numerous diseases and is steadily increasing due to new indications for IgG therapy. Besides classical indications such as immunodeficiencies, neurological, and autoimmune diseases are effectively treated with IgG, resulting in an increased IgG demand [1, 5–12]. At the same time, there is a shrinking donor population in most high-income countries due to demographic changes [13, 14]. Current guidelines limit the frequency and volume of plasma donation and since the latest revision of the German haemotherapy guidelines, plasma donors are permanently deferred if IgG levels fall three times below 6.0 g/L [2]. Therefore, self-sufficiency with plasma products is challenging and there is a need to optimize plasma collection while ensuring donor safety. The aim of the present study was to evaluate if plasma donors with IgG-measurements below the threshold might be at risk of AEs, especially infections.

In this study, 15,743 donors were evaluated, of which 1,462 were allocated to the control arm and 14,281 to the individualized arm. The donation-based incidence of severe, life-threatening, and fatal AEs was 0.019% in the control arm and 0.014% in the individualized arm. The number of AEs and infections were higher in the individualized arm due to the higher number or participants compared to the control arm. For infections, the donation-based incidence was 0.192% for control arm donors and no significant statistical differences were found with respect to causal relationships comparing donors with 0, 1, and 2 IgG levels below 6.0 g/L. The donation-based incidence rate of infections was 0.153% for individualized arm donors. A lower donation-based incidence rate for infections is possible due to the stratified study design for control arm donors with initial IgG levels of >6–<8 g/L to a donation programme with 26 donations per year. In these programmes, the total number of donations was lower and the donation intervals were longer resulting in longer recreation phase of IgG. 38.2% of control arm donors had ≥3 IgG-measurements below the threshold in comparison to 20.9% of individualized arm donors. There were no increased incidence rates of severe AEs or infections in donors with ≥3 measurements below the threshold in either donor's arm.

The Study on Intensified PLAsmapheresis analysed the safety of intensified donor plasmapheresis [3]. In this study, IgG became evident as an important factor of individualized donor management. However, no data were available for donors with more than two donations with an IgG level below the threshold of 5.8 g/L because these donors were excluded from the study immediately after the third donation below this level.

Between 2008 and 2011, Diekamp and colleagues evaluated 1,107,846 donations for the safety of donor plasmapheresis [15] Generally, AEs were regarded as technical issues or local or systemic reactions occurring during or within 24 h of donation (48–72 h for local reactions). The local incidence of AEs was 1.4%, systemic was 0.55% and technical was 4.6%, totalling 6.55% for overall corrected donation-based incidence of AEs. The most regularly documented AEs were repeat venepuncture and discontinued collection, and most systemic AEs were of mild or moderate intensity. Donation-based incidence of severe systemic AEs was 0.036% [16]. The results of our study can be considered in line with previously published data, particularly considering the differences in AE definitions and observation periods [16–18].

Burkhardt and co-workers investigated IgG levels before, during, and after plasmapheresis [19]. They showed that the IgG level drop during plasmapheresis was 9% and 13% from baseline for 200 and 800 mL plasma collections, respectively. At the termination of a single plasmapheresis, the IgG decrease was 11.4% ± 3.4% in male and 14.1% ± 3.0% in female donors. This IgG level drop should be accounted for when scheduling a follow-up plasmapheresis to ensure an appropriate IgG recovery period.

A limitation of the present data analysis is that not the entire donor population of the participating centres was evaluated but only the donors participating in the study. Most voluntary donors did not participate in the study because they preferred being free to schedule their own donations. Furthermore, there might be differences in terms of the population and standard procedures between the participating centres, and seasonal effects on plasma collection frequencies and AE rates should also be considered. An impact of donor characteristics such as age, gender, and weight on IgG levels cannot be excluded although there exist no specific IgG limits for these parameters. Furthermore, donor's initial IgG level at the start of the study may change during the donation career affecting the incidence of infections. Another limitation is the fact that the time at risk was short in some donors. This is due to the fact that there was a data cut-off in 2017 when new guidelines with a permanent donor deferral in the case of 3 donations with an IgG level below the threshold of 6.0 g/L came into force.

In conclusion, no increased incidence rates of infections or severe AEs were observed in either control or individualized arm donors with ≥3 measurements below the threshold. Based on these findings, we believe that there is no need for permanent deferral of donors with ≥3 IgG-measurements below 6.0 g/L.

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Statement of Ethics

This study protocol was reviewed and approved by Ethic Committees of state chambers of physicians. The approval number of the leading ethic committee of the chamber of physicians Rhineland-Palatinate is 2018-13855. Written informed consent was obtained from all donors to participate in the study.

Conflict of Interest Statement

The authors are employees of Octapharma Plasma GmbH, Langenfeld, Germany.

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Author Contributions

U.T. and L.T. designed the study, collected, and analysed the data. R.M. wrote the first draft of the manuscript. All authors critically reviewed, revised, and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available.

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