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UK PID Patients: Overview of perception on IgRT and infections using short survey

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Immunoglobulin replacement therapy (IgRT) has advanced over the years and is used to treat many patients with primary immunodeficiencies reducing the number of infections and the burden of disease. We investigated the perception of IgRT in two patient groups (UKPIPS and PID UK) and their condition through a short survey. The survey was a multiple-choice short survey consisting of 20 questions completed either online or on paper. Data analysis was performed using SAS analysis software using regression analysis, correlation analysis and t-tests. Statistical significance was considered with $p<0.05$. 278 surveys were analysed which showed that the majority of participants were satisfied with the immunoglobulin therapy they received (n=225, 80.9%). However, there was a small but significant number of participants (n=19, 6.9%) that still experienced severe and very severe infections despite adequate IgRT. 236 (84.9%) participants reported limitations in daily life due to infections. The dissatisfied participants (n=55, 18.3%) had more non-routine visits to healthcare providers, higher numbers of antibiotic treatments and more days absent from school, work, university or equivalent than the satisfied participants.

1. Introduction

Immunoglobulin replacement therapy (IgRT) has been shown to be effective in treating patients with primary immunodeficiency (PID) (Perez et al. 2017). More recently, “inborn errors of immunity” (IEI) has been used as a broader term to describe these disorders (Perez 2022; Seth et al. 2021). The majority of PID patients suffer from an impaired production of antibodies resulting in an increased susceptibility to infections and other immune dysfunctions which lead to significant morbidity and mortality if not treated (Mahlaoui et al. 2014). Common variable immunodeficiency (CVID) is the most frequently diagnosed compared to other PID disorders and is characterized by reduction of two or more immunoglobulin isotypes (IgG, IgA and/or IgM).

IgRT has become the standard therapy for PID patients effectively reducing the incidence of infection (Krivan et al. 2017). Over the years, there have been many advances in immunoglobulin products, such as quality, safety, tolerability and efficacy (Bienvenu et al. 2016). These improvements have increased life expectancy of patients with PID and have also provided a better quality of life (Espanol et al. 2014). Although IgRT is effective and improves quality of life in patients, many still suffer from an elevated number of infections. Thus, patient experience should be continuously explored to confirm therapy success and to drive further positive innovation. It is important to know whether patients still feel burdened or limited by their condition. Studies have shown IgRT decreases infectious complications and prevents organ damage progression if received after early diagnosis (Busse et al. 2002). While immunoglobulin levels and fewer infections are important to measure, many other aspects of patients’ lives are impacted and are often not captured in the clinical picture (Jones 2018). Patient perception and experience is crucial in clinical care and considering this view is important when trying to improve patient satisfaction and long-term outcome (Quinti et al. 2016).

PIDs are a class of heterogeneous disorders, the two most common forms of which are CVID and X-linked agammaglobulinaemia (XLA) (Wood 2009). The majority of patients experience recurrent infections and inflammatory/auto-immune complications, however the clinical phenotype is variable and pathogenesis is unknown for most cases (Bousfiha et al. 2018). XLA is a monogenic inherited disorder and being X-linked mostly affects the male population with presentation in infants usually as a result of recurrent bacterial infections (McCusker and Warrington, 2011). Suspicion of PID is usually raised through severe, recurrent or unusual infections. Bacterial infections are most common due to bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* which cause upper and lower respiratory tract infections. Although IgRT reduces the likelihood of an infection occurring, the therapy does not prevent some persistent infections therefore antibiotics and antibiotic prophylaxis are commonly used (Aguilar et al. 2014).

Early diagnosis is challenging due to variability in clinical presentation, age at onset and the overall heterogeneity of these disorders (Slade et al. 2018). Infections that PID patients experience can also be attributed to other disorders, therefore diagnosis may be protracted and challenging for physicians. Screening tests such as serum immunoglobulin concentration that can easily detect immunodeficiency are not routinely used (Holding et al. 2015). Hence, delay in diagnosis is common and many patients will already be suffering from severe organ damage and other complications by the time treatment commences. Studies have estimated the median diagnostic delay to be 4 to 6 years but this can vary between patients (Odnoletkova et al. 2018; Slade et al. 2018).

