International Journal of Immunopathology & Pharmacology

Original Research Article

Efficacy and safety of human intravenous immunoglobulin 5% (Ig VENA) in pediatric patients affected by primary immunodeficiency

International Journal of Immunopathology and Pharmacology
Volume 34: 1–10

DOI: 10.1177/2058738420943006
journals.sagepub.com/home/iji
SAGE

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Abstract

Patients affected by primary immunodeficiencies are characterized for high susceptibility for severe infections. Our data demonstrate Kedrion 5% intravenous immunoglobulin G (IVIg) treatment effective and safe as replacement therapy for children and adolescents affected by primary immunodeficiency. The particularities of our study are the selection of a long period of follow-up (71 patient-years of follow-up), and to the best of our knowledge, our study is one of few that assesses the safety and efficacy of intravenous immunoglobulin treatment of primary immunodeficiency specifically in a pediatric population.

Keywords

antibody defects, efficacy, immunoglobulin, infections, IVIg, primary immunodeficiency, safety

Date received: 8 January 2020; accepted: 25 May 2020

Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of disorders affecting one or more functions of the immune system. Although rare, PIDs are serious medical conditions due to their propensity to expose patients to serious and fatal infections.[1] Moreover, the emerging use of next-generation sequencing (NGS) has driven the rapid increase in the number of recognized disorders: the last classification of the International Union of Immunological Societies (IUIS) includes 416 immune defects.[2] More than half of all PIDs are characterized by impaired antibody production leading to increased susceptibility to infection. In these patients, chronic or recurrent upper and lower respiratory tract infections, sinusitis, and otitis media are the most common type of infections, but invasive bacterial diseases such as sepsis, meningitis, septic arthritis, and osteomyelitis can also occur.

Patients with antibody deficiencies require lifelong intravenous or subcutaneous immunoglobulin G (IVIg or SCIg, respectively) replacement therapy (IRT) to prevent serious bacterial and viral infections, reduce the number and duration of hospitalizations, and minimize lost school/work days.[3,4] Immunoglobulin replacement therapy has been standard treatment for patients with PID since its first use by Bruton[5] in 1952. Many authors have

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demonstrated that patients' health status improves rapidly once regular IVIg is initiated, reducing their activity limitations[6] with a positive impact on patients' outcomes and on long-term quality of life.[4,7] Most national and international guidelines suggest a mean dose of 0.4 to 0.6 g/kg/month for IRT.[8] However, IgG dosage needs to be adjusted on an individual basis, with the aim of reaching IgG trough levels greater than 5 g/L.[8]

IRT is standard therapy for patients with PID. Since most patients with PID will need long lifetime IRT, the efficacy and safety of prescribed IgG products are critically important. Adverse events (AEs) associated with IgG administration may not only be disturbing for the patients, but may also impact patients' compliance and adherence to therapy. A key focus of contemporary IRT is to improve manufacturing processes of IgG to ensure purity and tolerability while preserving effectiveness. We aimed to assess the efficacy and safety of Ig VENA 5% Kedrion SpA, Castelvecchio Pascoli, LU, Italy (IVIg 5%) replacement therapy in pediatric patients with PID.

Methods

Study design

This is a retrospective, observational, single-center study. The study enrolled 20 PID patients under 18 years of age and treated with IVIg 5% at a dose of 400–800 mg/kg body weight every 3–4 weeks for at least 12 months at the Paediatric Immunology Division, Meyer Children's University Hospital in Florence, Italy. The duration of study was 19 years (from 1998 to February 2017). PID is diagnosed in accordance with ESID criteria (available on https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria, latest version January, 22, 2019).

Patients' demographic characteristics, diagnosis, number of infections, IVIg dosages, adverse effects, and serum immunoglobulin levels were extracted from their medical records at the Hospital and added to the study database.

The study was approved by the Ethics Committee of Meyer Children's University Hospital and was conducted in accordance with the Declaration of Helsinki and current regulations for observational studies. Written informed consent from the patient and/or the patient's parent/legal guardian, as appropriate, was required before participation in the study.

Data were collected in accordance with the European Medicines Agency (EMA)[9] guidelines on the clinical investigation of human IVIg in force at the time of data collection.

Medication description

Ig VENA 5% Kedrion SpA, Castelvecchio Pascoli, LU, Italy IVIg 5%, is a ready-to-use, sterile, 5% liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration.

