Human immunoglobulin (KIOVIG®/GAMMAGARD LIQUID®) for immunodeficiency and autoimmune diseases: an observational cohort study

Aim: To document the therapeutic efficacy and safety of Human Normal Immunoglobulin 10% Liquid (KIOVIG®/GAMMAGARD LIQUID® [IVIG 10%]) under clinical routine conditions. **Patients & methods:** Subjects received IVIG 10% according to the prescribing information and were followed for 6 ± 1 weeks to 12 ± 2 months depending on indication. Efficacy, adverse events, infusion rates and duration and dose were recorded. **Results:** Overall efficacy of IVIG 10% was rated as good or very good by the investigator in 81.8% of subjects; overall tolerability was good or very good in 87.5%. One serious adverse drug reaction (ADR) occurred (urticaria); no severe ADRs occurred. **Conclusion:** In this observational study, the efficacy and safety of IVIG 10% in routine clinical practice was similar to that previously reported in clinical studies.

Keywords: autoimmune disease • GAMMAGARD LIQUID® • immunodeficiency • intravenous immunoglobulin • KIOVIG®

Replacement therapy with human plasma-derived polyclonal immunoglobulin (Ig) concentrates (administered at doses of 0.2–0.8 g/kg/month) is a life-saving treatment that has long been established as the standard of care in patients with primary immunodeficiency diseases (PID) [1,2]. In addition, replacement therapy with human Ig plays an important role in the management of patients with secondary antibody deficiency arising from hematological malignancies (e.g., chronic lymphocytic leukemia and multiple myeloma, which are licensed indications for Ig replacement) or their treatment [2–6]. At high doses of 1.0–2.0 g/kg/month, Ig is also used for immunomodulation which has become an essential treatment in many autoimmune conditions. Immunomodulation has been shown to be safe and efficacious for a wide array of autoimmune diseases in which effective alternative therapies are often lacking, including thrombocytopenic purpura (ITP), Guillain-Barré syndrome, Kawasaki syndrome, multifocal motor neuropathy and chronic inflamma-

tory demyelinating polyneuropathy, which are recognized as established indications for Ig therapy [2,6–9].

The mechanism by which Ig regulates the disordered immune response in autoimmune disease has not yet been fully elucidated. Pleiotropic actions of Ig on the effector cells and noncellular components of both innate and adaptive immunity are proposed, and have been described previously [2,10–15]. Moreover, the clinical evidence base in some of these indications is limited due to the difficulty in conducting randomized clinical studies on diseases that are rare or heterogeneous [8,16–17]. Data collected from patient registries and prospective noninterventional studies can assist in confirming the safety profile and characterizing the therapeutic outcomes of Ig treatment in a real-world setting [18,19]. In this postauthorization safety surveillance study, the safety, tolerability and efficacy of a virus-inactivated, 10% liquid preparation of Ig for intravenous administration was investigated in patients with immunodeficiency or autoimmune diseases.

Bohumír Blažek¹, Siraj A Misbah², Pere Soler-Palacin³, Barbara McCoy⁴, Heinz Leibl⁴, Werner Engl⁴, Victoria Empson⁴, David Gelmont⁵ & Nikolai Nikolov^{*6}

¹Faculty Hospital Ostrava, 17 Listopadu 1790, 708 52 Ostrava-Poruba, Czech Republic

²John Radcliffe 2 Hospital Academic Centre L4, Oxford, OX3 9DU, UK

³Hospital Universitari Vall D'Hebron, Passeig Vall d'Hebron, 119–129, 08035 Barcelona, Spain

⁴Baxter BioScience, Donau-City Strasse 7, 1220 Vienna, Austria

⁵Baxter Healthcare Corporation, 1 Baxter Way, Westlake Village, CA 3811, USA

⁶Baxter Healthcare SA, Zurich, Switzerland

*Author for correspondence: nikolai_nikolov@baxter.com

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Patients & methods

Human normal immunoglobulin 10% liquid (Baxter Healthcare Corporation, licensed as GAMMAGARD LIQUID® in the USA and KIOVIG® elsewhere, hereafter referred to as intravenous immunoglobulin 10% [IVIG 10%]), is a highly purified preparation of functionally intact Ig derived from large pools of human plasma with three dedicated virus clearance steps. IVIG 10% is supplied as a ready-to-use liquid formulation, stabilized with glycine (0.25 M) and formulated without added sugars, sodium or preservatives. The average concentration of IgA in IVIG 10% is 37 µg/ml. The pH is 4.6–5.1, and the osmolality is 240–300 mOsmol/kg. IVIG 10% was stored in a refrigerator (2–8°C), protected from light.