As part of the advance in immunoglobulin therapy, administration can now be achieved via alternative routes, intravenously or subcutaneously. Each route of administration has advantages and disadvantages and the choice of route must be individualised to suit the needs of each patient (Krivan et al. 2017). Intravenous immunoglobulin (IVIg) is administered every 3–4 weeks through venous access. IVIg raises serum IgG to an initial peak which then declines over time through pharmacokinetics which are patient specific until the trough level is reached prior to the next dose (Jolles et al. 2015). IV infusions are normally given at out-patient clinics but can also be managed by some patients at home with health system support (Bienvenu et al. 2016). Subcutaneous immunoglobulin (SCIg) involves the injection of smaller volumes of a higher concentration presentation (up to 20%) into the fatty tissue below the skin. This is done at multiple sites using smaller doses administered more frequently, thus resulting in lower variation between peak and trough IgG serum concentrations (Skoda-Smith et al. 2010). SCIg can be self-administered at home either using a mechanical pump or by direct manual injection and therefore may be preferred by certain patient groups due to the increased flexibility this route offers (Jones et al. 2018).

IgRT is used to reduce the burden of disease, however, burden of disease and the quality of life of a patient should not just focus on the physiological aspects but must also include the psychological and social aspects that are also associated with and affected by the disorder and its treatment (Seeborg et al. 2015). All immunoglobulin products are consisting mostly of IgG, however CVID, the most frequently diagnosed disorder, may affect more than one immunoglobulin isotype and may also involve dysregulation of other humoral or cellular aspects of the immune system. Therefore, patients with PID in general and in particular those suffering from CVID may be suffering due to a deficiency in the other immunoglobulin isotypes or non-immunoglobulin immune system components. The burden that patients feel in dealing with PID must be understood by clinicians, immunologists and industry to enable them to further improve clinical care and support (Quinti et al. 2016). We therefore aimed to take the first step in checking the value of the progress we have made by understanding the perspective that really matters; that of the patient.

Here, a survey was conducted to assess the quality of life and perception of patients with PID. In this study a questionnaire was designed in conjunction with and distributed by, two patient groups in the United Kingdom: UK Primary Immune-deficiency Patient Support (UKPIPS) and Primary Immunodeficiency UK (PID UK) (since re-named as Immunodeficiency UK or ID UK). The aim of the evaluation was to determine the patients' satisfaction with the current immunoglobulin replacement therapy and the number of participants that still experienced severe and very severe infections despite this therapy and thus the need for improved immunoglobulin replacement therapy among PID patients.

2. Investigations and results

A retrospective study on patient perception was performed using a survey focusing on immunoglobulin replacement therapy, satisfaction with therapy, and infections.

2.1. Survey participants

A survey was conducted by Biotest UK in collaboration with patient support groups PID UK and UKPIPS. Participants in this study were PID patients who were registered as members of either PID UK and/or UKPIPS. The inclusion criteria for this study were a PID diagnosis, current IgRT and informed consent. There was no age restriction. The exclusion criteria for this study were: informed consent not provided, not being diagnosed with a PID, not receiving IgRT or not answering the questions which were necessary to ascertain that the inclusion criteria had been fulfilled. All data was collected before the COVID-19 pandemic.

2.2. Survey design and administration

The survey was based on a bank of questions devised by Professor Klaus Warnatz of the Center for Chronic Immunodeficiency (CCI) at the Center for Translational Cell Research, Department of Rheumatology and Clinical Immunology, Freiburg, Germany. The appropriate questions were selected, translated into English, optimised for online use and then tailored for UK patients with the advice of the patient support groups UKPIPS and PID UK. UKPIPS and PID UK finally reviewed the online and paper versions of the survey for appropriateness using patients, patient representatives and clinical immunologists. Information was collected on type of PID, current treatment, infection suffered and patient satisfaction. The survey consisted of 20 questions that could be easily understood and would take approximately five minutes to complete. The majority of the questions were closed, multiple choice with only one open question with a free text written answer. Participants were given the option to leave certain answers blank if they could not answer. However, if no answers were given to the mandatory questions, those participants were excluded.

No data was collected on race, ethnicity or gender thus increasing anonymity of the patients. No sensitive data was collected except year of birth. All participants were volunteers, provided written informed consent and no compensation was provided.

