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Subcutaneous Gammanorm® by pump or rapid push infusion: impact of the device on quality of life in adult patients with primary immunodeficiencies

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Highlights (3-5, up to 85 characters each incl. spaces)

- Rapid push administration requires 25% less time, at >2 times higher frequency
- Both delivery devices proved to be clinically equivalent
- Rapid push is more cost-effective
- Rapid push administration was preferred by 34.5% of patients

Abstract

Many patients with immunodeficiencies require lifelong immunoglobulin replacement therapy (IgRT). In a multicenter, randomized, open-label, crossover, non-inferiority 3-month-trial, we compared the impact of the subcutaneous immunoglobulin Gammanorm® administered via pump or syringe (rapid push). Primary endpoint was the life quality index (LQI), secondary endpoints were QoL (SF36v2), satisfaction (TSQM-11), disease and treatment burden (PRISM), incidence of infections and adverse events (AE), treatment costs, and IgG levels. 28/30 patients completed the study. Most of the endpoints were comparable. Drug administrations with rapid push were more frequent, but reduced total time expenditure and some costs. Of the TSQM-11/LQI/SF36 components only "treatment interference with daily activities" was superior with pump and two QoL domains with rapid push. Both delivery devices showed favorable safety. Rapid push was preferred by 34.5% of patients. It proved to be an efficacious and cost-effective alternative to pumps adding to patient choice and increasing flexibility during long-term IgRT.

Keywords

Primary immunodeficiency; immunoglobulin replacement therapy; self-treatment; rapid push; quality of life

1 Introduction

Patients with primary immunodeficiency (PID) are at increased risk of severe recurrent infections, autoimmune diseases, and inflammatory and lymphoproliferative disorders [1]. PID confers shortened life expectancy, increased risk of disability due to recurrent infections, and decreased quality of life (QoL) [2, 3]. More than 50% of PID are due to a lack of antibody production [1]. Accordingly, the incidence of life-threatening infections can be substantially decreased by immunoglobulin replacement therapy (IgRT) which was also shown to mostly restore QoL [2, 4, 5]. However, burden of treatment might be high, as it needs to be administered parenterally and life-long.

The intravenous (i.v.) route requires patients to attend hospitals or specialized medical practices. Doses of 400 mg/kg/month have been recommended to be administered i.v. once every 3 to 4 weeks. However, the main drawbacks of this approach are rare, but potential anaphylactic reactions and suboptimal IgG levels in-between i.v. infusions [6, 7]. The subcutaneous (s.c.) route allows injections to be administered at home, usually once or twice per week (up to biweekly) at lower doses of 100 mg/kg/week [8], which maintains more consistent IgG replacement. Thus SCIg provides potential benefit when compared to i.v. treatment [9].

To further improve patient convenience different SCIg delivery devices have been developed. With automatic, programmable compact pumps, patients may infuse at different sites such as abdomen, thighs, upper arms, lower back and hips and with several infusion lines simultaneously; infusion rates are usually ~25 mL/h per site and up to 40 mL/h [10-13]. However, infusions still take some time (e.g. ~1.6 h for a monthly dose of 0.4 g/kg in a patient with 70 kg body weight infused at one site or multiple sites weekly) during which patients are restrained in their activities. More frequent and rapid manual administration of low viscosity products via a syringe could be an alternative method, as the duration of administration at higher infusion rates (1 to 2 mL/min) may decrease to around 10 minutes per injection [13-15]. Moreover, the use of syringes might be easier and more cost effective as compared to pumps [1, 16].

The current study, conducted in UK, Germany, Italy, and Australia, aimed to evaluate patients' QoL and satisfaction with Gammanorm® 165 mg/mL, a product with very low viscosity, when administered with either pump or rapid push. In this study infusion rates and volumes were allowed to exceed those recommended in another, similar study conducted in France [17].

2 Methods

2.1 Study design

This was a multi-center, open-label, randomized, cross-over, non-inferiority trial in adult PID patients treating themselves at home with Gammanorm® 165 mg/mL over two consecutive 3-month periods using different SCIg delivery devices, i.e. pump and rapid push. There was no wash-out in-between both periods. At baseline and at the end of each treatment period, study endpoints were determined on site. In addition, adverse events (AEs), infections, and self- treatments were recorded in patient diaries. The study was approved by local Ethics Committees, registered on Clinicaltrials.gov (NCT02503293), and conducted in compliance with GCP, the Declaration of Helsinki, and all applicable national legislation.

2.2 Patients

Adult patients (≥18 years) with any type of PID and familiar with SCIg for at least 1 month were eligible. Pregnant women and patients who participated in another interventional clinical trial or had received any investigational medicinal product within the 3 months before, were excluded. All patients provided written informed consent prior to enrolment.

2.3 Treatment

Patients were treated with Gammanorm® 165 mg/mL, a human normal immunoglobulin product with low viscosity, at cumulative monthly doses of approximately 0.4 to 0.8 g/kg. The monthly dose was divided and administered at repeated intervals (from approximately once per week to every other

day). Dose adjustment was permitted for each patient, based on pharmacokinetic data and clinical response, at the discretion of the treating physician. Treatment was initiated and the dose and dosing interval adjusted on site. After on-site training on how to use each device, patients self-administered and documented treatment at home. For pump infusions several body sites could be used.

Flow rate was recommended to start at 15 mL/h/site during the first infusion and then to gradually increase by 1-2 mL/h/site up to 25 mL/h/site during subsequent infusions, as tolerated. The maximum volume per injection site was not to exceed 25 mL for 10 infusions and then to gradually increase to up to 35 mL, if tolerated. For rapid push infusions, a single infusion site was to be used and the weekly dose could be divided into three injections administered every other day. The proposed maximum infusion rate was 1-2 mL/minute and the maximum volume not to exceed 25 mL.

2.4 Endpoints

Primary endpoint was the PID-specific LQI factor I, which assessed the interference of treatment with daily life (such as interference with social/family life/usability/convenience etc.) [18]. Secondary endpoints were LQI-II (treatment problems) and -III (treatment setting), QoL measured by SF-36v2 [19], satisfaction with treatment using the Treatment Satisfaction Questionnaire for Medication (TSQM) [20], burden of disease and treatment, both measured by pictorial representation of illness and self-measure (PRISM) [21], incidence of infections, direct and indirect costs of treatment, and residual IgG plasma levels. Direct costs such as expenses for immunoglobulin, pumps (assuming a life span of 4 years), injection kits and nursing time were calculated per treatment period and per month. Given that expenses for Gammanorm® represent the main part of direct costs, direct costs excluding those for immunoglobulin were also calculated in order to specifically compare expenses for materials and care between the two devices. Indirect costs were estimated based on the time spent by the patient to prepare the infusion, the infusion itself, and also involved costs of disposal of material. The costs of infectious episodes were not included in the calculation.

All rating methods were validated and used as previously described in detail [17]. For safety, adverse events (AEs) and local reactions were monitored and coded according to MedDRA.

2.5 Statistical Methods

The delivery devices were compared using a mixed model with sequence, device, and period as fixed factors and patient within sequence as random factor. Since for both treatment periods the same baseline was used, no baseline term was introduced in the model. Least square means (LS means) were calculated from this model and the effect size of the delivery device was estimated by the ratio syringe: pump. Results were expressed as mean of ratios and two-sided 95% confidence interval (CI). For the primary endpoint (LQI factor I, measuring treatment interference), the study tested a non-inferiority hypothesis. The non-inferiority threshold for this ratio was set at 0.90, applicable to the lower bound of the two-sided 95% confidence interval (CI). Based on a coefficient of variation of 0.15, a sample size of 27 patients was calculated.

The 3-month incidence of infection was estimated using a Poisson regression model and the logarithm of follow-up duration (expressed as a multiple of 3 months) as offset term. Proportions of patients with at least one infection were compared using a non-linear mixed model (Ezzet and Whitehead's random model approach). Patient preference for rapid push or pump was described along with its two-sided 95%CI and compared to the null hypothesis of equal preference. Residual IgG levels from baseline and the proportion of patients with levels <6 g/L were described for each delivery device, along with two-sided 95% CI (Fisher's exact method). The proportion of infusions with local/systemic reactions was described for each period. The statistical analysis was performed using SAS (version 9.4).

3 Results

3.1 Baseline characteristics

From July 2015 to June 2017, 34 patients were screened by 12 active centers in Europe and Australia. Of these, 30 patients (13 from the UK, 7 from Germany, 5 from Italy, and 5 from Australia) were randomized and received at least one dose of study medication, and 28 completed the study. One patient was excluded from the intention-to-treat (IIT) population as the patient did not satisfy the requirements regarding the LQI scale population (LQI data at V2 and V3 were missing). A further 3

patients were excluded from the per-protocol (PP) population due to missing data. Of those, two patients prematurely withdrew from the study, one was lost to follow-up and another one prematurely discontinued due to an AE. Accordingly, the safety, ITT, and the PP populations comprised 30, 29, and 26 patients, respectively.