Patients requiring treatment for diseases for which IVIG 10% held marketing approval were enrolled in this postauthorization safety surveillance study. Prior to enrollment, patients or their parent/legally authorized representative provided written informed consent, and were informed that their medical records would be accessed and transferred to the sponsor. The following additional inclusion criteria were applicable: the patient had been prescribed IVIG 10% for the first time; for patients with immunodeficiency, stable plasma IgG trough levels >5 g/l (if pretreated for immunodeficiency) and requirement for replacement therapy for ≥6 months; for patients with acute or chronic ITP, a baseline platelet count <30 × 10⁹/l and/or requirement to treat or prevent bleeding complications; for patients with Kawasaki disease, clinical diagnosis of acute disease; for patients with Guillain-Barré syndrome: clinical diagnosis, based on onset of weakness, inability to walk and neurological disability score [20]. The exclusion criteria were: known hypersensitivity to the components of IVIG 10% or to homologous proteins; active renal disease, history of thromboembolic adverse events (AEs); congestive heart failure; history of severe adverse reactions to plasma-derived products. Subjects were tested for plasma anti-IgA antibodies as part of the screening procedure to determine eligibility for enrolment.

20 study sites participated in the study in Austria, Czech Republic, Denmark, France, Germany, Great Britain, Spain and Sweden. In accordance with local requirements, the study protocol and informed consent form were reviewed and/or approved by the appropriate independent ethics committee.

Patients were treated with IVIG 10% according to the local standard of care for patients with immunological diseases. The dose and dosage regimen were as specified in the prescribing information: for primary immunodeficiencies, a single dose of 0.4–0.8 g/kg followed by 0.2–0.8 g/kg every 3–4 weeks; for secondary

immunodeficiencies, 0.2–0.4 g/kg every 3–4 weeks; for ITP, 0.8–1 g/kg given once or repeated within 3 days, or 0.4 g/kg given daily for 2–5 days; for Kawasaki disease, 1.6–2 g/kg administered in divided doses over 2–5 days or 2.0 g/kg as a single dose; for Guillain Barré syndrome, 0.4 g/kg/day over 5 days. Dosing for replacement therapy was individualized based on pharmacokinetic and clinical response. If required, dilution of IVIG 10% with 5% glucose solution was permitted. IVIG 10% was infused intravenously at an initial rate of 0.5 ml/kg body weight (BW)/h to 6 ml/kg BW/h for 30 min. Subjects were monitored throughout the infusion period and for at least 20 min after initiating administration. If well tolerated, the rate of administration was gradually increased to a maximum of 6 ml/kg BW/h. Treatment or premedication for AEs was permitted at the discretion of the investigator. Efficacy, AEs, infusion duration and infusion rates were recorded. Infusions administered as a series of installments were considered as a single infusion if the treatment-free interval was ≤3 h. Visits were scheduled as deemed appropriate by treating physicians, except for hospitalized patients, for whom visits were to be documented for every IVIG 10% administration or a minimum of every 7 ± 2 days. The duration of observation and follow-up were principally dependent on the condition treated: 6 ± 1 months for subjects with immunodeficiency requiring regular IVIG 10% replacement therapy, 6 ± 1 weeks for ITP, 4 ± 1 weeks or until discharge from hospital as well as a postobservation follow-up at 12 ± 2 months after enrolment for Guillain-Barré syndrome and Kawasaki disease.

Descriptive statistical analyses were performed for all parameters relating to the evaluation of safety, tolerance and efficacy. Data analyses were stratified by indication.

Results

Demographics & other baseline characteristics

A total of 88 subjects were enrolled in the study: 39 subjects with immunodeficiency and 49 with acute autoimmune diseases (ITP: n = 26; Guillain-Barré syndrome: n = 14; Kawasaki disease: n = 9) (Table 1). Among the subjects with immunodeficiency, 32 had primary immunodeficiency diseases; the most frequently recorded diagnoses were common variable immunodeficiency disorder (n = 17) and X-linked agammaglobulinemia (n = 3). Seven subjects had secondary immunodeficiency which resulted from lymphoid or hematopoietic malignancy in six subjects; in one subject the type of secondary immunodeficiency was not specified. A total of 23 out of 39 subjects with immunodeficiency had received Ig replacement therapy prior to the study, at a median dose of 500 mg/