The survey was completed through either online or paper methods. The online survey was made available to patients through PID UK and UKPIPS and was distributed through their mailing lists, the website of the organization, at meetings and through social media. The host website of the survey was surveymonkey.com and was available for a month from February 2016 to March 2016. IP address blocking was used to prevent the patients repeating the survey. Paper questionnaires were available upon request.

2.3. Data (statistical) analysis

Descriptive analysis was used on all data. Statistical analysis was performed using SAS software including regression analysis, correlation analyses and t-tests. Statistical significance was set at $p<0.05$.

Table 1: Participant characteristics

Parameter		Number of subjects (N=278) n (%)
Administration of current immunoglobulin therapy	Intravenous infusion (iv)	114 (41.0%)
	Subcutaneous injection/infusion (sc)	160 (57.6%)
	Missing	4 (1.4%)
Duration of current immunoglobulin therapy	Less than 1 year	44 (15.8%)
	1-5 years	104 (37.4%)
	5-10 years	46 (16.5%)
	10-15 years	24 (8.6%)
	More than 15 years	58 (20.9%)
	Missing	2 (0.7%)
Persistent tendency to infection	Yes	226 (81.3%)
	No	41 (14.7%)
	Missing	11 (4.0%)

Abbreviations: N = number of subjects; n = number of subjects in a specified category

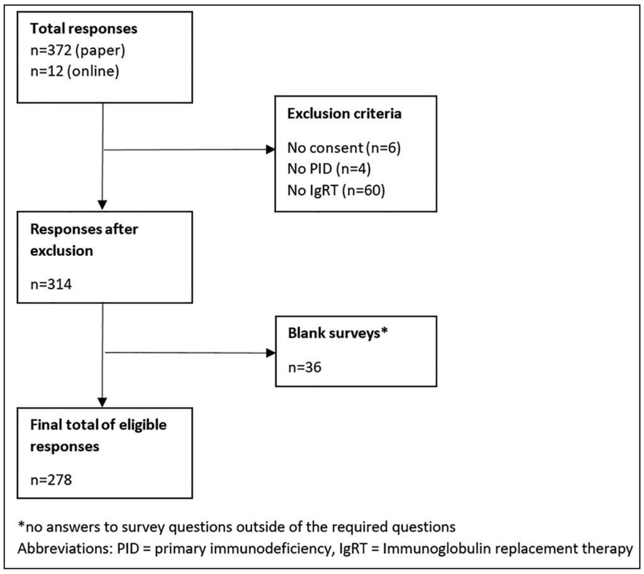
2.4. Results

In total, 384 responses were collected through paper and online methods. After exclusion criteria were used, 278 responses were eligible for data analysis (Fig. 1). 68.3% (n=190) of the participants had CVID, 5.8% (n=16) had XLA, 10.1% (n=28) had other hypogammaglobulineamias, 12.5% (n=32) had other PIDs and 4.3% (n=11) of participants did not disclose which type of PID they had (Table 1). The mean (SD) age of the participants was 44.5 (18.16). The ages ranged from 1 to 110 years old, the median age was 45.0. A majority of the participants were within the age range 30-59 years old.

The majority of the participants received SCIg as the route of administration (57.6%, n=160). The remaining participants received either IVIg (41.0%, n=114) or did not state the route of administration 1.4% (n=4) (Table 1).

To the question "Do you suffer from infections?" 226 (82.3%) participants stated a persistent tendency to infection, 41 stated that they did not suffer infections and 11 did not answer the questions (Table 1). However, 4 of the 11 participants answered the other infection questions, stating how many infections they experienced in the last 12 months.