Mean patient age at baseline was 46.2 (range: 20 to 73) years and exactly half of the patients were male; 90% of patients were diagnosed with common variable immunodeficiency or hypogammaglobulinemia, on average 12 years prior to enrolment and had received IgRT soon after diagnosis. All patients had been continuously on IgRT for at least 1 year prior to inclusion and 80% of patients already treated themselves at home. During the 12 months prior to enrollment patients experienced a median of 2.5 (range: 0-39) infections. In 13.3% of patients, at least one of these was severe (Table 1).

3.2 Exposure

Patients received a total of 362 infusions via pump and 894 infusions via rapid push during the study (on average 13.4 and 30.8 infusion per patient, respectively). The total and monthly administered doses were comparable with both devices (Table 2). The number of infusions overall and per site were >2 times higher with rapid push than with the pump; the total infusion rate was >3 times higher while total time expenditure for dosing was considerably shorter with rapid push than with the pump (Table 2). Infusions with the pump comprised >2 times the dose administered with rapid push and lasted about 3 times longer. With either device, the main infusion site was the abdomen, and the general preference for the abdomen as the primary infusion site only slightly decreased with rapid push in favor of the thigh. Hardly any infusions were administered in the arm (Table 2)

3.3 Residual IgG levels and infection rate

During the study, treatment efficacy and compliance with both devices was comparable, as suggested by the 3-month incidence rates of infections (pump 1.50 [95%CI: 1.10-2.04] versus rapid push 1.10 [0.76-1.58], n=29) and residual serum IgG levels (pump: 9.5±1.6 g/L and rapid push: 9.4±1.9 g/L, both

n=28; vs. 9.2±1.9 g/L, n=29 at baseline). During the rapid push period, one patient suffered from a severe infection and one patient in each device group was hospitalized. Concomitant use of antibiotics was comparable (16 and 14 patients with pump and rapid push, respectively).

3.4 Quality of life and patients' satisfaction

Overall, patients exhibited high levels of satisfaction regarding IgRT at home. The treatment interference with daily activities (LQI I) was rated slightly worse for rapid push than for the pump, both in the ITT and in the PP population (LS means ratio of LQI $I_{syringe}$/LQI I_{pump} was 93.5 [87.6-99.8] and 94.6 [88.5-100.99], respectively). As the lower bound of the 95% CI of the syringe: pump ratio was <90%, the hypothesis of rapid push not being inferior to the pump had to be rejected for this endpoint (Table 3). No difference between the delivery devices was found for therapy-related problems (LQI II) and setting (LQI III). On the SF36v2-QoL scale, the domain 'Vitality' was rated significantly higher for rapid push than for the pump, in both the ITT (43.1 [38.9-47.8] vs. 47 [42.4-52.1]; ratio 109.4 [100.9-117.8]) and the PP population, and the domain 'Role Physical' in the PP population only (47.0 [95%CI 42.1-52.4] vs. 44.2 [39.6-49.3]; ratio 106.3 [100.3-112.7]). No other SF36-domain nor the PRISM scores for disease and treatment burden demonstrated any difference between devices (Table 3). Furthermore, at the end of each treatment period, 11 (37.9%) patients using the pump and 9 (31.0%) patients using rapid push considered their health better than 1 year ago as compared to 8 (27.6%) at baseline.

While TSQM scores indicated comparable patient satisfaction with both treatment modalities (Table 3), more patients rated satisfaction positive with the pump than with rapid push, i.e. 23 (79.3%) vs. 18 (62.1%) patients. Accordingly, out of the 29 patients, 19 patients preferred the pump over the syringe and 10 patients vice versa (65.5% [95%CI 46%-82%] vs 34.5% [18-54%]). However, none of these differences was significant.

3.5 Treatment costs

Direct treatment costs excluding the cost for Gammanorm® were lower with rapid push as compared to the pump (rapid push: 100.2±65.8 (range 22.5-283.5) vs. pump: 178.2±102.6 (range 64.4-464.6) EUR

per month). By contrast, total indirect costs (based on the time spent by the patient to prepare the infusion, the infusion itself, and also costs of disposal of material) were about the same with both devices and pretreatment costs generally appeared negligible (Table 4).

3.6 Safety and tolerability

Gammanorm® was generally well tolerated. Overall, 27 patients (90.0%) experienced 320 systemic treatment-emergent adverse events (TEAEs), 136 while using the pump and 184 while using rapid push. Of these, 101 TEAEs in 11 patients were considered at least possibly related to study treatment (pump: 44 vs. rapid push: 57 TEAEs). The most common TEAEs were feeling cold (47 episodes in 2 patients), chills (41/4), myalgia (16/2) and nausea (15/5). Overall, 8 AEs reported by 3 patients were serious. Of these, one (embolism -aortic and bi-femoral blood clot) was assessed as possibly related to treatment and led to the patient's premature discontinuation of the trial.

Local infusion reactions were observed in 20 (69.0%) and 24 patients (80.0%) while using the pump and rapid push, respectively. Of the 362 infusions administered per pump, 54.1% were associated with at least one local reaction as compared to 46.8% out of 894 rapid push injections. The most frequently occurring local reaction observed with both delivery devices was local skin redness (Table 5). Overall, the incidence of AEs and local reactions per patient was lower with the pump than with rapid push, but less reactions occurred per infusion with rapid push.

4 Discussion

Over the last 25 years the use of SCIg has become a well-accepted first-line treatment option for patients with PID. Compared to IVIg, SCIg allows self-administration outside a clinical setting (e.g. at home) which has reduced costs and increased patient convenience and independence. Using automatic, programmable compact pumps, SCIg doses of 100 mg/kg are usually self-administered once or twice per week [8], which despite simultaneous infusion at several sites takes quite some time potentially restricting patients in their activities. SCIg are commercially available as 20% and 16.5% products. The latter have a lower viscosity and can be injected with less injection force allowing a more

comfortable infusion experience which might be particularly relevant for elderly patients or those suffering from hand dexterity symptoms [22]. Due to its low viscosity, Gammanorm®, a well-established 16.5% SCIg with proven tolerability and efficacy, enables self-administration not only by pumps, but also by using standard equipment (i.e. butterfly needle and syringe) with a new technique called rapid push. Since 2017, this technique is approved as an alternative method for Gammanorm® administration in the EU.

In the present study of patients from Europe and Australia, increased infusion parameters were used as compared to a previous study conducted in France [17]. As confirmed here, with rapid push delivering similar drug exposure, patients achieve similar residual plasma IgG levels, anti-infective efficacy, and tolerability compared to pump infusion. Moreover, rapid push enabled faster infusion and reduced the total time spent for drug administration by 25%, at a >2 times higher dosing frequency though. This trade-off might still be improved in the future by prefilled syringes which will reduce administration time expenditure even further. While there were high levels of patient satisfaction with both delivery devices, the interference of treatment with daily activities (LQI-I) remained the only tested psychometric measure for which non-inferiority to the pump could not be demonstrated (Table 3). A similar finding was reported in the parallel trial of identical design conducted in France [17]. It is noteworthy though, that patients were not treatment-naïve at baseline, i.e. most were familiar with the pump administration, for which a routine was already established, but not with rapid push. This technique was new to the majority of patients who had to get accustomed to the different procedure and the higher dosing frequency. It is thus perhaps not surprising that both these differences may affect daily activities, at least short-term. Both, the French and current trial compared the devices in adult populations familiar with pumps and over 3 months only, which might have been too short to establish a new routine. Interestingly, when a significantly younger and SCIg-naïve patient population was offered to choose between both devices at initiation and to switch at any time during treatment, 71% spontaneously opted for rapid push and only 12% later wished to switch to the pump, whereas 44.8% of the patients starting with the pump eventually switched to rapid push [14]. These

retrospectively analyzed data are suggestive of a preference for rapid push, at least in young, SCIg-naïve patients. However, even in our adult population well-accustomed to the use of the pump, still about one third stated that they preferred rapid push at the end of the study , which is fully in line with the results of the study in France [17].