Endpoints

The primary efficacy endpoint was the mean serum pre-infusion IgG levels after start of treatment and the rate of serious bacterial infections (SBIs, defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess)[9] per patient-year on treatment. Secondary endpoints were the number of episodes per patient-year of no serious infections (any other infection that was not classifiable as SBI), the number of days of antibiotic use per patient-year on treatment and type, and the number of days of absence from school per patient-year on treatment. These data were collected from previously compiled patient records.

Safety data included the type and frequency of AEs retrospectively collected from patient records. The severity of AEs was described as mild (no significant discomfort to patient or change in routine activities), moderate (limitation in activity with possible need for some assistance; no or minimal medical intervention/therapy required), or severe (marked limitation in activity requiring assistance; medical intervention/therapy required). AEs were identified as serious (SAEs) if they resulted in death or persistent or significant disability/incapacity, were life-threatening, required hospitalization or prolongation of existing hospitalization, or other important medical event may jeopardize the patient or may require intervention to prevent one of the other previous listed serious outcomes.

Statistical analysis

The sample size for the study was determined based on feasibility criteria. Based on the number of patients with PIDs treated with intravenous immunoglobulins managed at our center, it was

considered reasonable to include 20 patients. Precision of the estimates was evaluated in terms of confidence intervals (CIs) for the SBI rate based on reports of previous studies with intravenous immunoglobulins therapies, and we calculated the minimum requested number of patient-years exposure.

Statistical analysis was performed using SPSS (Version 25.0, SPSS, Inc., Chicago, IL, USA). Metric data were tested for normal distribution. Continuous variables were expressed as mean values and standard deviations. The rate of serious infections/year for each patient was presented as point estimates of the rate along with a 99% confidence interval (CI) and was calculated as total number of serious infections / patient-years on 5% IVIg treatment. Appropriate non-parametric statistical tests were used, wherever applicable, to determine the statistically significant differences ($P < 0.05$) between two periods (P1 vs P2).

Results

Patient data

In total, 20 patients affected by PID were enrolled, in accordance with the inclusion criteria reported into the study protocol. Briefly, the mean age of this population at diagnosis was 6.6 years (range 0–17 years). At diagnosis, the patients started IVIg and therefore 6.6 years is also the mean age of inclusion in the study. The mean duration of exposure to IVIg 5% in the 20 pediatric patients included in the study was 3.5 ± 2.4 years. The minimum follow-up period was 1 year and the maximum follow-up period was 11 years (Table 1). The first patient started treatment in 1998 and the last patient started treatment in November 2015. Treatment end dates ranged from 2003 to February 2017. Nine of 20 patients (45%) were affected by agammaglobulinemia (2 patients with autosomal recessive (AR) agammaglobulinemia and 7/20 patients with X-linked agammaglobulinemia (XLA)), 8/20 patients (40%) were affected by common variable immunodeficiency (CVID), and 3/20 patients (15%) were affected by hypogammaglobulinemia (1 patient with transient hypogammaglobulinemia of infancy and 2 patients with 22q11 deletion).

All patients (n = 20) received a dose of between 400 and 800 mg/kg per month for each infusion. The mean total amount infused was 632.4 ± 435.7 g (range 60.0–1,605.0 g) and a total of 12,647.50 g of IVIg 5% was infused in these 20 patients over a total of 71 patient-years of follow-up.

All demographic and disease characteristics for the 20 patients included are presented in Table 1.

Efficacy

Primary endpoint. Mean serum IgG levels before starting replacement therapy were reported for 19 patients and was 221.2 ± 164.6 mg/dl (range 0–668.0 mg/dl) (Table 1). No patients have received before other immunoglobulin replacement therapy. Patients affected by agammaglobulinemia showed a mean serum IgG levels lower than CVID patients (Student *t* test, *P*: 0.034). Mean serum pre-infusion IgG levels during follow-up were 654.5 ± 120.0 mg/dl (range 528.0–958.0 mg/dl) (Table 1), without significant differences between agammaglobulinemia and CVID subgroups.

In total, 132 patient-years were observed prior to clinical diagnosis and initiation of IVIg treatment. The pre-treatment clinical picture was characterized by frequent and severe infections including pneumonia in 8/20 patients (40%), sepsis in 2/20 patients (10%), chronic diarrhea in 2/20 patients (10%), otitis with perforation in 3/20 patients (15%), and disseminated varicella zoster virus infections in 2/20 patients (10%). The proportion of patients who reported severe infections before starting IgG replacement therapy was 85% (17/20), with a total of 17 episodes in 132 patients-years.