Of all patients (N=278), 2 (0.7%) stated they were extremely dissatisfied, 12 (4.3%) were dissatisfied and 37 (13.3%) were



*no answers to survey questions outside of the required questions

Abbreviations: PID = primary immunodeficiency, IgRT = Immunoglobulin replacement therapy

Fig. 1: Flow chart for exclusion and selection of participants surveys

Table 2: Comparison of the survey answers from the satisfied and dissatisfied participants

Parameter (related to the past 12 month)		Dissatisfied (N=51) n (%)	Satisfied (N=225) n (%)	Missing (N=2) n (%)	Total (N=278) n (%)
Number of infection	Missing	5 (9.8%)	15 (6.7%)	2 (100.0%)	22 (7.9%)
	1-3 infections	16 (31.4%)	93 (41.3%)	0 (0.0%)	109 (39.2%)
	4-6 infections	17 (33.3%)	69 (30.7%)	0 (0.0%)	86 (30.9%)
	7-9 infections	5 (9.8%)	37 (16.4%)	0 (0.0%)	42 (15.1%)
	10-14 infections	4 (7.8%)	7 (3.1%)	0 (0.0%)	11 (4.0%)
	15 or more	4 (7.8%)	4 (1.8%)	0 (0.0%)	8 (2.9%)
Severity of infections	Minor	6 (11.8%)	13 (5.8%)	0 (0.0%)	19 (6.8%)
	Mild	6 (11.8%)	33 (14.7%)	0 (0.0%)	39 (14.0%)
	Moderate	8 (15.7%)	67 (29.8%)	0 (0.0%)	75 (27.0%)
	Somewhat severe	19 (37.3%)	55 (24.4%)	0 (0.0%)	74 (26.6%)
	Severe	5 (9.8%)	30 (13.3%)	0 (0.0%)	35 (12.6%)
	Very severe	3 (5.9%)	11 (4.9%)	0 (0.0%)	14 (5.0%)
	Missing	4 (7.8%)	16 (7.1%)	2 (100.0%)	22 (7.9%)
Number of absence days (work/school/university/related)	0 days	4 (7.8%)	42 (18.7%)	0 (0.0%)	46 (16.5%)
	1-5 days	7 (13.7%)	40 (17.8%)	0 (0.0%)	47 (16.9%)
	6-10 days	6 (11.8%)	31 (13.8%)	0 (0.0%)	37 (13.3%)
	11-20 days	5 (9.8%)	21 (9.3%)	0 (0.0%)	26 (9.4%)
	20 or more	19 (37.3%)	49 (21.8%)	0 (0.0%)	68 (24.5%)
	Missing	10 (19.6%)	42 (18.7%)	2 (100.0%)	54 (19.4%)
Number of non-routine visits to any health care providers	0 visits	5 (9.8%)	17 (7.6%)	0 (0.0%)	22 (7.9%)
	1-5 visits	10 (19.6%)	102 (45.3%)	0 (0.0%)	112 (40.3%)
	6-10 visits	15 (29.4%)	38 (16.9%)	0 (0.0%)	53 (19.1%)
	11-20 visits	9 (17.6%)	26 (11.6%)	0 (0.0%)	35 (12.6%)
	More than 20 visits	3 (5.9%)	6 (2.7%)	0 (0.0%)	9 (3.2%)
	Missing	9 (17.6%)	36 (16.0%)	2 (100.0%)	47 (16.9%)
Number of times treated with antibiotics	0 courses	4 (7.8%)	19 (8.4%)	0 (0.0%)	23 (8.3%)
	1-5 courses	20 (39.2%)	131 (58.2%)	0 (0.0%)	151 (54.3%)
	6-10 courses	8 (15.7%)	48 (21.3%)	0 (0.0%)	56 (20.1%)