In accordance with previous evidence rapid push was demonstrated to be superior to the pump in the SF36-QoL domain 'Vitality' (Table 3). This might warrant further investigation with other available validated tools, such as the Fatigue Symptom Inventory (FSI) and the Functional Assessment of Chronic Illness Therapy (FACIT) which tested the same QoL domain more comprehensively in other chronic diseases [23, 24]. Furthermore, both studies demonstrated savings in direct costs with rapid push (Table 4) although in our study those appeared much smaller than in the French study [17]. Notably, in the present study, costs of the pump were assumed to be amortized after 4 years, but costs may also differ among countries due to different health care systems. Importantly, data on safety (Table 5) and efficacy (IgG trough levels, 3-month incidence rate of infection and concomitant use of antibiotics) were similar for syringe and pump administration.

A general limitation of our study remains the rather low number of available patients in this indication and the consequently limited power, particularly regarding QoL parameters as these are not hard clinical endpoints. However, there are a number of studies with similar design now, which may call for a meta- or even pooled analysis of QoL-data.

In conclusion, our study confirmed self-administration of 16.5% low viscosity SCIg via rapid push to be a clinically equivalent alternative to the pump and an additional valuable option for patients, in particular the elderly or those suffering from hand dexterity symptoms. This method increases the physician's armamentarium for IgRT and consequently helps to better address patients' individual needs. Studies on potential additional benefits during long-term use are warranted.

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6 Disclosure of Conflicts of Interest

Klaus Warnatz: KW has received speaking honoraria from TAKEDA/Shire, CSL Behring, Roche Pharma, has participated in advisory boards of TAKEDA/Shire, LFB Biomedicaments and has received a research grant by Bristol Myers Squibb.

Stephen Jolles: SJ reports grants from CSL Behring and Takeda and personal fees from CSL Behring, Octapharma, Pharming, Takeda, LFB, Grifols, Biotest, and UCB pharma; SJ also served on advisory boards for CSL Behring, Octapharma, Pharming, LFB, Grifols, and Biotest, and on data and safety monitoring boards for Biotest and UCB Pharma. SJ is a member of the IPOPI SAFE Taskforce.

Carlo Agostini: Consultancies: Octapharma, Takeda, CSL Behring; honoraria: Octapharma, Takeda, CSL Behring; grants or other funding: Octapharma, Takeda/Shire, CSL Behring.

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Michael Borte: MB´s institution has received research grant support from CSL Behring, Octapharma, Baxalta and Takeda, and he has participated in advisory boards for CSL Behring, Octapharma and Baxalta.

Claire Bethune: Employment University Hospital Plymouth NHS Trust only, no conflicts of interest.

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Alex Richter: Employment University of Birmingham, Speaker fees 2021: Oxford Immunotec, Octapharma, Scientific advisory board: Pfizer; grants or other funding (in 2020/2021):

• 2021: Investigation of proven vaccine breakthrough: SIREN consortium and PITCH plus pathway. UKRI COVID-19 Rapid Response Initiative £1,966,280. CI.

- 2020: COV-AD: Covid infection in antibody deficiency. DHSC/UKRI COVID-19 Rapid Response Initiative £ 682,863.58. PI.
- 2020: IMPACT The Influence Of Psychosocial And Lifestyle Factors On Immune Health And Injury Incidence During Phase One. Military of Defence. £176,400. PI.
- 2020: Covidence - Longitudinal population-based observational study of coronavirus disease in the UK population. Co-Investigator. Barts Charity award £125,911. CI.
- 2020: MRC CIC Serum/saliva testing to assess protection against influenza infection and vaccination efficacy £89,510. PI.
- 2020: Protective Immunity from T cells to Covid-19 in Health workers – DHSC £260,000. CI.
- 2020: COPE-Birmingham: The contribution of occupational exposures to risk of COVID-19 and approaches to control among healthcare workers. DHSC/UKRI COVID-19 Rapid Response Initiative £441,309.09.

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7 References

[1] A. Gardulf, Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route, BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 21 (2007) 105-116.

[2] A. Gardulf, H. Bjorvell, R. Gustafson, L. Hammarstrom, C.I. Smith, The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions, Clinical and experimental immunology, 92 (1993) 200-204.

[3] H. Tcheurekdjian, T. Palermo, R. Hostoffer, Quality of life in common variable immunodeficiency requiring intravenous immunoglobulin therapy, Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology, 93 (2004) 160-165.

[4] J.A. Winkelstein, M.E. Conley, C. James, V. Howard, J. Boyle, Adults with X-linked agammaglobulinemia: impact of disease on daily lives, quality of life, educational and socioeconomic status, knowledge of inheritance, and reproductive attitudes, Medicine, 87 (2008) 253-258.

[5] A. Gardulf, U. Nicolay, Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies, Current opinion in allergy and clinical immunology, 6 (2006) 434-442.

[6] R.H. Buckley, R.I. Schiff, The use of intravenous immune globulin in immunodeficiency diseases, The New England journal of medicine, 325 (1991) 110-117.

[7] P. Cherin, J. Cabane, Relevant criteria for selecting an intravenous immunoglobulin preparation for clinical use, BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 24 (2010) 211-223.

[8] A. Gardulf, U. Nicolay, O. Asensio, E. Bernatowska, A. Bock, B.C. Carvalho, C. Granert, S. Haag, D. Hernandez, P. Kiessling, J. Kus, J. Pons, T. Niehues, S. Schmidt, I. Schulze, M. Borte, Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study, Journal of clinical immunology, 26 (2006) 177-185.

[9] H. Abolhassani, M.S. Sadaghiani, A. Aghamohammadi, H.D. Ochs, N. Rezaei, Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis, Journal of clinical immunology, 32 (2012) 1180-1192.

[10] M. Berger, Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency, Immunology and allergy clinics of North America, 28 (2008) 413-437, x.

[11] A. Gardulf, H. Bjorvell, R. Gustafson, L. Hammarstrom, C.I. Smith, Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency, Immunodeficiency, 4 (1993) 81-84.

[12] J. Gaspar, B. Gerritsen, A. Jones, Immunoglobulin replacement treatment by rapid subcutaneous infusion, Archives of disease in childhood, 79 (1998) 48-51.

[13] S. Hansen, R. Gustafson, C.I. Smith, A. Gardulf, Express subcutaneous IgG infusions: decreased time of delivery with maintained safety, Clinical immunology, 104 (2002) 237-241.

[14] R. Shapiro, Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis, Journal of clinical immunology, 30 (2010) 301-307.

[15] R.S. Shapiro, Why I use subcutaneous immunoglobulin (SCIG), Journal of clinical immunology, 33 Suppl 2 (2013) S95-98.

[16] J. Beaute, P. Levy, V. Millet, M. Debre, Y. Dudoit, L. Le Mignot, A. Tajahmady, C. Thomas, F. Suarez, I. Pellier, O. Hermine, N. Aladjidi, N. Mahlaoui, A. Fischer, P.I.D.s.g.C. French, Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies, Clinical and experimental immunology, 160 (2010) 240-245.

[17] B. Bienvenu, G. Cozon, Y. Mataix, D. Lachaud, A. Alix, C. Hoarau, D. Antier, E. Hachulla, S. Brice, J.F. Viallard, S. Tamisier, A.L. Fauchais, F. Renon-Carron, P. Clerson, Y. Fardini, J.C. Crave, P. Miossec, Rapid Push vs Pump-Infused Subcutaneous Immunoglobulin Treatment: a Randomized Crossover Study of Quality of Life in Primary Immunodeficiency Patients, Journal of clinical immunology, 38 (2018) 503-512.

[18] U. Nicolay, S. Haag, F. Eichmann, S. Herget, D. Spruck, A. Gardulf, Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy, Quality of life research, 14 (2005) 1683-1691.

[19] J.E. Ware Jr, K.K. Snow, M. Kosinski, B. Gandek, SF36 health survey. Manual and interpretation guide, Lincoln: Quality-Metrics Inc.2000.

[20] M.J. Atkinson, A. Sinha, S.L. Hass, S.S. Colman, R.N. Kumar, M. Brod, C.R. Rowland, Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease, Health and quality of life outcomes, 2 (2004) 12.

[21] S. Büchi, T. Sensky, PRISM: Pictorial Representation of Illness and Self Measure. A brief nonverbal measure of illness impact and therapeutic aid in psychosomatic medicine, Psychosomatics, 40 (1999) 314-320.

[22] N. Gelbmann, A. Zochling, A. Pichotta, T. Schmidt, A. Muranyi, T. Ernegger, K. Pock, J. Romisch, Octanorm [cutaquig(R)], a new immunoglobulin (human) subcutaneous 16.5% solution for injection (165mg/mL) - Biochemical characterization, pathogen safety, and stability, Biologicals : journal of the International Association of Biological Standardization, 60 (2019) 60-67.