kg/month in the 3 months before enrollment. Median IgG trough levels at screening in subjects with immunodeficiency were 7.22 g/l in IgG-naïve subjects (two of whom had specific antibody deficiency with IgG trough levels >9 g/l) and 8.20 g/l in pretreated subjects. In subjects with ITP the median platelet count at diagnosis was $7.0 \times 10^9/l$ (range: $1.00\text{--}28.00 \times 10^9/l$). At study start, seven out of nine subjects with Kawasaki disease met ≥ 5 of the six diagnostic criteria according to Ayusawa *et al.* [21] and the median C-reactive protein (CRP) concentration was 3.73 mg/dl ($n = 7$). Of the 14 subjects diagnosed with Guillain-Barré syndrome, six subjects had acute inflammatory demyelinating polyneuropathy, four had acute motor axonal neuropathy, one had an acute panautonomic neuropathy (such as Miller Fisher syndrome), and for three subjects no disease subtype was recorded. At screening, all 14 subjects with Guillain-Barré syndrome demonstrated symptoms rated as Grade 2 or higher using the disability score [20].

Over half of the study participants (57/88) were children or adolescents aged <18 years. The distribution of subjects by age varied according to indication; the median ages were 34.9 years in subjects with immunodeficiency, 4.25 years in subjects with ITP, 30.6 years in subjects with Guillain-Barré syndrome and 3.3 years in subjects with Kawasaki disease (Table 1). For each indication male subjects predominated. Overall, 53

male subjects (60.2%) and 35 female subjects (39.8%) enrolled in the study.

79 subjects completed the study and nine subjects (all of whom had immunodeficiency) terminated their participation prematurely. One subject discontinued participation in the study due to an adverse reaction to IVIG 10% (chills and high blood pressure, both of moderate severity). One subject, who was diagnosed with acute myeloid leukemia prior to the use of IVIG 10%, died as a consequence of her illness during the study period. The remaining subjects were withdrawn by the attending physician for nondrug-related reasons ($n = 4$) or for unspecified reasons ($n = 1$), withdrew their consent ($n = 1$), or were lost to follow-up ($n = 1$).

Exposure to IVIG 10%

A total of 346 IVIG 10% infusions were administered to subjects with immunodeficiency and 159 infusions were administered to subjects with autoimmune disease.

In subjects with immunodeficiency, the mean duration of the observational period (from first treatment to study termination) was 210.8 days (range: 149–287 days), during which time subjects received a median dose of 0.58 g/kg BW/month (range: 0.19–1.41 g/kg BW/month) (Table 1). In subjects with ITP, the median total dose of IVIG 10% was 1.69 g/kg BW (range: 0.78–2.36 g/kg BW), which was administered over 1 or 2 days in most subjects (69.2%). Subjects with

Table 1. Subject characteristics and intravenous immunoglobulin 10% treatment.

Characteristic	Immunodeficiency (n = 39)	ITP (n = 26)	Guillain-Barré syndrome (n = 14)	Kawasaki disease (n = 9)
Gender: n (%)				
– Male	22 (56.4)	15 (57.7)	9 (64.3)	7 (77.8)
– Female	17 (43.6)	11 (42.3)	5 (35.7)	2 (22.2)
Median age in years (range)	34.9 (1.7–84.1)	4.25 (0.1–62.3)	30.6 (5.5–61.1)	3.3 (0.5–8.7)
Prestudy Ig replacement therapy	Ig-naïve: 16 Previously treated: 23	n.a.	n.a.	n.a.
Median dose of IVIG 10% (range)	0.58 (0.19–1.41) g/kg/month	1.69 (0.78–2.36) g/kg	1.94 (0.99–2.13) g/kg	1.93 (1.08–2.06) g/kg
Subjects (%) received acute treatment on:				
– 1 day	n.a.	7 (26.9)	2 (14.3)	4 (44.4)
– 2 days		11 (42.3)	1 (7.1)	5 (55.6)
– 3 days		1 (3.8)	0	0
– >3 days		7 (26.9)	11 (78.6)	0
Median maximum infusion rate, ml/kg body weight/h (range)	3.02 (1.07–6.46)	1.80 (0.66–6.00)	2.41 (0.73–4.07)	1.54 (0.87–4.35)
Duration of completed infusions in hours (range) [†]	2.75 (1.35–5.25)	6.00 (2.57–13.50)	11.25 (5.50–16.25)	3.00 (1.00–5.67)

[†]Infusions administered as a series of instalments were considered as a single infusion if the treatment-free interval was ≤ 3 h.
Ig: Immunoglobulin; ITP: Immune thrombocytopenic purpura; IVIG: Intravenous immunoglobulin; n.a.: Not applicable.