	11-20 courses	7 (13.7%)	13 (5.8%)	0 (0.0%)	20 (7.2%)
	More than 20 courses	10 (19.6%)	7 (3.1%)	0 (0.0%)	17 (6.1%)
	Missing	2 (3.9%)	7 (3.1%)	2 (100.0%)	11 (4.0%)
Number of non-routine visits to any health care providers	0 visits	5 (9.8%)	17 (7.6%)	0 (0.0%)	22 (7.9%)
	1-5 visits	10 (19.6%)	102 (45.3%)	0 (0.0%)	112 (40.3%)
	6-10 visits	15 (29.4%)	38 (16.9%)	0 (0.0%)	53 (19.1%)
	11-20 visits	9 (17.6%)	26 (11.6%)	0 (0.0%)	35 (12.6%)
	More than 20 visits	3 (5.9%)	6 (2.7%)	0 (0.0%)	9 (3.2%)
	Missing	9 (17.6%)	36 (16.0%)	2 (100.0%)	47 (16.9%)
Assessment of success of infection control	Very poor	3 (5.9%)	1 (0.4%)	0 (0.0%)	4 (1.4%)
	Poor	11 (21.6%)	14 (6.2%)	0 (0.0%)	25 (9.0%)
	Fair	14 (27.5%)	37 (16.4%)	0 (0.0%)	51 (18.3%)
	Average	10 (19.6%)	60 (26.7%)	0 (0.0%)	70 (25.2%)
	Good	5 (9.8%)	69 (30.7%)	0 (0.0%)	74 (26.6%)
	Excellent	4 (7.8%)	38 (16.9%)	0 (0.0%)	42 (15.1%)
	Missing	4 (7.8%)	6 (2.7%)	2 (100.0%)	12 (4.3%)
Type of immunodeficiency	CVID	36 (70.6%)	153 (68.0%)	1 (50.0%)	190 (68.3%)
	XLA	2 (3.9%)	14 (6.2%)	0 (0.0%)	16 (5.8%)
	Other hypogammaglobulinaemia	6 (11.8%)	22 (9.8%)	0 (0.0%)	28 (10.1%)
	Other	5 (9.8%)	27 (12.0%)	0 (0.0%)	32 (11.5%)
	Unknown	1 (2.0%)	7 (3.1%)	1 (50.0%)	9 (3.2%)
	Missing	1 (2.0%)	2 (0.9%)	0 (0.0%)	3 (1.1%)

Abbreviations: CVID = Common variable immunodeficiency, XLA = X-linked agammaglobulinaemia, N = number of subjects; n = number of subjects in a specified category

somewhat dissatisfied with their current immunoglobulin therapy. 61 (21.9%) stated they were somewhat satisfied, 71 (25.5%) were satisfied and 93 (33.5%) were very satisfied (missing N=2) (Figure 2). There were no meaningful differences between the patients using IVIg or SCIg. For further analysis the patients were grouped into satisfied (N=225) and dissatisfied (N=51) participants.

14 patients (5.0%) used antibiotic prophylaxis seasonally, 30 (10.8%) intermittently, and 130 (46.8%) continuously, 95 patients (34.2%) did not receive antibiotic prophylaxis, with data missing for 9 patients (3.2%). There was no clinically meaningful difference between those patients satisfied or dissatisfied with their therapy.

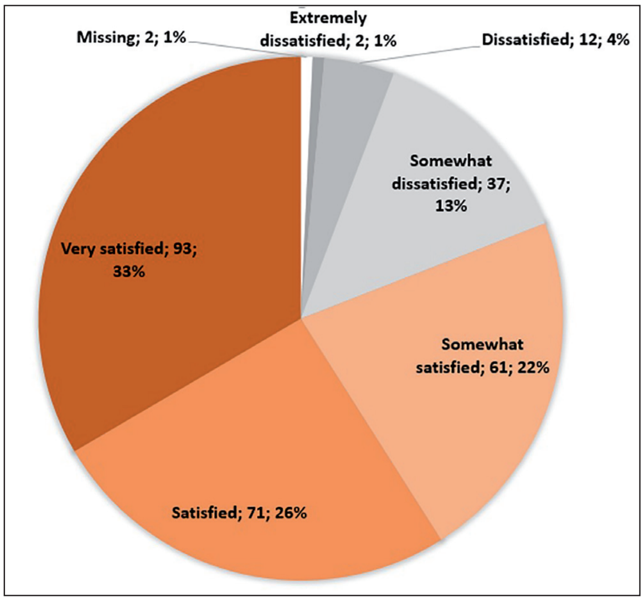


Fig. 2: Satisfaction with the current immunoglobulin therapy (N=278), n (%)

The participants were asked "Is your life limited by infections?" 18 (6.5%) of the patients stated they were severely limited; 32 (11.5%) very often limited; 51 (18.3%) often limited, 69 (24.8%) fairly limited, and 66 (23.7%) somewhat limited in daily life due to the infections. 32 patients (11.5%) were not limited at all, with data missing for 10 (3.6%) of the 278 participants. When asked "How many infections did you have during the last 12 months?" 109 (39.2%) of the participants suffered from 1 to 3 infections, 86 (30.9%) from 4 to 6 infections and 61 (22.0%) suffered from greater than 6 infections in the past 12 month. An indication of the impact of PID on a patient's life can be understood when we consider that 25% of patients reported missing school or work on more than 20 days/year due to infections. The results for the subgroups of those satisfied with their therapy and those dissatisfied can be seen in Table 2.