[23] D. Harel, B.D. Thombs, M. Hudson, M. Baron, R. Steele, G. Canadian Scleroderma Research, Measuring fatigue in SSc: a comparison of the Short Form-36 Vitality subscale and Functional Assessment of Chronic Illness Therapy-Fatigue scale, Rheumatology, 51 (2012) 2177-2185.

[24] L.F. Brown, K. Kroenke, D.E. Theobald, J. Wu, Comparison of SF-36 vitality scale and Fatigue Symptom Inventory in assessing cancer-related fatigue, Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 19 (2011) 1255-1259.

Tables

Table 1 Baseline characteristics of the study population (n=30)

Age (years), n=30	at baseline	46.2±14.7
	at PID diagnosis	34.2±18.8
	at start of IgRT	35.4±19.4
Sex, n=30	Female	15 (50.0%)
	Male	15 (50.0%)
PID type, n=30	Agammaglobulinaemia	1 (3.3%)
	X-linked agammaglobulinaemia	1 (3.3%)
	Hypogammaglobulinaemia	4 (13.3%)
	Common variable immunodeficiency	23 (76.7%)
	Other	1 (3.3%)
Previous IgRT (12 months prior to inclusion), n=30	at home only	22 (73.3%)
	at hospital only	5 (16.7%)
	at hospital, then at home	2 (6.7%)
	other	1 (3.3%)
	One product	20 (66.7%)
	Two products	7 (23.3%)
	Three products	3 (10.0%)
	Duration of previous IgRT (with most recent product; years), n=30	1.8 (0.2-9.6)
	Dose (mg/kg/month), n=29	476 (250-937)
	Number of injections / months, n=30	4.3 (4-13)
Infections, n=30	Total number	2.5 (0-39)
	• mild	1 (0-39)
	• moderate	0 (0-24)
	• severe	0 (0-2)
	Patients with ≥1 severe infection	4 (13.3%)
	Days of hospitalization, n=26	0 (0-56)
	Days with antibiotics, n=28	27.5 (0-365)

Values are n (%) and either means ± standard deviation or median (range), if data was not normally distributed.

Table 2 In-use data for the two delivery devices

		Pump	Rapid push
Per patient	**N (patients)**	**27**	**29**
Duration of Treatment (days)	mean±SD	85.7±5.9	81.0±17.5
	median (range)	84 (77-106)	84 (23-106)
Dose per period (mg/kg)	mean±SD	1378±464	1350±586
	median (range)	1342 (712-2648)	1343 (366-2782)
Dose per month (mg/kg/month)	mean±SD	492±166	507±177
	median (range)	482 (258-888)	488 (257-933)
Number of infusions/site	mean±SD	13.4±3.5	30.8±11.2
	median (range)	13 (9-25)	36 (9-47)
Total duration of infusions (min)	mean±SD	763±256	579±287
	median (range)	750 (330-1466)	560 (45-1190)
Maximum volume/h, all sites (mL/h)	mean±SD	48.0±23.1	144.0±102.7
	median (range)	43.4 (15-90)	120 (35.3-400)
Maximum volume/h/kg (mL/h/kg)	mean±SD	0.6±0.4	1.9±1.4
	median (range)	0.6 (0.2-1.3)	1.6 (0.4-5.3)
Per infusion	**N (infusions)**	**362**	**894**
Dose (g)	mean±SD	8.0±2.9 (n=360)	3.4±1.9 (n=888)
	median (range)	8.3 (1.6-14.9)	3.3 (1.1-9.9)
Dose/kg (mg/kg)	mean±SD	103.4±41.4 (n=360)	44.1±20.9 (n=888)
	median (range)	106.2 (17.6-208.5)	42.3 (12.3-110)
Duration (min)	mean±SD	57.7±24.6 (n=357)	18.9±17.9 (n=889)
	median (range)	60 (7-246)	14 (2-165)
Sites*			
• Abdomen	N(%)	308 (85.1%)	704 (78.7%)
• Arm	N(%)	0 (0.0%)	1 (0.1%)
• Thigh	N(%)	66 (18.2%)	190 (21.3%)
Flow rate (mL/h)	mean±SD	35.1±17.5 (n=356)	84.2±51.8 (n=885)
	median (range)	31.8 (6-90)	60 (10.9-400)
Volume, all sites (mL)	mean±SD	50.4±16.4	21.6±12.3
	median (range)	50 (10-90)	20 (10-60

* Percentages are calculated based on the number of infusions (of note, several sites may have been used during an infusion)

Table 3 QoL and other psychometric outcomes in the ITT population (n=29)

		Rapid Push	Pump	Ratio rapid push : pump
LQI	I: Interference	78.9 [74.7-83.2]	84.3 [79.8-89.1]	**93.5 [87.6-99.8]**
	II: therapy-related problems	73.5 [67.8-79.7]	73.7 [67.8-80.1]	99.7 [92.1-108.0]
	III: therapy setting	87.7 [82.8-92.8]	87.0 [82.1-92.2]	100.8 [95.8-106.0]
SF36v2	Physical Functioning	46.8 [41.5-52.7]	47.1 [41.8-53.0]	99.3 [94.9-104.0]
	Role Physical	47.6 [42.0-53.9]	47.4 [41.9-53.7]	100.4 [96.1-104.9]
	Bodily Pain	47.1 [41.9-53.0]	47.3 [42.0-53.2]	99.6 [90.8-109.2]
	General Health	36.1 [32.4-40.2]	34.6 [31.2-38.5]	104.2 [97.0-111.8]
	Summary Physical	43.5 [39.0-48.6]	43.9 [39.4-48.9]	99.3 [93.1-105.8]
	Vitality	47.0 [42.4-52.1]	43.1 [38.9-47.8]	**109.0 [100.9-117.8]**
	Social Functioning	46.6 [41.7-52.0]	43.6 [39.1-48.7]	106.8 [98.8-115.6]
	Role-emotional	46.2 [41.1-52.0]	44.60 [39.7-50.2]	103.6 [96.1-111.7]
	Mental Health	49.7 [46.0-53.8]	48.2 [44.6-52.1]	103.2 [97.0-109.8]
	Summary Mental	47.6 [43.2-52.5]	44.8 [40.7-49.3]	106.3 [99.2-113.9]
TSQM	Satisfaction with treatment	76.8 [70.6-83.6]	75.9 [69.8-82.6]	101.2 [89.8-113.9]
PRISM	Burden of disease	9.4 [6.2-14.3]	8.2 [5.3-12.6]	114.9 [79.4-166.4]
	Burden of device	7.9 [5.5-11.4]	9.3 [6.4-13.6]	84.9 [58.3-123.7]

Values are Least Square means and 95% CI; ratios with 95% CIs not including 100% indicate significant differences between groups; significant differences are given in bold.

Table 4 Monthly costs of treatment with both devices, in [€]

	Pump (N=29)	Rapid push (N=29)
Total direct costs[1]	1849.2±577.6 (26)	1798.8±577.0 (27)
• without Ig	178.2±102.6 (26)	100.2±65.8 (27)
Total indirect costs	66.0±20.0 (27)	63.6±24.8 (28)
• preparation	8.7±4.9 (27)	13.4±9.0 (27)
• infusion	52.1±18.1 (27)	41.3±18.3 (28)
• disposal of material	5.6±3.4 (25)	9.8±8.0 (27)
Total pre-treatment costs[2]	0.02±0.05 (27)	0.36±1.70 (27)

Values are means ± standard deviation

[1] incl. costs for product, material and care; the costs of a pump was amortized assuming a life span of ~4 years.

[2] incl painkillers, heparin etc

Table 5 Percentage of infusions with local reactions

Infusions with local reactions:	Pump (N=362)	Rapid push (N=894)
• any	54.1 [48.9-59.4]	46.8 [43.4-50.1]
• redness	46.6 [41.3-51.8]	38.0 [34.8-41.3]
• swelling	1.1 [0.3-2.8]	0 [-]
• induration	10.1 [7.2-13.7]	9.3 [7.5-11.4]
• pruritus	5.0 [3.0-7.7]	5.3 [3.9-6.9]
• hemorrhage	1.1 [0.3-2.8]	0.6 [0.2-1.3]
• rash	1.9 [0.8-3.9]	0.3 [0.1-1.0]
• bruise	5.2 [3.2-8.1]	6.2 [4.7-7.9]
• pain	8.7 [6.0-12.1]	5.4 [4.0-7.1]

Values are % of infusions along with 95% CI.