Guillain-Barré syndrome received a median total dose of 1.94 g/kg BW (range: 0.99–2.13 g/kg BW), administered over 5 days in 78.6% of subjects. In subjects with Kawasaki disease, the median total dose was 1.93 g/kg BW (range: 1.08–2.06 g/kg BW) administered over 1 or 2 days.

The median maximum infusion rate in subjects with immunodeficiency was 3.02 ml/kg BW/h, and the median infusion duration was 2.75 h, ranging from 1.35 and 5.25 h (Table 1). For subjects with autoimmune diseases the median maximal infusion speed was 1.89 ml/kg BW/h. The median infusion duration for each of these subjects ranged between 1.00 and 16.25 h (median: 5.67 h).

IVIG 10% treatment outcomes
Overall efficacy rating

The overall efficacy of IVIG 10% was rated by the investigators as being very good or good in the majority of subjects (62.5 and 19.3% of all subjects, respectively), and was rated particularly highly in subjects with Guillain-Barré syndrome and Kawasaki disease (very good in 71.4 and 77.8% of subjects, respectively) (Table 2). Overall efficacy ratings were available in only 3/7 subjects with secondary immunodeficiency; in all three subjects efficacy was evaluated as being very good. Poor efficacy was reported in six subjects (6.8%) overall: one with immunodeficiency, four with ITP and one with Kawasaki disease. Efficacy ratings were unavailable for five subjects overall (5.7%).

Efficacy in subjects with primary and secondary immunodeficiency

The median IgG trough level at the end of the study (8.3 g/l, n = 17) was similar to that at the screening visit (8.2 g/l, n = 34), however, IgG trough levels at study termination were unavailable for a substantial number of subjects.

Overall, the mean annual serious infection rates were 0.08 in the 12-month prestudy period which was documented retrospectively, and 0.18 during the prospective observational period (mean duration:

210.8 days) (Table 3). Among the Ig-naïve subjects, the mean annual serious bacterial infection rate per subject was 0.13 prior to and 0.32 during the study. In subjects who had been previously treated with Ig, the mean annual serious bacterial infection rates were 0.04 in the previous 12-month period and 0.08 during the study. The monthly rate of all infections (regardless of seriousness) per subject was 0.333 prior to the study and 0.500 during the study among subjects who were Ig-naïve. For those who had previous received Ig replacement therapy the monthly infection rates were 0.125 before the study and 0.167 during the study.

The mean annual number of days hospitalized due to infection was 2.87 in the 12 months prior to the study and 1.72 during the observation period. In the Ig-naïve subjects the mean annual number of days hospitalized due to infection was 2.47 prior to and 0.64 during the study; for pretreated subjects the means were 3.13 and 2.47, respectively.

Efficacy in subjects with ITP

Twenty (20) of the 26 subjects with ITP (76.9%) had existing bleeding episodes at the initiation of IVIG 10% treatment that resolved during the study, the median duration of bleeding being 5 days. New bleeding episodes began during the observational period in four subjects with a median duration of 5.5 days. One bleeding episode that began during the study was ongoing at the termination visit. Whereas at diagnosis, a median platelet count of $7 \times 10^9/l$ was observed, the median of the individual maximal platelet counts increased to $356 \times 10^9/l$ during the observational period (range: $41\text{--}887 \times 10^9/l$). The median time to reach the maximal value was 19.5 days. The median time taken to reach a platelet count of $>50 \times 10^9/l$ was 3 days. Platelet counts remained $>50 \times 10^9/l$ until study termination in 22 of the 26 subjects with ITP.

Efficacy in subjects with Kawasaki disease

At the end of the observational period, no subjects met ≥ 5 diagnostic criteria for Kawasaki disease according

Table 2. Overall efficacy of intravenous immunoglobulin 10% as assessed by investigator.					
Indication	Very good, n (%)	Good, n (%)	Moderate, n (%)	Poor, n (%)	Not assessable, n (%)
Immunodeficiency (n = 39)	22 (56.4)	11 (28.2)	1 (2.6)	1 (2.6)	4 (10.3)
ITP (n = 26)	16 (61.5)	3 (11.5)	3 (11.5)	4 (15.4)	0 (n.a.)
Kawasaki syndrome (n = 9)	7 (77.8)	0 (n.a.)	1 (11.1)	1 (11.1)	0 (n.a.)
Guillain-Barré syndrome (n = 14)	10 (71.4)	3 (21.4)	0 (n.a.)	0 (n.a.)	1 (7.1)
Total (n = 88)	55 (62.5)	17 (19.3)	5 (5.7)	6 (6.8)	5 (5.7)
ITP: Immune thrombocytopenic purpura; n.a.: Not applicable.					