Among the above-listed infections, recurrent pneumonia (in 8 patients) and sepsis (in 2 patients) were classified as serious infections in accordance with the EMA Guideline on the Clinical Investigation of Human Normal IVIg.[9] No other serious infections as defined by this guideline, such as bacteremia or sepsis, bacterial meningitis, osteomyelitis, septic arthritis, or visceral abscess, were reported.

During the post-treatment period, two patients (10%) reported two serious infectious episode events; these were pneumonia and pneumococcal pneumonia. The serious infectious diseases rate during follow-up is 0.028 per patient per year (Table 2).

The overall number of SBIs during the pre-treatment period was 17, whereas the total number of SBIs during the treatment period was 2. A McNemar exact test reveals a significant difference in SBI

Table 1. Study drug administration enrolled set.

Patient number	Age of patient at the diagnosis (years)	Diagnosis of primary immunodeficiency	Follow-up (years)	IgG levels before starting the replacement therapy (mg/dl)	Mean serum pre-infusion IgG level during the follow-up period (mg/dl)
1	9	Hypogammaglobulinemia in patient with 22q11 deletion syndrome	6	283	733
2	12	Hypogammaglobulinemia in patient with 22q11 deletion syndrome	3	271	893
3	1 .2	CVID	3	196	560
4	11	CVID	1	439	545
5	13	CVID	3	108	533
6	13	CVID	3	362	693
7	11	CVID	2	188	620
8	9	CVID	1.3	279	770
9	3.25	AR Agammaglobulinemia	3	0	752
10	0.7	XL Agammaglobulinemia	5	87	557
11	0.6	AR Agammaglobulinemia	3	69.2	650
12	1.3	XL Agammaglobulinemia	3	10.00	690
13	0	XL Agammaglobulinemia	11	250	528
14	11	XL Agammaglobulinemia	7	25	578
15	1,6	XL Agammaglobulinemia	1	NA	547
16	14	CVID	1.2	668	958
17	17	CVID	1.2	187	610
18	0.7	THI	3	188	688
19	1.7	XL Agammaglobulinemia	5	363	580
20	0.6	XL Agammaglobulinemia	5	228	625

IgG: immunoglobulin G; CVID: common variable immunodeficiency; AR: autosomal recessive; XL: X-linked; THI: Transient Hypogammaglubulinemia of Infancy.

Table 2. Serious bacterial infections (SBIs) and severe infections per patient-year in the study population before and during the replacement therapy.

	Before the starting of replacement therapy	During follow-up	*P*
Total no. of serious bacterial infections	10	2	*0.170*
Bacterial pneumonia	8	2	
Sepsis	2	0	
Other severe infections	7	0	***0.048***
All serious and severe infections	17	2	***0.019***
Total number of patients with SBIs	10	2	*0.170*
Number of patient-years exposure	132	71	
Rate of severe infections per patient-year	0.13	0.028	***0.021***

Note: Bold values denote statistical significance at the p < 0.05 level.

rate between the pre-treatment and treatment period ($P = 0.021$).

One patient (01) presented chronic Evans syndrome associated with hypogammaglobulinemia at diagnosis. During long follow-up of 6 years, only one episode of thrombocytopenia occurred, and anemia has been resolved.

Secondary endpoints. Overall, there were 287 non-serious infectious events reported by 18/20 patients (90%) during the follow-up period. The non-serious infection rate was 4.06 per patient per year, and the annualized all-infections rate was 4.08 per patient-year.

The most frequently reported event was upper respiratory tract infections, with 161 events (56.1%) reported by 12 patients (161/287; 56.1%), followed by gastrointestinal disorders (38/287; 13.2%), sinusitis and otitis (37/287; 12.9%), and others (enterobiasis, oral candidiasis, conjunctivitis, pharyngitis,

Table 3. Display of all non-serious infectious episodes and therapy related adverse events during follow-up by MeDRA System Organ Class (SOC) and Preferred Term (PT).