Data analysis comparing the satisfied and dissatisfied participants had shown that there were no statistical differences between the two groups for most infection related questions (Table 3). However, there was significance in the different amounts of chronic infections participants experienced in 12 months. The dissatisfied participants had more non-routine visits to healthcare providers, higher number of antibiotic treatments and more days absent from school, work, university or equivalent than the satisfied participants (Tables 2 and 3). Statistical significance was also found for the success of infection control. There was no statistical significance found for type, amount and severity of infections, and rating of life limitation by infections between the dissatisfied group and satisfied group of participants ($p<0.05$, Table 3).

Regression analyses were performed for the potential influence of number, type and severity of the infections on the duration of immunodeficiency and duration of the current immunoglobulin therapy. In no cases was the p-value significant ($p<0.05$).

The correlation analysis, performed to analyze the relation between the variables, resulted in several significant p-values with $p<0.05$.

An optimal correlation (defined as a correlation coefficient [ρ] >0,8) was found for the duration of immunodeficiency and the duration of immunoglobulin therapy ($\rho=0.902$, if not stated

Table 3: Comparing the groups of subjects satisfied / dissatisfied with immunoglobulin therapy – Results of t-tests (selection)

Parameter	p-values (t-test)
Which infections did you suffer from in the last 12 months?	0.7996
How many infections did you have during the last 12 months?	0.0909
How many of the infections above were chronic?	0.0491*
Please rate the overall severity of your infections	0.9988
How many days did you miss as a consequence of infections in the last 12 months?	0.0072**
How many non-routine visits did you make to any healthcare providers due to infections in the last year?	0.0176*
How many days did you spend in hospital due to infections in the last 12 months?	0.0506
How many times were you treated with antibiotics in the last 12 months?	0.0022**
Do you receive antibiotics prophylactically?	0.4800
Overall how do you rate the success of your infection control?	<.0001***
Is your life limited by infections?	0.0699

$^*p<0.05$ $^{**}p<0.01$ $^{***}p<0.001$

otherwise, all of the following correlations showed a p-value of p<0.0001), which could be expected, despite the well-known diagnostic delay. A strong correlation was identified for the number of infections during the last 12 months and the number of chronic infections during this period (ρ=0.608).

Several moderate correlations have been identified (defined as 0.4<ρ<=0.6). The number of infections in the past 12 month was positively correlated with the number of non-routine visits to any healthcare providers (ρ=0.471) and the number of antibiotics treatments (ρ=0.552). The number of chronic infections was positively related to the severity of infections (ρ=0.466). The days missed as a consequence of infections were related to the non-routine visits (ρ=0.423), the hospitalized days (ρ=0.434), and again the number of antibiotics treatments (ρ=0.409). Also the non-routine visits were positively correlated to the times treated with antibiotics (ρ=0.502). Days spent in hospital were linked to the number of antibiotic treatments (ρ=0.502). All of the above were positively correlated to life limitations (ρ=0.322 to 0.497). Further, a positive correlation was found for the satisfaction of the immunoglobulin therapy with the success of infection control (ρ=0.434).

A negative correlation was documented for life limitations and the success of infection control (ρ=-0.583). The success of infection control correlated negatively to several other factors: the number of infections in the past 12 month (ρ=-0.45), the number of chronic infections (ρ=-0.432), the days missed from school or work (ρ=-0.446), the number of non-routine healthcare visits (ρ=-0.416), and the number of antibiotic treatments (ρ=-0.447).

Several more significant correlations were identified with a p-value <0.05, however the correlation was weak or poor (defined as ρ<=0.4).