Table 3. Annual serious bacterial infection rate in subjects with immunodeficiency.

		n	Mean	Min	Max
Retrospectively documented 12 month period prior to enrollment	IgG naive	16	0.13	0.00	1.00
	IgG pretreated	23	0.04	0.00	1.00
	Total	39	0.08	0.00	1.00
Prospective observational period (first IVIG 10% treatment to subject termination visit)	IgG naive	12	0.32	0.00	3.86
	IgG pretreated	18	0.08	0.00	1.50
	Total	30	0.18	0.00	3.86

Ig: Immunoglobulin; IVIG: Intravenous immunoglobulin.

to Ayusawa *et al.* [21], compared with seven subjects who met five or more criteria at screening. Substantial decreases in the numbers of subjects with cutaneous symptoms (7 vs 1) and elevated body temperature (9 vs 1) were also observed at the end of IVIG 10% treatment compared with study start, and the only case of myocardiopathy resolved during treatment. CRP decreased from 15.1 mg/dl at screening to 1.70 mg/dl at the end of the observational period in the one subject in whom the CRP level was determined after treatment with IVIG 10%. Coronary artery lesion was reported in one subject at study start and was ongoing at study termination. No cases of aseptic meningitis were observed. No long-term complications were recorded at the 12-month follow-up visit, however 4/9 subjects were lost to follow-up.

Efficacy in subjects with Guillain-Barré syndrome

Following IVIG 10% treatment (but prior to the 12-month follow-up period), seven subjects with Guillain-Barré syndrome demonstrated symptoms rated as Grade 2 or higher using the disability score, whereas disability scores $\geq$ Grade 2 were recorded for all 14 subjects at the study start (Figure 1). At the 12-month follow-up visit, 71.4% of subjects were rated Grade 0 ('healthy'), and only two subjects had scores $\geq$ Grade 2. Four subjects (28.6%) with Guillain-Barré syndrome were unable to walk at least 5 m at screening, compared with two subjects (14.3%) who could not accomplish this task at the end of the observation period. While all subjects demonstrated overall (limb, neck and respiratory) muscle weakness at the beginning of the observational period, three subjects were determined to have no overall muscle weakness by the end of the study. Fewer subjects had proximal or distal muscle weakness at the end of the observational period than at study start. The two subjects who required supplemental oxygen at the first assessment no longer required it at the end of the observation period. Long-term complications were reported at the 12-month follow-up visit for two subjects, both of whom had acute motor axonal neuropathy; one subject was reported to be bedridden

and the other had difficulties with fine motor skills and required a cane to walk more than 50–100 m.

Safety & tolerability of IVIG 10%

The tolerability of IVIG 10% was assessed by the investigator as being good or very good in the majority of subjects (87.5%). Very good tolerability was reported for all subjects diagnosed with Kawasaki disease and all but one with Guillain-Barré syndrome. Tolerability was good or very good in 6/7 subjects with secondary immunodeficiency. Poor tolerability was reported in two subjects with immunodeficiency (one with acute lymphoblastic leukemia and one with primary immunodeficiency related to impaired B cell differentiation) and a further two subjects with ITP.

A total of 67 drug reactions (ADRs; i.e., related to IVIG 10% administration) were documented in 27 subjects over the observation period: in 12 (30.8%) subjects with immunodeficiency, 12 (46.2%) subjects with ITP and 3 (21.4%) subjects with Guillain-Barré syndrome (Table 4). No ADRs were reported among subjects with Kawasaki disease. The majority of ADRs (50/67) occurred within 72 h of the start of the initial IVIG 10% infusion. ADRs resulted in temporary interruption of an infusion and/or dose adjustment in 12 subjects. One of these 12 subjects discontinued IVIG 10% treatment due to an ADR, but later resumed treatment. One additional subject discontinued IVIG 10% permanently due to an ADR without prior dose adjustment or interruption of infusions. No severe ADRs occurred; 14 subjects experienced mild ADRs and moderate ADRs occurred in 13 subjects. All but 2 ADRs were transient: one instance of mild headache and one of moderate pruritus were recorded as ongoing at the final visit; both occurred in subjects with immunodeficiency. The most commonly reported ADRs were headache, vomiting, pyrexia and chills. No thromboembolic ADRs occurred.