System Organ Class Preferred term	All patients (n = 20)		
	Number (%) of subjects	Number of events	Therapy-related events
At least one non-serious infectious episode	18 (90.0%)	287	0
Gastrointestinal disorders	5 (25.0%)	19	0
Diarrhoea[a]	3 (15.0%)	10	0
Vomiting[a]	2 (10.0%)	9	0
General disorders and administration site conditions	1 (5.0%)	1	0
Pyrexia	1 (5.0%)	1	0
Infections and infestations	18 (90.0%)	259	0
Campylobacter gastroenteritis	1 (5.0%)	1	0
Conjunctivitis	2 (10.0%)	6	0
Ear infection	1 (5.0%)	3	0
Enterobiasis	1 (5.0%)	12	0
Gastroenteritis	5 (25.0%)	17	0
Gastroenteritis rotavirus	1 (5.0%)	1	0
Influenza	2 (10.0%)	2	0
Oral candidiasis	1 (5.0%)	1	0
Otitis media	1 (5.0%)	5	0
Pharyngitis	1 (5.0%)	1	0
Pharyngitis streptococcal	1 (5.0%)	2	0
Respiratory tract infection	2 (10.0%)	13	0
Sinusitis	5 (25.0%)	29	0
Skin infection	1 (5.0%)	1	0
Upper respiratory tract infection	12 (60.0%)	161	0
Urinary tract infection	1 (5.0%)	3	0
Varicella zoster virus infection	1 (5.0%)	1	0
Respiratory, thoracic, and mediastinal disorders	1 (5.0%)	8	0
Cough[a]	1 (5.0%)	8	0

Two patients each reported a non-serious infection (diarrhea and cough) without specifying the number of occurrences and hence are not included in this table.

[a]Diarrhoea, vomiting, and cough were considered non-serious infections by the Investigator. The original causes of these events were not reported in the clinical records of the patients and were not inserted into the CRFs accordingly; for this reason the events were included into the database as they were.

skin infection, 51/287; 17.8%). All non-serious infections events are detailed in Table 3.

Antibiotics were administered to treat a serious or non-serious infections in 15/20 patients (75%) during the observational period. Of these, two patients (02 and 06) needed antibiotic therapy for serious infections during the follow-up period. One patient was treated for pneumonia for a period of 11 days with azithromycin, clarithromycin, and ceftriaxone; the second patient was treated for pneumococcal pneumonia with ceftriaxone for an unspecified period. The penicillin combination product amoxicillin and clavulanic acid was the most frequently prescribed antibiotic (12/15; 80%).

Overall, 10/20 patients (50%) lost school days due to non-serious infectious episodes. In these patients, the number of days lost ranged from 2 to 20 days for a total of 110 days in a total across 68 patient-years of follow-up. Nine patients (9/20; 45%) did not miss any school days. These data were not available for one patient because the patient was not included in the community during the follow-up period. The number of school days missed before treatment was not known.

Safety results

During 71 patient-years of follow-up, 287 non-serious and two severe infections were recorded. Six patients (6/20; 30%) were hospitalized during the follow-up period. The causes of hospitalization were diarrhea and thrombocytopenia (n = 1), seizures and

Table 4. Display of hospitalizations during follow-up.

Patient number	Diagnosis of primary immunodeficiency	Hospitalization occurred during the follow-up period	Days of hospitalization	If yes, specify	Was the hospitalization due to the occurrence of an adverse reaction
1	Hypogammaglobulinemia in patient with 22q11 deletion syndrome	yes	16	Thrombocytopenia	no
			na	Rotavirus gastroenteritis	no
2	Hypogammaglobulinemia in patient with 22q11 deletion syndrome	yes	11	Seizures during pneumonia	no
3	CVID	no			
4	CVID	no			
5	CVID	no			
6	CVID	yes	5	Gastroenteritis with dehydration	no
7	CVID	no			
8	CVID	no			
9	AR Agammaglobulinemia	no			
10	XL Agammaglobulinemia	no			
11	AR Agammaglobulinemia	yes	3	Scheduled surgery for reduction of turbinates	no
12	XL Agammaglobulinemia	yes	3	Gastroenteritis with dehydration	no
13	XL Agammaglobulinemia	yes	2	Videocapsule endoscopy	no
14	XL Agammaglobulinemia	no			
15	XL Agammaglobulinemia	no			
16	CVID	no			
17	CVID	no			
18	THI	no			
19	XL Agammaglobulinemia	no			
20	XL Agammaglobulinemia	no			

CVID: common variable immunodeficiency; AR: autosomal recessive; XL: X-linked.

pneumonia (n = 1), gastroenteritis (n = 2), and scheduled surgery procedure (n = 2). The reasons for hospitalization are detailed in Table 4. In a total period of 71 patient-years of follow-up of these 20 patients, 41 days of hospitalization were recorded (rate of hospitalization 0.58 per person-year). The exact number of days of hospitalization in the pre-treatment period was not available because patients were followed at other hospital centers. No deaths or withdrawals due to AEs were reported during the study period.