Clin Immunol

Subcutaneous Gammanorm® by pump or rapid push infusion: impact of the device on quality of life in adult patients with primary immunodeficiencies

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Highlights (3-5, up to 85 characters each incl. spaces)

- Rapid push administration requires 25% less time, at >2 times higher frequency
- Both delivery devices proved to be clinically equivalent
- Rapid push is more cost-effective
- Rapid push administration was preferred by 34.5% of patients

Abstract

Many patients with immunodeficiencies require lifelong immunoglobulin replacement therapy (IgRT). In a multicenter, randomized, open-label, crossover, non-inferiority 3-month-trial, we compared the impact of the subcutaneous immunoglobulin Gammanorm® administered via pump or syringe (rapid push). Primary endpoint was the life quality index (LQI), secondary endpoints were QoL (SF36v2), satisfaction (TSQM-11), disease and treatment burden (PRISM), incidence of infections and adverse events (AE), treatment costs, and IgG levels. 28/30 patients completed the study. Most of the endpoints were comparable. Drug administrations with rapid push were more frequent, but reduced total time expenditure and some costs. Of the TSQM-11/LQI/SF36 components only "treatment interference with daily activities" was superior with pump and two QoL domains with rapid push. Both delivery devices showed favorable safety. Rapid push was preferred by 34.5% of patients. It proved to be an efficacious and cost-effective alternative to pumps adding to patient choice and increasing flexibility during long-term IgRT.

Keywords

Primary immunodeficiency; immunoglobulin replacement therapy; self-treatment; rapid push; quality of life

1 Introduction

Patients with primary immunodeficiency (PID) are at increased risk of severe recurrent infections, autoimmune diseases, and inflammatory and lymphoproliferative disorders [1]. PID confers shortened life expectancy, increased risk of disability due to recurrent infections, and decreased quality of life (QoL) [2, 3]. More than 50% of PID are due to a lack of antibody production [1]. Accordingly, the incidence of life-threatening infections can be substantially decreased by immunoglobulin replacement therapy (IgRT) which was also shown to mostly restore QoL [2, 4, 5]. However, burden of treatment might be high, as it needs to be administered parenterally and life-long.

The intravenous (i.v.) route requires patients to attend hospitals or specialized medical practices. Doses of 400 mg/kg/month have been recommended to be administered i.v. once every 3 to 4 weeks. However, the main drawbacks of this approach are rare, but potential anaphylactic reactions and suboptimal IgG levels in-between i.v. infusions [6, 7]. The subcutaneous (s.c.) route allows injections to be administered at home, usually once or twice per week (up to biweekly) at lower doses of 100 mg/kg/week [8], which maintains more consistent IgG replacement. Thus SCIg provides potential benefit when compared to i.v. treatment [9].

To further improve patient convenience different SCIg delivery devices have been developed. With automatic, programmable compact pumps, patients may infuse at different sites such as abdomen, thighs, upper arms, lower back and hips and with several infusion lines simultaneously; infusion rates are usually ~25 mL/h per site and up to 40 mL/h [10-13]. However, infusions still take some time (e.g. ~1.6 h for a monthly dose of 0.4 g/kg in a patient with 70 kg body weight infused at one site or multiple sites weekly) during which patients are restrained in their activities. More frequent and rapid manual administration of low viscosity products via a syringe could be an alternative method, as the duration of administration at higher infusion rates (1 to 2 mL/min) may decrease to around 10 minutes per injection [13-15]. Moreover, the use of syringes might be easier and more cost effective as compared to pumps [1, 16].

The current study, conducted in UK, Germany, Italy, and Australia, aimed to evaluate patients' QoL and satisfaction with Gammanorm® 165 mg/mL, a product with very low viscosity, when administered with either pump or rapid push. In this study infusion rates and volumes were allowed to exceed those recommended in another, similar study conducted in France [17].

2 Methods

2.1 Study design

This was a multi-center, open-label, randomized, cross-over, non-inferiority trial in adult PID patients treating themselves at home with Gammanorm® 165 mg/mL over two consecutive 3-month periods using different SCIg delivery devices, i.e. pump and rapid push. There was no wash-out in-between both periods. At baseline and at the end of each treatment period, study endpoints were determined on site. In addition, adverse events (AEs), infections, and self- treatments were recorded in patient diaries. The study was approved by local Ethics Committees, registered on Clinicaltrials.gov (NCT02503293), and conducted in compliance with GCP, the Declaration of Helsinki, and all applicable national legislation.

2.2 Patients

Adult patients (≥18 years) with any type of PID and familiar with SCIg for at least 1 month were eligible. Pregnant women and patients who participated in another interventional clinical trial or had received any investigational medicinal product within the 3 months before, were excluded. All patients provided written informed consent prior to enrolment.

2.3 Treatment

Patients were treated with Gammanorm® 165 mg/mL, a human normal immunoglobulin product with low viscosity, at cumulative monthly doses of approximately 0.4 to 0.8 g/kg. The monthly dose was divided and administered at repeated intervals (from approximately once per week to every other

day). Dose adjustment was permitted for each patient, based on pharmacokinetic data and clinical response, at the discretion of the treating physician. Treatment was initiated and the dose and dosing interval adjusted on site. After on-site training on how to use each device, patients self-administered and documented treatment at home. For pump infusions several body sites could be used.

Flow rate was recommended to start at 15 mL/h/site during the first infusion and then to gradually increase by 1-2 mL/h/site up to 25 mL/h/site during subsequent infusions, as tolerated. The maximum volume per injection site was not to exceed 25 mL for 10 infusions and then to gradually increase to up to 35 mL, if tolerated. For rapid push infusions, a single infusion site was to be used and the weekly dose could be divided into three injections administered every other day. The proposed maximum infusion rate was 1-2 mL/minute and the maximum volume not to exceed 25 mL.

2.4 Endpoints

Primary endpoint was the PID-specific LQI factor I, which assessed the interference of treatment with daily life (such as interference with social/family life/usability/convenience etc.) [18]. Secondary endpoints were LQI-II (treatment problems) and -III (treatment setting), QoL measured by SF-36v2 [19], satisfaction with treatment using the Treatment Satisfaction Questionnaire for Medication (TSQM) [20], burden of disease and treatment, both measured by pictorial representation of illness and self-measure (PRISM) [21], incidence of infections, direct and indirect costs of treatment, and residual IgG plasma levels. Direct costs such as expenses for immunoglobulin, pumps (assuming a life span of 4 years), injection kits and nursing time were calculated per treatment period and per month. Given that expenses for Gammanorm® represent the main part of direct costs, direct costs excluding those for immunoglobulin were also calculated in order to specifically compare expenses for materials and care between the two devices. Indirect costs were estimated based on the time spent by the patient to prepare the infusion, the infusion itself, and also involved costs of disposal of material. The costs of infectious episodes were not included in the calculation.

All rating methods were validated and used as previously described in detail [17]. For safety, adverse events (AEs) and local reactions were monitored and coded according to MedDRA.

2.5 Statistical Methods

The delivery devices were compared using a mixed model with sequence, device, and period as fixed factors and patient within sequence as random factor. Since for both treatment periods the same baseline was used, no baseline term was introduced in the model. Least square means (LS means) were calculated from this model and the effect size of the delivery device was estimated by the ratio syringe: pump. Results were expressed as mean of ratios and two-sided 95% confidence interval (CI). For the primary endpoint (LQI factor I, measuring treatment interference), the study tested a non-inferiority hypothesis. The non-inferiority threshold for this ratio was set at 0.90, applicable to the lower bound of the two-sided 95% confidence interval (CI). Based on a coefficient of variation of 0.15, a sample size of 27 patients was calculated.

The 3-month incidence of infection was estimated using a Poisson regression model and the logarithm of follow-up duration (expressed as a multiple of 3 months) as offset term. Proportions of patients with at least one infection were compared using a non-linear mixed model (Ezzet and Whitehead's random model approach). Patient preference for rapid push or pump was described along with its two-sided 95%CI and compared to the null hypothesis of equal preference. Residual IgG levels from baseline and the proportion of patients with levels <6 g/L were described for each delivery device, along with two-sided 95% CI (Fisher's exact method). The proportion of infusions with local/systemic reactions was described for each period. The statistical analysis was performed using SAS (version 9.4).

3 Results

3.1 Baseline characteristics

From July 2015 to June 2017, 34 patients were screened by 12 active centers in Europe and Australia. Of these, 30 patients (13 from the UK, 7 from Germany, 5 from Italy, and 5 from Australia) were randomized and received at least one dose of study medication, and 28 completed the study. One patient was excluded from the intention-to-treat (IIT) population as the patient did not satisfy the requirements regarding the LQI scale population (LQI data at V2 and V3 were missing). A further 3

patients were excluded from the per-protocol (PP) population due to missing data. Of those, two patients prematurely withdrew from the study, one was lost to follow-up and another one prematurely discontinued due to an AE. Accordingly, the safety, ITT, and the PP populations comprised 30, 29, and 26 patients, respectively.