One serious AE occurred during the study that was considered to be related to IVIG 10% treatment: moderate urticaria that resolved within the observational

Figure 1. Guillain-Barré syndrome disability score.

Grade 0: a healthy state; Grade 1: minor symptoms and capable of running; Grade 2: able to walk 10 m or more without assistance but unable to run; Grade 3: able to walk 10 m across an open space with help; Grade 4: bedridden or chair bound; Grade 5: requiring assisted ventilation for at least part of the day; Grade 6: dead.

period was reported in a subject with immunodeficiency. The remaining five serious AEs reported were reflective of the underlying diseases and unrelated to treatment with IVIG 10% according to the investigator's assessment: one subject died due to pre-existing severe acute myeloid leukemia, and four subjects with ITP had a low platelet count that resolved during the study in all but one subject.

54 AEs (includes those related or unrelated to IVIG 10%) were reported in 18 (46.2%) subjects with immunodeficiency and 67 AEs were reported in 27

(55.1%) subjects with autoimmune disease during the observational period (Table 5). The severity of AEs was generally mild or moderate in subjects with immunodeficiency while the majority of AEs in subjects with autoimmune disease were mild.

Discussion

The current postauthorization, observational study was designed to document the safety and tolerability to IVIG 10% under routine clinical conditions when administered to treat the following licensed indications: primary and secondary immunodeficiency, ITP, Guillain-Barré syndrome and Kawasaki disease. In addition, the efficacy of IVIG 10% was evaluated. While recognizing the limitations of the uncontrolled, noninterventional study design and the small population sizes inherent to these rare conditions, this study contributes to the limited clinical data available and reflects the utility of IVIG 10% in these indications in actual clinical settings.

The dosage and infusion rates of IVIG 10% used in the study were found to be within the range recommended in the prescribing information, and were similar to those used in previous clinical studies. In subjects with immunodeficiency, the median dose of IVIG 10% (0.58 g/kg/month) was comparable to the mean dose administered in a prior clinical study of IVIG 10% in patients with hypo- or agammaglobulinemia (0.41 g/per kg/infusion/21 days) [22]. The intersubject variability observed in the IVIG 10% dosage in this study (range of median: 0.19–1.41 g/kg/month) may reflect differences in clinical subtypes of immunodeficiency and – to a lesser extent – individualized dosing based on serum trough levels of IgG. The infusion rate of IVIG 10% used in subjects with immunodeficiency (median maximum: 3.02 ml/kg BW/h) was well below the recommended maximum rate. With respect to the treatment of autoimmune disease, the median total dose of IVIG 10% was as expected (1.7–1.9 g/kg BW), and for ITP, was comparable to that administered in a prior clinical study of IVIG 10% in ITP (2.00 g/kg BW) [23]. Compared to the infusion rate used in subjects with immunodeficiency, IVIG 10% was infused more slowly (median maximum flow rate: 1.89 ml/kg BW/h) in subjects with autoimmune disease, in whom prior exposure to Ig concentrates was presumably uncommon.

The study protocol for this observational study did not make stipulations beyond documentation of the normal standard of care for immunologic disease. Therefore, the efficacy rating scale used in this study did not specify predefined criteria, but allowed the investigators to make an overall assessment using his/her clinical judgement based on the available physi-

Table 4. Adverse drug reactions to intravenous immunoglobulin 10%.

Indication	Subjects with at least one ADR by severity (n)				ADR (n)	Rate of subjects with ADRs (%)
	Mild	Moderate	Severe	Total		
All autoimmune diseases	9	6	0	15	32	30.6
ITP	7	5	0	12	29	46.2
Guillain-Barré syndrome	2	1	0	3	3	21.4
Kawasaki syndrome	0	0	0	0	0	n.a.
Immunodeficiency	5	7	0	12	35	30.8

ADR: Adverse drug reaction; ITP: Immune thrombocytopenic purpura; n.a.: not applicable.

ological parameters, laboratory results, and other relevant clinical information for each patient. This is consistent with the methodology used in previously published observational studies on Ig preparations [24–26]. The overall efficacy of IVIG 10% as assessed by the investigators was very good or good in the majority of subjects (62.5 and 19.3% of all subjects, respectively). Poor efficacy was reported in 6.8% of subjects overall, and was most commonly observed in subjects with ITP (15.4%), which is consistent with the expected response rate to intravenous Ig of approximately 80% among adults and children with ITP [7]. Prediction of nonresponders to Ig therapy in patients with autoimmune conditions for which intravenous Ig is a first-line therapy remains a critical area of research, although a number of potential immunological biomarkers have been identified [27].