None of the reported infections and/or hospitalizations were assessed to be related to the IVIg 5% use (Tables 3 and 4).

Discussion

Efficacy: primary and secondary endpoints

Primary antibody deficiencies are characterized by impairment of clinically effective Ig responses. Patients most commonly present with recurrent respiratory infections. Lifelong IRT with Ig increases life expectancy and reduces the frequency and severity of infections.[10] IVIg replacement is indicated in all patients with IgG levels < 2 g/L, in patients with documented frequent bacterial or viral infections and a specific antibody deficiency with IgG levels between 2 g/L and 5 g/L, and in patients with IgG levels > 5 g/L but with severe and recurrent infections combined with a specific antibody deficiency.[8] All patients included in this study present one of these characteristics.

The Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology considers maintenance of IgG trough levels > 5 g/L in hypogammaglobulinemic patients as definitely beneficial to reduce infectious consequences.[8]

Accordingly, in our study, IgG levels following IVIg administration were above the protective

limit of 5 g/L for all patients enrolled, demonstrating the efficacy of IVIg 5% in reaching the recommended levels with a dose of 400–800 mg/kg/month.

The EMA guideline in force at the time of data collection for the efficacy evaluation required a finding of serious infection rate per patient-year of < 1.0 to demonstrate adequate evidence of efficacy of IVIg as substitution therapy.[9] The annual number of SBIs was 0.028 per patient, significantly lower than the predefined threshold of 1.0 infection/patient/year, confirming the efficacy of IVIg 5% in preventing the occurrence of serious infections in PID patients. Previously, several studies have analyzed the efficacy of Ig treatment in patients affected by PID.[11–18] Although these studies are heterogeneous in study design (i.e. prospective or retrospective), patient characteristics (e.g. pediatric or adult populations, number of years exposure), and methodology, our data are nonetheless largely comparable to those presented in the literature (Table 5). Our study included children with a higher number of patient-years exposure than the majority of other similar studies (Table 5). The rate of acute SBIs is well in line with the literature ranging from 0 to 0.1, and ranks among the lowest. The annual all-infections rate (4.06 per patient/year) and the annual rate of days missed from school (1.6 days/patient/year) are comparable to those seen in other PID studies (Table 5) and also to studies in healthy children attending daycare,[21,22] confirming that the dosing and corresponding trough levels observed in this study were adequate. As expected, in patients affected by humoral defects, most infections involved the respiratory tract. Our study did not find a significant correlation between IgG trough levels and number of all infections (one-way analysis of variance; $P > 0.05$, data not shown). The rate of antibiotic use in our study (75% of all patients) appears high but is lower than that found in another pediatric study.[11] Moreover, as Ochs and colleagues suggest, it is not possible to correlate the use of antibiotics with the severity of infection since antibiotic therapy is promptly recommended by most clinicians during each acute infection in immunocompromised patients, due to their increased risk of complications.

For more than 20 years, immunoglobulins are widely used as a modulatory factor in the treatment of autoimmune and inflammatory diseases that represent a common finding in primary immunodeficiecies.[23,24] Patient 01 was affected by Evans syndrome in the context of 22q11 deletion. IVIg, even through at replacement dose (400 mg/kg/28 days) improved his clinical disease course. The mechanism of immunoglobulin effect on the immune system is complex and still remains a topic of research; the hypothesized beneficial role in blood disorders is based mainly on Fc phagocyte receptor saturation and neutralization of anti-platelet antibodies by anti-idiotypic antibodies. Recently, Wang et al.[25] demonstrated in their study that IVIg therapy results in increasing of Tregs, which suppresses innate lymphoid cells proliferation, associated with platelet response. Data from literature indicate that in patients with PID, IVIg exert an active effect, rectifying the defective signaling.[26]

Safety

IVIg treatment is a lifelong and complex therapy, and can lead to AEs. In 1982, the World Health Organization (WHO) established requirements for safety and quality of IVIg preparations for the first time. Since then, the manufacturing processes of Ig have evolved: analytical methods and purification processes are being continuously improved to maximize both safety and structural/functional integrity of highly purified human immunoglobulins.