3. Discussion

Primary immunodeficiencies are complex conditions and the burden of the disease is underreported (Abolhassani et al. 2020). IgRT is essential for many patients to reduce the frequency of recurrent infections, improve quality of life and transforms the lives of many patients. Over the last few years there has been significant progress and advances in the treatment of PID and particularly in immunoglobulin therapy (Perez, 2022; Seth et al. 2021). These advances have no doubt further improved patients' quality of life, however their personal perception and opinion is vital for continuous advancement and improvements in therapeutic choices and in immunoglobulin products (Seeborg et al. 2015). In this study, a short survey was designed to elicit an overview of how patients feel about their immunoglobulin therapy, how they perceive its effectiveness and provide information on their experiences with infection.

It was found that majority of the patients in this study (n=225, 80.9%) were satisfied with their IgRT which coincides with other studies where the majority have been satisfied with the therapy (Jones et al. 2018); there was a proportion of patients (n=93, 33.5%) who rated themselves to be very satisfied (Fig. 2). However, 51 of 278 participants (18%) reported that they were dissatisfied with their immunoglobulin therapy. Statistical analysis showed that there was no significant difference between the two groups (satisfied vs. dissatisfied) with regard to the direct infection-related questions. Both satisfied and dissatisfied participants experienced similar type, number and severity of infections, although there was a trend toward more infections in the dissatisfied group (p=0.0909, Table 2). The majority of infections seen were rated as moderate and somewhat severe but there was a number of participants (n=49, 17.6%, Fig. 3) who reported experiencing severe and very severe infections.

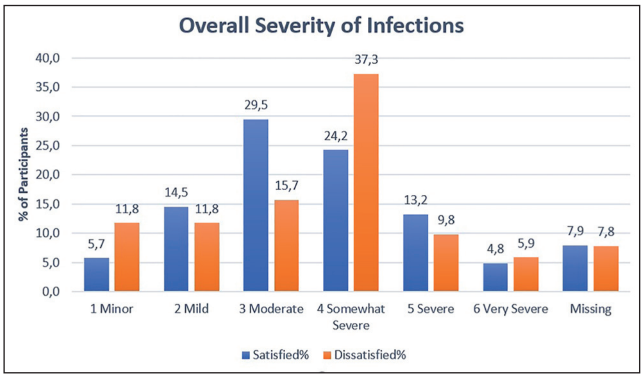


Fig. 3: Overall Severity of Infections

From this analysis, it was concluded that infections themselves were not perceived to be a contributing factor to the dissatisfaction rating those participants gave. However, although both groups were reporting similar infections, there was a high statistical significance found between the groups in the ratings for assessing successfulness of infection control (p<0.0001, Table 2). Dissatisfied participants did not feel as though their infections were controlled successfully (Fig. 4).

In terms of the total number of patients nationally, the doctors organisation UK Primary Immunodeficiency Network (UKPIN) registry recorded 4,758 PID patients in 2018 (Shillitoe et al. 2018) which had doubled from 2013 of which 2,821 had antibody disorders of some type. Therefore, up to 18% of these patients could be dissatisfied with the therapy they are receiving. However, we

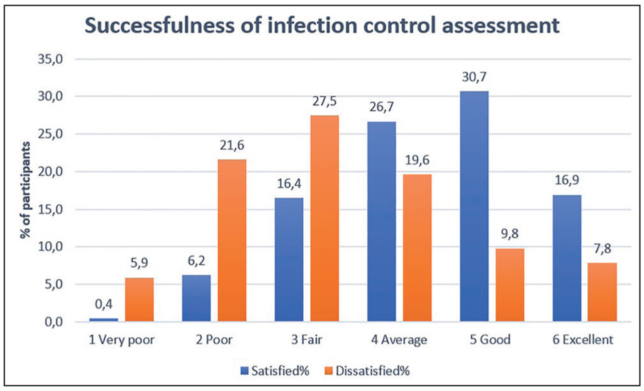


Fig. 4: Successfulness of infection control assessment

do recognise the limitations associated with survey data collected from a cohort of patients who are self-selecting.

Further study into patient perception of infection control needs to be undertaken as patient perception may not coincide with that of the immunologists and clinical scientists. However, it is vital to gain this information for the improvement of patient focussed healthcare.