Disease-specific treatment outcomes provided further evidence of the efficacy of IVIG 10% in subjects with immunodeficiency. The median IgG trough level at study termination (8.3 g/l) was comparable to that previously reported in subjects with PID who had been treated with IVIG 10% (8.5 g/l) [22]. Efficacy in subjects with immunodeficiency was also assessed by the documentation of infections. The mean annual serious bacterial infection rate was 0.18 ($n = 30$), which is substantially below the threshold of <1.0 that is considered to demonstrate efficacy of replacement therapy in PID [28]. The rate of serious bacterial infections was, however, higher than in a previously published study on IVIG 10% in 61 subjects with PID in which no serious acute bacterial infections were reported [29]. Methodological differences may partly account for this observation. In the study by Church and colleagues, serious bacterial infections were validated according to predefined diagnostic criteria, a method that was not used in the present study. In this study, in which evaluation of infection rates was not a primary objective, the seriousness of infections was determined by the investigator based on his/her clinical judgment. Although the clinical outcomes observed in subjects with immunodeficiency in this study were in line with

expectations, comparison of results in the prospective observational period with those in the retrospectively-documented 12-month prestudy period did not show consistent trends. For example, the annual number of days hospitalized decreased during the study compared with in the prestudy period, yet the converse was true for the rate of infections. Formal statistical analysis of the efficacy results for these two periods is precluded, since comparison of prospectively and retrospectively collected data would introduce potential bias due to underreporting of less severe events. Furthermore, infection rates determined in the prospective study period do not fully represent seasonal variation as observation did not span a full year (the median duration of observation was 210.8 days), which hinders direct comparison with the 12-month prestudy period.

The efficacy of IVIG 10% in subjects with secondary immunodeficiency is of particular interest, as published data on the response to Ig replacement in these patients are scarce [17]. Overall efficacy assessments were available for three out of seven subjects with secondary immunodeficiency (one with chronic lymphoid leukemia, one with follicular lymphoma and diffuse large B-cell lymphoma, and one with unspecified secondary immunodeficiency) and were ‘very good’ in all cases. This result is in agreement with the conclusion of a recent cohort study showing that patients with secondary immunodeficiency (which manifested after chemotherapy treatment of B-cell lymphoma in 11/26 subjects) benefit from Ig-replacement therapy based on a significant reduction in infections [17]. However, due to incomplete data, no firm conclusions on the efficacy of IVIG 10% in this indication can be made.

Subjects treated for ITP in this study demonstrated a high response rate to IVIG 10% as shown by the resolution of bleeding episodes and posttreatment platelet counts $>30 \times 10^9/l$ in all subjects. All but one subject attained platelet counts $>50 \times 10^9/l$ within a median of 3 days after initiating treatment, in contrast to 71.4% of subjects who did so within 15 days in a previously reported clinical study on the same Ig preparation [23].

Table 5. Adverse events (related or unrelated to intravenous immunoglobulin 10%).						
Indication	Subjects with at least one AE by severity (n)				AEs (n)	Rate of subjects with AEs (%)
	Mild	Moderate	Severe	Total		
All autoimmune diseases	16	10	1	27	67	55.1
– ITP	11	7	1	19	54	73.1
– Guillain-Barré syndrome	3	2	0	5	7	35.7
– Kawasaki syndrome	2	1	0	3	6	33.3
Immunodeficiency	6	8	4	18	54	46.2

AE: Adverse event; ITP: Immune thrombocytopenic purpura.

The higher response rate documented in the present study may be attributed to the acute subtype of ITP that was diagnosed in all subjects, while in the earlier study all subjects had chronic ITP, which in some subjects becomes refractory to treatment [23].

Intravenous Ig is a standard first-line treatment of Kawasaki disease based on the demonstration of efficacy in previous clinical studies [30]. In the present study, IVIG 10% appeared to be highly effective in this indication: no subjects met ≥ 5 of the diagnostic criteria for Kawasaki disease defined by Ayusawa *et al.* [21] at the end of the study, and all subjects were free of complications at the 12-month follow-up period.

The high overall efficacy ratings of IVIG 10% by the investigators in subjects with Guillain-Barré syndrome were corroborated by assessments following treatment using the Guillain-Barré syndrome disability score [20]. Long-term complications of Guillain-Barré syndrome were reported at the 12-month follow-up visit for two subjects, both of whom had severe disability at baseline (Grade 4 and Grade 5). This finding is not unexpected; despite immune therapy, severe disability has been reported to persist in up to 20% of patients with Guillain-Barré syndrome [9].