Safety data were collected from previously filled clinical records of patients with PID. Nevertheless, it is significant that during the entire observational study, no related mild or moderate AEs or notable changes in laboratory parameters, vital signs, and physical examination were reported. Of the 287 non-serious infections recorded during follow-up (Table 3), no correlation was established with the use of IVIg 5%. SAEs leading to hospitalization occurred in 6 patients. These were considered unrelated to the use of IVIg 5% (Table 4).

Our data demonstrate that IVIg 5% at a dose between 400 and 800 mg/kg/3–4 weeks is a well-tolerated and safe product in this pediatric population.

Conclusions

To the best of our knowledge, our study is one of few that assesses the safety and efficacy of intravenous immunoglobulin treatment of PID specifically in a

Table 5. Efficacy data of intravenous immunoglobulin (IVIG) treatment in literature.

	Panzyga® 10%[11]	Panzyga® 10%[12]	Privigen® 10%[13]	Flebogamma® 10%[14]	Flebogamma® 5%[15]	Kiovig® 10%[16]	Biotest IVIG®10%[17]	Octagam® 5%[18]	IGIV® 10%[19]	Flebogamma® 5%[20]	**Kedrion® 5% [current study]**
Study population	Children	Children and adults	Children and adults	Children and adults	Children and adults	Children and adults	Children and adults	Children and adults	Children and adults	**Children**	**Children**
Dose	200–800 mg/kg every 3 or 4 weeks	200-800 mg/kg every 3 or 4 weeks	200-888 mg/kg every 3 or 4 weeks	300-600 mg/kg every 3 or 4 weeks	300-600 mg/kg every 3 or 4 weeks	300–450 mg/kg every 3 weeks	254–1029 mg/kg infused every 3 or 4 weeks	300-600 mg/kg every 3 or 4 weeks	300-600 mg/kg every 3 or 4 weeks	300-800 mg/kg every 3 or 4 weeks	**400-800 mg/kg every 3 or 4 weeks**
Number of patient-years exposure	25	50.2	80	46	52	22	63	46	61	24	**71**
SBIs rate/patient/year	0.04	0.08	0.08	0.025	0.061	0	0.035	0.1	0.060	0.05	**0.028**
All-infections rate/patient/year	3.7–6.7	3.68	3.55	2.2	na	5.76	2.2	na	na	na	**4.08**
Days missed /patient/year	3.2-7.4	3.64	7.94	3.0	na	0-1.58	2.28	5	na	na	**1.6**

In bold the results of our study. In the parenthesis there is the number of the reference.

pediatric population. This study has some limitations due to the retrospective nature of the study design. First is the low patient size; for this reason, we have selected a long follow-up (71 patient-years exposure) to provide an adequate IRT exposure period. Second, many laboratory and clinical data were not available due to the retrospective nature of study design. Third, according to the study protocol, it was no possible to compare different products, but we provided a theoretical comparison with other products, previously described in literature.

The findings of this study are limited by the retrospective and observational design; however, these results may still inform the use of Kedrion 5% IVIg in normal clinical practice in this population. The treatment is effective in reducing SBI rate, with no AEs determined to be related to treatment, thus demonstrating its suitability as replacement therapy for children and adolescents affected by PID.

Acknowledgements

The authors thank the patients who took part in this study The authors also acknowledge the help of Dr. Nguyen Huy-Binh who provided advice during the writing of this manuscript.

Author contributions

SR, FL, CC, and CA were involved in the study design development, oversaw the study at the main recruiting sites, data collection and analysis, and they were extensively involved in the manuscript writing and reviewing process. C.G. and R.M. were the clinical project managers at Kedrion SpA and were involved in study design and manuscript reviewing process. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declare that this study received funding from Kedrion SpA. The funder had the following involvement with the study: study design and manuscript reviewing process.

S.R. and F.L. received support for travel and participation fees for scientific meeting from Kedrion SpA in the last 3 years.

FL has received fees as a consultant for Kedrion SpA in the last 3 years. C.A.'s institution has received research grant support from Kedrion SpA for this study. C.G. and R.M. are employers of Kedrion SpA. C.C. declares no conflicts of interest.

Ethics approval

Ethical approval for this study was obtained from Tuscan Regional Ethics Committee. Protocol no: KBOs008 (143/2017).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Kedrion SpA.

Informed consent

Written informed consent was obtained from parents or legally authorized representatives of patients before the study.

Trial registration

Not applicable because it is observational retrospective study.

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