Mean patient age at baseline was 46.2 (range: 20 to 73) years and exactly half of the patients were male; 90% of patients were diagnosed with common variable immunodeficiency or hypogammaglobulinemia, on average 12 years prior to enrolment and had received IgRT soon after diagnosis. All patients had been continuously on IgRT for at least 1 year prior to inclusion and 80% of patients already treated themselves at home. During the 12 months prior to enrollment patients experienced a median of 2.5 (range: 0-39) infections. In 13.3% of patients, at least one of these was severe (Table 1).

3.2 Exposure

Patients received a total of 362 infusions via pump and 894 infusions via rapid push during the study (on average 13.4 and 30.8 infusion per patient, respectively). The total and monthly administered doses were comparable with both devices (Table 2). The number of infusions overall and per site were >2 times higher with rapid push than with the pump; the total infusion rate was >3 times higher while total time expenditure for dosing was considerably shorter with rapid push than with the pump (Table 2). Infusions with the pump comprised >2 times the dose administered with rapid push and lasted about 3 times longer. With either device, the main infusion site was the abdomen, and the general preference for the abdomen as the primary infusion site only slightly decreased with rapid push in favor of the thigh. Hardly any infusions were administered in the arm (Table 2)

3.3 Residual IgG levels and infection rate

During the study, treatment efficacy and compliance with both devices was comparable, as suggested by the 3-month incidence rates of infections (pump 1.50 [95%CI: 1.10-2.04] versus rapid push 1.10 [0.76-1.58], n=29) and residual serum IgG levels (pump: 9.5±1.6 g/L and rapid push: 9.4±1.9 g/L, both

n=28; vs. 9.2±1.9 g/L, n=29 at baseline). During the rapid push period, one patient suffered from a severe infection and one patient in each device group was hospitalized. Concomitant use of antibiotics was comparable (16 and 14 patients with pump and rapid push, respectively).

3.4 Quality of life and patients' satisfaction

Overall, patients exhibited high levels of satisfaction regarding IgRT at home. The treatment interference with daily activities (LQI I) was rated slightly worse for rapid push than for the pump, both in the ITT and in the PP population (LS means ratio of LQI $I_{syringe}$/LQI I_{pump} was 93.5 [87.6-99.8] and 94.6 [88.5-100.99], respectively). As the lower bound of the 95% CI of the syringe: pump ratio was <90%, the hypothesis of rapid push not being inferior to the pump had to be rejected for this endpoint (Table 3). No difference between the delivery devices was found for therapy-related problems (LQI II) and setting (LQI III). On the SF36v2-QoL scale, the domain 'Vitality' was rated significantly higher for rapid push than for the pump, in both the ITT (43.1 [38.9-47.8] vs. 47 [42.4-52.1]; ratio 109.4 [100.9-117.8]) and the PP population, and the domain 'Role Physical' in the PP population only (47.0 [95%CI 42.1-52.4] vs. 44.2 [39.6-49.3]; ratio 106.3 [100.3-112.7]). No other SF36-domain nor the PRISM scores for disease and treatment burden demonstrated any difference between devices (Table 3). Furthermore, at the end of each treatment period, 11 (37.9%) patients using the pump and 9 (31.0%) patients using rapid push considered their health better than 1 year ago as compared to 8 (27.6%) at baseline.

While TSQM scores indicated comparable patient satisfaction with both treatment modalities (Table 3), more patients rated satisfaction positive with the pump than with rapid push, i.e. 23 (79.3%) vs. 18 (62.1%) patients. Accordingly, out of the 29 patients, 19 patients preferred the pump over the syringe and 10 patients vice versa (65.5% [95%CI 46%-82%] vs 34.5% [18-54%]). However, none of these differences was significant.

3.5 Treatment costs

Direct treatment costs excluding the cost for Gammanorm® were lower with rapid push as compared to the pump (rapid push: 100.2±65.8 (range 22.5-283.5) vs. pump: 178.2±102.6 (range 64.4-464.6) EUR

per month). By contrast, total indirect costs (based on the time spent by the patient to prepare the infusion, the infusion itself, and also costs of disposal of material) were about the same with both devices and pretreatment costs generally appeared negligible (Table 4).

3.6 Safety and tolerability

Gammanorm® was generally well tolerated. Overall, 27 patients (90.0%) experienced 320 systemic treatment-emergent adverse events (TEAEs), 136 while using the pump and 184 while using rapid push. Of these, 101 TEAEs in 11 patients were considered at least possibly related to study treatment (pump: 44 vs. rapid push: 57 TEAEs). The most common TEAEs were feeling cold (47 episodes in 2 patients), chills (41/4), myalgia (16/2) and nausea (15/5). Overall, 8 AEs reported by 3 patients were serious. Of these, one (embolism -aortic and bi-femoral blood clot) was assessed as possibly related to treatment and led to the patient's premature discontinuation of the trial.

Local infusion reactions were observed in 20 (69.0%) and 24 patients (80.0%) while using the pump and rapid push, respectively. Of the 362 infusions administered per pump, 54.1% were associated with at least one local reaction as compared to 46.8% out of 894 rapid push injections. The most frequently occurring local reaction observed with both delivery devices was local skin redness (Table 5). Overall, the incidence of AEs and local reactions per patient was lower with the pump than with rapid push, but less reactions occurred per infusion with rapid push.

4 Discussion

Over the last 25 years the use of SCIg has become a well-accepted first-line treatment option for patients with PID. Compared to IVIg, SCIg allows self-administration outside a clinical setting (e.g. at home) which has reduced costs and increased patient convenience and independence. Using automatic, programmable compact pumps, SCIg doses of 100 mg/kg are usually self-administered once or twice per week [8], which despite simultaneous infusion at several sites takes quite some time potentially restricting patients in their activities. SCIg are commercially available as 20% and 16.5% products. The latter have a lower viscosity and can be injected with less injection force allowing a more

comfortable infusion experience which might be particularly relevant for elderly patients or those suffering from hand dexterity symptoms [22]. Due to its low viscosity, Gammanorm®, a well-established 16.5% SCIg with proven tolerability and efficacy, enables self-administration not only by pumps, but also by using standard equipment (i.e. butterfly needle and syringe) with a new technique called rapid push. Since 2017, this technique is approved as an alternative method for Gammanorm® administration in the EU.

In the present study of patients from Europe and Australia, increased infusion parameters were used as compared to a previous study conducted in France [17]. As confirmed here, with rapid push delivering similar drug exposure, patients achieve similar residual plasma IgG levels, anti-infective efficacy, and tolerability compared to pump infusion. Moreover, rapid push enabled faster infusion and reduced the total time spent for drug administration by 25%, at a >2 times higher dosing frequency though. This trade-off might still be improved in the future by prefilled syringes which will reduce administration time expenditure even further. While there were high levels of patient satisfaction with both delivery devices, the interference of treatment with daily activities (LQI-I) remained the only tested psychometric measure for which non-inferiority to the pump could not be demonstrated (Table 3). A similar finding was reported in the parallel trial of identical design conducted in France [17]. It is noteworthy though, that patients were not treatment-naïve at baseline, i.e. most were familiar with the pump administration, for which a routine was already established, but not with rapid push. This technique was new to the majority of patients who had to get accustomed to the different procedure and the higher dosing frequency. It is thus perhaps not surprising that both these differences may affect daily activities, at least short-term. Both, the French and current trial compared the devices in adult populations familiar with pumps and over 3 months only, which might have been too short to establish a new routine. Interestingly, when a significantly younger and SCIg-naïve patient population was offered to choose between both devices at initiation and to switch at any time during treatment, 71% spontaneously opted for rapid push and only 12% later wished to switch to the pump, whereas 44.8% of the patients starting with the pump eventually switched to rapid push [14]. These

retrospectively analyzed data are suggestive of a preference for rapid push, at least in young, SCIg-naïve patients. However, even in our adult population well-accustomed to the use of the pump, still about one third stated that they preferred rapid push at the end of the study , which is fully in line with the results of the study in France [17].

In accordance with previous evidence rapid push was demonstrated to be superior to the pump in the SF36-QoL domain 'Vitality' (Table 3). This might warrant further investigation with other available validated tools, such as the Fatigue Symptom Inventory (FSI) and the Functional Assessment of Chronic Illness Therapy (FACIT) which tested the same QoL domain more comprehensively in other chronic diseases [23, 24]. Furthermore, both studies demonstrated savings in direct costs with rapid push (Table 4) although in our study those appeared much smaller than in the French study [17]. Notably, in the present study, costs of the pump were assumed to be amortized after 4 years, but costs may also differ among countries due to different health care systems. Importantly, data on safety (Table 5) and efficacy (IgG trough levels, 3-month incidence rate of infection and concomitant use of antibiotics) were similar for syringe and pump administration.