The assessment of ADRs in this study confirms the existing safety profile of IVIG 10%. A total of 35 ADRs were reported in 12 out of 39 subjects (30.8%) with immunodeficiency, and 32 occurred in 15 out of 49 subjects (30.6%) with autoimmune disease. This occurrence of ADRs is in line with reports that systemic ADRs to intravenously administered Ig preparations occur at some point during therapy in 20–40% of patients [31,32]. ADRs are expected to occur more frequently in subjects receiving intravenous Ig at high doses for immunomodulation than in those receiving replacement therapy [32]; this was evident in the higher rate of ADRs per infusion seen in subjects with autoimmune diseases in the present study (0.20 per infusion) compared with in those with immunodeficiency (0.10 ADRs per infusion). Severe ADRs to intravenous Ig are uncommon [33]

and were not reported for any indication in this study. One case of moderate urticaria occurred in a 3-year-old immunodeficient male, which was considered to be a serious ADR because the subject was hospitalized. There were no systemic symptoms and the subject was discharged from hospital after several hours. The event resolved without sequelae. Although rare severe urticarial reactions associated with intravenous Ig treatment have been reported, they generally present with mild local symptoms, resolving within several hours of the infusion [33]. The most frequently documented ADRs to IVIG 10% documented in this study were headache, vomiting, pyrexia and chills, which is consistent with previous studies of IVIG 10% and of other intravenously infused Ig preparations. ADRs occurred more frequently in subjects with ITP (46.2% of subjects) than other autoimmune indications (21.4% of subjects with Guillain-Barré syndrome and no subjects with Kawasaki disease); however, the incidence of ADRs in subjects with ITP was within the range reported in previous clinical studies on intravenously administered Ig preparations in patients with ITP [34–37]. In agreement with the occurrence of ADRs, the overall tolerability of IVIG 10% in the present study was assessed by the investigators as being very good in the majority of subjects. Of interest, several small clinical studies have suggested that the tolerability of the liquid Ig preparation IVIG 10% is similar to that of the freeze-dried predecessor product GAMMAGARD S/D (Baxter Healthcare Corporation) in individuals with immunodeficiency and autoimmune disease [22,38–39]. However, differing methodologies hinder a robust comparison of these findings with the results of the present study.

Conclusion

The findings of this study confirm the therapeutic profile of IVIG 10% (GAMMAGARD LIQUID/KIOVIG) with regard to safety, tolerability and efficacy. IVIG 10% is well tolerated in routine clinical use. The ADRs reported are consistent with those previously seen following IVIG 10% administration

and are expected with IVIG treatment in general with regard to their nature, severity, and frequency. In addition, the results of this study provide evidence that the efficacy of IVIG 10% in clinical practice is comparable to that observed in prelicensure clinical studies in immunodeficiency and ITP, and indicate that IVIG 10% is also effective in treating Kawasaki disease and Guillain-Barré syndrome.

Financial & competing interests disclosure

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owns Baxter stock options. W Engl is an employee of Baxter Innovations GmbH. VG Empson is an employee of Baxter Innovations GmbH. D Gelmont is an employee of Baxter Healthcare Corporation. N Nikolov is an employee and shareholder of Baxter Healthcare SA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- The safety, tolerability and efficacy of intravenous immunoglobulin (IVIG) 10% (GAMMAGARD LIQUID®/KIOVIG®) in treating immunodeficiency, immune thrombocytopenic purpura (ITP), Kawasaki disease and Guillain-Barré syndrome were confirmed in a real-world setting.
- A total of 88 subjects were enrolled in the study: 39 subjects with immunodeficiency, 26 with acute ITP, 14 with Guillain-Barré syndrome and 9 with Kawasaki disease.
- Dosing and infusion rates of IVIG 10% were found to be in accordance with the prescribing information.
- The efficacy of IVIG 10% as assessed by the investigators was very good or good in the majority of subjects overall (81.8%).
- The efficacy of IVIG 10% in clinical practice was comparable to that observed in prelicensure clinical studies in immunodeficiency and ITP.
- The results of this study indicate that IVIG 10% was effective in treating Kawasaki disease and Guillain-Barré syndrome.
- The tolerability of IVIG 10% was assessed by the investigator as being good or very good in the majority of subjects (87.5%).
- The nature, severity and frequency of adverse drug reactions reported in this study were consistent with those previously observed following IVIG 10% administration and are expected for intravenous Ig treatment in general.

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