Through this survey we could not determine the exact reason why those participants were dissatisfied with their treatment as not all aspects of the treatment could be considered. For example, Jones et al. (2018) found that participants preferred the treatment to be administered at home instead of continually going to the hospital for their treatment, however, this was not considered in this survey. Overall, through this survey we found that a significant minority (18 to 25%) of PID patients are suffering from their condition despite full health system and patient group support. The need for higher trough levels of ≥10 g/L in IV therapy in some patients is recommended to minimise infection or progressive end organ damage (Grigoriadou et al. 2022). The focus here were infections and immunoglobulin replacement however, dissatisfaction could also be due to factors not or only marginally influenced by immunoglobulin replacement e.g. T-cell or macrophage dysfunction/dysregulation. The majority of the participants in this study had CVID and made up most of the dissatisfied participants (36 of 51, Table 3). Patients with CVID can suffer non-infectious complications such as autoimmunity, chronic lung disease and lymphoid hyperplasia/splenomegaly (Ho and Cunningham-Rundles 2020). Immunoglobulin products mostly consist of IgG alone which could also be a contributing factor as to why CVID patients may be suffering as patients with CVID have been shown to have a reduction of more than one immunoglobulin isotype (Baumann et al. 2018).

A further possible improvement in therapy could be the addition of IgA and/or IgM enriched immunoglobulins (Langereis et al. 2018). This is supported by Stubbs et al. (2018) using data from the UKPIN registry. They concluded that despite adequate IgRT many patients with agammaglobulinaemia can still go on to develop chronic lung disease and progressive impairment of lung function with a history of pneumonia being a contributory factor. Hodkinson et al. (2017) again based on data from the UKPIN registry, reported that analysis of data of antibody class levels in PID patients demonstrated that patients deficient in IgA and IgM in addition to IgG had a higher prevalence of bronchiectasis. Quinti et al. (2011) found a similar high risk profile in patients with low IgG and IgA at diagnosis in a prospective study of 201 patients on the IPINet registry.

Although there have been many advances in immunoglobulin therapy, research into non-infectious complications including the psychological effect of PID needs to be considered. Although this study did not conclude that infections were a direct factor in patient satisfaction with immunoglobulin therapy it seems likely to be the case. To close this gap future studies could consider using the 36-Item Short Form Health Survey Questionnaire (SF-36), the EQ-5D-5L survey or the 32-item survey developed specifically for CVID (Quinti et al. 2016) along with the short survey used in this study. The SF-36 form is widely used and has credible validity (Lins and Carvalho 2016). Our survey focussed on infections and the utility of therapeutic IgRT, whereas the SF-36 evaluates the physical and mental state of a patient. Combined responses from the surveys mentioned above would give more in depth understanding and clear evidence as to why participants are dissatisfied with the immunoglobulin therapy. This information could then be used to improve delivery of immunoglobulin therapy and immunoglobulin products. We can then target these aspects and raise awareness of mental or psychological issues that primary immunodeficiency patients suffer. Psychological impact also includes worry and fear of needles, adverse effects of the therapy and time consumption (Jones et al. 2018). However, interviews with patients and more open questions could help increase understanding of the psychological impact.

This was a short survey where most of the questions were multiple choice; there was one open question about the number of chronic infections the participant had experienced in the last 12 months. From the data, it was shown that there was no statistical significance in the amount or severity of infections between the satisfied and dissatisfied participants (Table 3). However, there was a significant difference found in the amount of chronic infections between the two groups (p=0.0491) which is slightly inconsistent. Also, the multiple choice Likert scale answers lack validity as the categories were broad. In addition, the validity of the answers may be questioned as some participants said they did not experience infections but answered other infection-related questions which suggested they did experience infections. Therefore, it may be assumed that the participant may have incorrectly selected ‘no’ as an answer while answering the survey online.

Most of the participants were satisfied with the therapy they received (SCIg or IVIg) and most gave a reasonable rating for their infection control. However, there were a small but significant number of participants that still experienced severe and very severe infections despite adequate IgRT. Further research is needed to identify treatment options for this patient group.

Data availability: The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of interest: JH, PG and CS are employees of Biotest AG, Dreieich, Germany. AN was employee of Biotest (U.K.) Ltd. at the time of the study.

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Author contributions: JH and PG were involved in the conception and the design of the study; JH, PG and AN analysed and interpreted the data. CS contributed to the interpretation of data and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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