A general limitation of our study remains the rather low number of available patients in this indication and the consequently limited power, particularly regarding QoL parameters as these are not hard clinical endpoints. However, there are a number of studies with similar design now, which may call for a meta- or even pooled analysis of QoL-data.

In conclusion, our study confirmed self-administration of 16.5% low viscosity SCIg via rapid push to be a clinically equivalent alternative to the pump and an additional valuable option for patients, in particular the elderly or those suffering from hand dexterity symptoms. This method increases the physician's armamentarium for IgRT and consequently helps to better address patients' individual needs. Studies on potential additional benefits during long-term use are warranted.

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6 Disclosure of Conflicts of Interest

Klaus Warnatz: KW has received speaking honoraria from TAKEDA/Shire, CSL Behring, Roche Pharma, has participated in advisory boards of TAKEDA/Shire, LFB Biomedicaments and has received a research grant by Bristol Myers Squibb.

Stephen Jolles: SJ reports grants from CSL Behring and Takeda and personal fees from CSL Behring, Octapharma, Pharming, Takeda, LFB, Grifols, Biotest, and UCB pharma; SJ also served on advisory boards for CSL Behring, Octapharma, Pharming, LFB, Grifols, and Biotest, and on data and safety monitoring boards for Biotest and UCB Pharma. SJ is a member of the IPOPI SAFE Taskforce.

Carlo Agostini: Consultancies: Octapharma, Takeda, CSL Behring; honoraria: Octapharma, Takeda, CSL Behring; grants or other funding: Octapharma, Takeda/Shire, CSL Behring.

Fabrizio Vianello: no conflicts of interest.

Michael Borte: MB´s institution has received research grant support from CSL Behring, Octapharma, Baxalta and Takeda, and he has participated in advisory boards for CSL Behring, Octapharma and Baxalta.

Claire Bethune: Employment University Hospital Plymouth NHS Trust only, no conflicts of interest.

Sofia Grigoriadou: employed by Barts Health NHS Trust, no conflicts of interest.

Alex Richter: Employment University of Birmingham, Speaker fees 2021: Oxford Immunotec, Octapharma, Scientific advisory board: Pfizer; grants or other funding (in 2020/2021):

• 2021: Investigation of proven vaccine breakthrough: SIREN consortium and PITCH plus pathway. UKRI COVID-19 Rapid Response Initiative £1,966,280. CI.

- 2020: COV-AD: Covid infection in antibody deficiency. DHSC/UKRI COVID-19 Rapid Response Initiative £ 682,863.58. PI.
- 2020: IMPACT The Influence Of Psychosocial And Lifestyle Factors On Immune Health And Injury Incidence During Phase One. Military of Defence. £176,400. PI.
- 2020: Covidence - Longitudinal population-based observational study of coronavirus disease in the UK population. Co-Investigator. Barts Charity award £125,911. CI.
- 2020: MRC CIC Serum/saliva testing to assess protection against influenza infection and vaccination efficacy £89,510. PI.
- 2020: Protective Immunity from T cells to Covid-19 in Health workers – DHSC £260,000. CI.
- 2020: COPE-Birmingham: The contribution of occupational exposures to risk of COVID-19 and approaches to control among healthcare workers. DHSC/UKRI COVID-19 Rapid Response Initiative £441,309.09.

Rashmi Jain: Employment: Oxford University Hospitals NHS Foundation Trust; grants or other funding: Received funding for attending educational events from CSL, Takeda.

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Cinzia Milito: no conflicts of interest.

Matthew C. Cook: In the past 5 years honoraria or consultancy fees from Shire PLC, GlaxoSmithKline and Takeda Australia.

7 References

[1] A. Gardulf, Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route, BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 21 (2007) 105-116.

[2] A. Gardulf, H. Bjorvell, R. Gustafson, L. Hammarstrom, C.I. Smith, The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions, Clinical and experimental immunology, 92 (1993) 200-204.

[3] H. Tcheurekdjian, T. Palermo, R. Hostoffer, Quality of life in common variable immunodeficiency requiring intravenous immunoglobulin therapy, Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology, 93 (2004) 160-165.

[4] J.A. Winkelstein, M.E. Conley, C. James, V. Howard, J. Boyle, Adults with X-linked agammaglobulinemia: impact of disease on daily lives, quality of life, educational and socioeconomic status, knowledge of inheritance, and reproductive attitudes, Medicine, 87 (2008) 253-258.

[5] A. Gardulf, U. Nicolay, Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies, Current opinion in allergy and clinical immunology, 6 (2006) 434-442.

[6] R.H. Buckley, R.I. Schiff, The use of intravenous immune globulin in immunodeficiency diseases, The New England journal of medicine, 325 (1991) 110-117.

[7] P. Cherin, J. Cabane, Relevant criteria for selecting an intravenous immunoglobulin preparation for clinical use, BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 24 (2010) 211-223.

[8] A. Gardulf, U. Nicolay, O. Asensio, E. Bernatowska, A. Bock, B.C. Carvalho, C. Granert, S. Haag, D. Hernandez, P. Kiessling, J. Kus, J. Pons, T. Niehues, S. Schmidt, I. Schulze, M. Borte, Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study, Journal of clinical immunology, 26 (2006) 177-185.

[9] H. Abolhassani, M.S. Sadaghiani, A. Aghamohammadi, H.D. Ochs, N. Rezaei, Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis, Journal of clinical immunology, 32 (2012) 1180-1192.

[10] M. Berger, Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency, Immunology and allergy clinics of North America, 28 (2008) 413-437, x.

[11] A. Gardulf, H. Bjorvell, R. Gustafson, L. Hammarstrom, C.I. Smith, Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency, Immunodeficiency, 4 (1993) 81-84.

[12] J. Gaspar, B. Gerritsen, A. Jones, Immunoglobulin replacement treatment by rapid subcutaneous infusion, Archives of disease in childhood, 79 (1998) 48-51.

[13] S. Hansen, R. Gustafson, C.I. Smith, A. Gardulf, Express subcutaneous IgG infusions: decreased time of delivery with maintained safety, Clinical immunology, 104 (2002) 237-241.

[14] R. Shapiro, Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis, Journal of clinical immunology, 30 (2010) 301-307.

[15] R.S. Shapiro, Why I use subcutaneous immunoglobulin (SCIG), Journal of clinical immunology, 33 Suppl 2 (2013) S95-98.

[16] J. Beaute, P. Levy, V. Millet, M. Debre, Y. Dudoit, L. Le Mignot, A. Tajahmady, C. Thomas, F. Suarez, I. Pellier, O. Hermine, N. Aladjidi, N. Mahlaoui, A. Fischer, P.I.D.s.g.C. French, Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies, Clinical and experimental immunology, 160 (2010) 240-245.

[17] B. Bienvenu, G. Cozon, Y. Mataix, D. Lachaud, A. Alix, C. Hoarau, D. Antier, E. Hachulla, S. Brice, J.F. Viallard, S. Tamisier, A.L. Fauchais, F. Renon-Carron, P. Clerson, Y. Fardini, J.C. Crave, P. Miossec, Rapid Push vs Pump-Infused Subcutaneous Immunoglobulin Treatment: a Randomized Crossover Study of Quality of Life in Primary Immunodeficiency Patients, Journal of clinical immunology, 38 (2018) 503-512.

[18] U. Nicolay, S. Haag, F. Eichmann, S. Herget, D. Spruck, A. Gardulf, Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy, Quality of life research, 14 (2005) 1683-1691.

[19] J.E. Ware Jr, K.K. Snow, M. Kosinski, B. Gandek, SF36 health survey. Manual and interpretation guide, Lincoln: Quality-Metrics Inc.2000.

[20] M.J. Atkinson, A. Sinha, S.L. Hass, S.S. Colman, R.N. Kumar, M. Brod, C.R. Rowland, Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease, Health and quality of life outcomes, 2 (2004) 12.

[21] S. Büchi, T. Sensky, PRISM: Pictorial Representation of Illness and Self Measure. A brief nonverbal measure of illness impact and therapeutic aid in psychosomatic medicine, Psychosomatics, 40 (1999) 314-320.

[22] N. Gelbmann, A. Zochling, A. Pichotta, T. Schmidt, A. Muranyi, T. Ernegger, K. Pock, J. Romisch, Octanorm [cutaquig(R)], a new immunoglobulin (human) subcutaneous 16.5% solution for injection (165mg/mL) - Biochemical characterization, pathogen safety, and stability, Biologicals : journal of the International Association of Biological Standardization, 60 (2019) 60-67.

[23] D. Harel, B.D. Thombs, M. Hudson, M. Baron, R. Steele, G. Canadian Scleroderma Research, Measuring fatigue in SSc: a comparison of the Short Form-36 Vitality subscale and Functional Assessment of Chronic Illness Therapy-Fatigue scale, Rheumatology, 51 (2012) 2177-2185.

[24] L.F. Brown, K. Kroenke, D.E. Theobald, J. Wu, Comparison of SF-36 vitality scale and Fatigue Symptom Inventory in assessing cancer-related fatigue, Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 19 (2011) 1255-1259.

Tables

Table 1 Baseline characteristics of the study population (n=30)

Age (years), n=30	at baseline	46.2±14.7
	at PID diagnosis	34.2±18.8
	at start of IgRT	35.4±19.4
Sex, n=30	Female	15 (50.0%)
	Male	15 (50.0%)
PID type, n=30	Agammaglobulinaemia	1 (3.3%)
	X-linked agammaglobulinaemia	1 (3.3%)
	Hypogammaglobulinaemia	4 (13.3%)
	Common variable immunodeficiency	23 (76.7%)
	Other	1 (3.3%)
Previous IgRT (12 months prior to inclusion), n=30	at home only	22 (73.3%)
	at hospital only	5 (16.7%)
	at hospital, then at home	2 (6.7%)
	other	1 (3.3%)
	One product	20 (66.7%)
	Two products	7 (23.3%)
	Three products	3 (10.0%)
	Duration of previous IgRT (with most recent product; years), n=30	1.8 (0.2-9.6)
	Dose (mg/kg/month), n=29	476 (250-937)
	Number of injections / months, n=30	4.3 (4-13)
Infections, n=30	Total number	2.5 (0-39)
	• mild	1 (0-39)
	• moderate	0 (0-24)
	• severe	0 (0-2)
	Patients with ≥1 severe infection	4 (13.3%)
	Days of hospitalization, n=26	0 (0-56)
	Days with antibiotics, n=28	27.5 (0-365)

Values are n (%) and either means ± standard deviation or median (range), if data was not normally distributed.

Table 2 In-use data for the two delivery devices

		Pump	Rapid push
Per patient	**N (patients)**	**27**	**29**
Duration of Treatment (days)	mean±SD	85.7±5.9	81.0±17.5
	median (range)	84 (77-106)	84 (23-106)
Dose per period (mg/kg)	mean±SD	1378±464	1350±586
	median (range)	1342 (712-2648)	1343 (366-2782)
Dose per month (mg/kg/month)	mean±SD	492±166	507±177
	median (range)	482 (258-888)	488 (257-933)
Number of infusions/site	mean±SD	13.4±3.5	30.8±11.2
	median (range)	13 (9-25)	36 (9-47)
Total duration of infusions (min)	mean±SD	763±256	579±287
	median (range)	750 (330-1466)	560 (45-1190)
Maximum volume/h, all sites (mL/h)	mean±SD	48.0±23.1	144.0±102.7
	median (range)	43.4 (15-90)	120 (35.3-400)
Maximum volume/h/kg (mL/h/kg)	mean±SD	0.6±0.4	1.9±1.4
	median (range)	0.6 (0.2-1.3)	1.6 (0.4-5.3)
Per infusion	**N (infusions)**	**362**	**894**
Dose (g)	mean±SD	8.0±2.9 (n=360)	3.4±1.9 (n=888)
	median (range)	8.3 (1.6-14.9)	3.3 (1.1-9.9)
Dose/kg (mg/kg)	mean±SD	103.4±41.4 (n=360)	44.1±20.9 (n=888)
	median (range)	106.2 (17.6-208.5)	42.3 (12.3-110)
Duration (min)	mean±SD	57.7±24.6 (n=357)	18.9±17.9 (n=889)
	median (range)	60 (7-246)	14 (2-165)
Sites*			
• Abdomen	N(%)	308 (85.1%)	704 (78.7%)
• Arm	N(%)	0 (0.0%)	1 (0.1%)
• Thigh	N(%)	66 (18.2%)	190 (21.3%)
Flow rate (mL/h)	mean±SD	35.1±17.5 (n=356)	84.2±51.8 (n=885)
	median (range)	31.8 (6-90)	60 (10.9-400)
Volume, all sites (mL)	mean±SD	50.4±16.4	21.6±12.3
	median (range)	50 (10-90)	20 (10-60

* Percentages are calculated based on the number of infusions (of note, several sites may have been used during an infusion)

Table 3 QoL and other psychometric outcomes in the ITT population (n=29)

		Rapid Push	Pump	Ratio rapid push : pump
LQI	I: Interference	78.9 [74.7-83.2]	84.3 [79.8-89.1]	**93.5 [87.6-99.8]**
	II: therapy-related problems	73.5 [67.8-79.7]	73.7 [67.8-80.1]	99.7 [92.1-108.0]
	III: therapy setting	87.7 [82.8-92.8]	87.0 [82.1-92.2]	100.8 [95.8-106.0]
SF36v2	Physical Functioning	46.8 [41.5-52.7]	47.1 [41.8-53.0]	99.3 [94.9-104.0]
	Role Physical	47.6 [42.0-53.9]	47.4 [41.9-53.7]	100.4 [96.1-104.9]
	Bodily Pain	47.1 [41.9-53.0]	47.3 [42.0-53.2]	99.6 [90.8-109.2]
	General Health	36.1 [32.4-40.2]	34.6 [31.2-38.5]	104.2 [97.0-111.8]
	Summary Physical	43.5 [39.0-48.6]	43.9 [39.4-48.9]	99.3 [93.1-105.8]
	Vitality	47.0 [42.4-52.1]	43.1 [38.9-47.8]	**109.0 [100.9-117.8]**
	Social Functioning	46.6 [41.7-52.0]	43.6 [39.1-48.7]	106.8 [98.8-115.6]
	Role-emotional	46.2 [41.1-52.0]	44.60 [39.7-50.2]	103.6 [96.1-111.7]
	Mental Health	49.7 [46.0-53.8]	48.2 [44.6-52.1]	103.2 [97.0-109.8]
	Summary Mental	47.6 [43.2-52.5]	44.8 [40.7-49.3]	106.3 [99.2-113.9]
TSQM	Satisfaction with treatment	76.8 [70.6-83.6]	75.9 [69.8-82.6]	101.2 [89.8-113.9]
PRISM	Burden of disease	9.4 [6.2-14.3]	8.2 [5.3-12.6]	114.9 [79.4-166.4]
	Burden of device	7.9 [5.5-11.4]	9.3 [6.4-13.6]	84.9 [58.3-123.7]

Values are Least Square means and 95% CI; ratios with 95% CIs not including 100% indicate significant differences between groups; significant differences are given in bold.

Table 4 Monthly costs of treatment with both devices, in [€]

	Pump (N=29)	Rapid push (N=29)
Total direct costs[1]	1849.2±577.6 (26)	1798.8±577.0 (27)
• without Ig	178.2±102.6 (26)	100.2±65.8 (27)
Total indirect costs	66.0±20.0 (27)	63.6±24.8 (28)
• preparation	8.7±4.9 (27)	13.4±9.0 (27)
• infusion	52.1±18.1 (27)	41.3±18.3 (28)
• disposal of material	5.6±3.4 (25)	9.8±8.0 (27)
Total pre-treatment costs[2]	0.02±0.05 (27)	0.36±1.70 (27)

Values are means ± standard deviation

[1] incl. costs for product, material and care; the costs of a pump was amortized assuming a life span of ~4 years.

[2] incl painkillers, heparin etc

Table 5 Percentage of infusions with local reactions

Infusions with local reactions:	Pump (N=362)	Rapid push (N=894)
• any	54.1 [48.9-59.4]	46.8 [43.4-50.1]
• redness	46.6 [41.3-51.8]	38.0 [34.8-41.3]
• swelling	1.1 [0.3-2.8]	0 [-]
• induration	10.1 [7.2-13.7]	9.3 [7.5-11.4]
• pruritus	5.0 [3.0-7.7]	5.3 [3.9-6.9]
• hemorrhage	1.1 [0.3-2.8]	0.6 [0.2-1.3]
• rash	1.9 [0.8-3.9]	0.3 [0.1-1.0]
• bruise	5.2 [3.2-8.1]	6.2 [4.7-7.9]
• pain	8.7 [6.0-12.1]	5.4 [4.0-7.1]

Values are % of infusions along with 95% CI.