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Rapid infusions of human normal immunoglobulin 50 g/l are safe and well tolerated in immunodeficiencies and immune thrombocytopenia

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ABSTRACT

Intravenous immunoglobulin (IVIg) is accepted as an effective and well-tolerated treatment for primary and secondary immunodeficiencies (ID) and immune thrombocytopenia (ITP). Adverse reactions of IVIg are usually mild, comprising transient flu-like symptoms, change in blood pressure and tachycardia. However IVIg therapy can be burdensome for both patients and healthcare facilities, since the infusion may take up to 4 h to administer. The objective of our multicentre, prospective, open-label phase III trial was to evaluate the tolerability and safety of human normal immunoglobulin 50 g/l (Ig VENA) at high intravenous infusion rates in adult patients with ID and ITP who had previously tolerated IVIg treatment, by progressively increasing infusion rate up to 8 ml/kg/hr. 39 ID patients received three infusions, 5 ITP patients received up to a maximum of 5 infusions for a maximum of 5 days. Overall 55 adverse events were reported in 18 patients, and all were mild and self-limiting. Two serious adverse events occurred in ID patients and 1 in an ITP patient; none was fatal or treatment-related. No clinically significant changes or abnormalities were observed in vital signs, laboratory results and HRQoL. In summary, in this study, more rapid IVIg infusions were well tolerated by ID and ITP patients, while maintaining their quality of life, helping to minimise the time spent in outpatient hospital visiting to potentially optimise adherence to treatment.

1. Introduction

Immunoglobulins (Ig) are proteins produced by the lymphocyte B cell line, and are the humoral immune system's main effector molecules. Human normal Ig produced from human plasma is now included among the World Health Organization's model lists of essential medicines for adults and children [1,2]. Intravenous immoglobulin (IVIg) is accepted as an effective and well-tolerated treatment for rare disorders such as primary and secondary immunodeficiencies (ID) and immune thrombocytopenia (ITP) [3]. Treatment consists of two- to four-weekly infusions in ID and daily infusions for up to 5 days in acute or relapsed ITP. Adverse reactions of IVIg are usually mild, comprising transient flu-like symptoms that include headache, facial flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, change in blood pressure and tachycardia [4–6].

IVIg therapy can be burdensome for both patients and healthcare facilities, since the infusion alone may take up to 4 h to administer. Consequently, shorter infusion times have the potential to improve patient quality of life and adherence and maximise use of health resources. Clinical trials have concluded that IVIg can be infused at higher rates without compromising the tolerability and safety of treatment in

Abbreviations: ADR, Adverse drug reaction; AE, Adverse event; BMI, Body mass index; bpm, Beats per minute; CKD, Chronic kidney disease; HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HRQoL, Health-related quality of life; ID, Immunodeficiency; Ig, Immunoglobulins; ITP, Immune thrombocytopenia; ITT, Intention-to-treat; IVIg, Intravenous immoglobulin; kg/m^2, Kilograms per metre squared; ml/kg/h, Millilitres per kilogram per hour; NAT, Nucleic acid testing; NYHA, New York Heart Association; PP, Per protocol; SAE, Serious adverse event; SD, Study drug; SF-36v2, 36-Item Short Form Survey questionnaire version 2.

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patients with documented good tolerability to this therapy [7,8]. The present study was designed to evaluate the tolerability and safety of human normal immunoglobulin 50 g/l (Ig VENA; the study drug [SD]) at high intravenous infusion rates in adult patients with ID (hypogammaglobulinaemia, and agammaglobulinaemia) and ITP.

2. Materials and methods

2.1. Product

First registered in Italy in 1984, the SD is a standard intravenous human immunoglobulin 50 g/l solution. It is currently available in over 30 countries, and was supplied for this study by the marketing authorisation holder in Italy, Kedrion S.p.A. The Summary of Product Characteristics specifies an initial infusion rate of 0.46–0.92 ml/kg/h for 20–30 min, gradually increasing to a maximum of 1.85 ml/kg/h. The objective of this study was to investigate whether, by progressively increasing infusion rate up to 8 ml/kg/h, the SD could be administered at a higher infusion rate to patients who had tolerated previous IVIg treatment.

2.2. Study design

The study was designed as multicentre, prospective, open-label phase III trial. The pre-specified endpoints were: the incidence and severity of any adverse events; local tolerance at the infusion site; vital signs (blood pressure, heart rate, temperature and respiratory rate) at 10 min before each infusion, 5 min before each increase in infusion rate, and 15 min after the end of each infusion; haematology, biochemistry and virology test results; and health-related quality of life (HRQoL) using the generic SF-36v2 at the baseline screening visit and at the follow-up visit.

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. The study protocol, the protocol amendments, the Investigator's Brochure, the patient information sheets and the informed consent documents were submitted to the

Independent Ethics Committee of each participating centre before the start of any study-related procedure. Approval of the conduct of the trial was obtained from the Ethics Committee of the Co-ordinating Centre and from the Ethics Committee and National Competent Authorities of each participating centre. To ensure fully informed consent, before the start of the study every patient received full verbal and written explanations of the study's aims, and the benefits, potential discomforts and risks of participation.

Laboratory analyses for the study (haematology, blood chemistry and virological tests) were performed locally at each centre using standard clinically approved and validated protocols. If local laboratories were unable to perform these tests (for example, NAT HAV, NAT HBV, NAT HCV, NAT HIV and NAT parvovirus B19), they were performed in an external laboratory located in Austria (Osterreichisches Rotes Kreuz, 4017 Linz). Data Management and Statistical Analysis were carried out by CROS NT (Via Germania 2, 37135 Verona).

2.3. Patients

Male and female patients aged 18–64 were recruited from 6 centres (4 in Italy and 2 in Germany). A total of 44 patients were screened for enrolment (39 ID, 5 ITP) using the inclusion and exclusion criteria shown in Table 1.

2.4. Infusion schedule

The planned treatment schedule for ID patients was a total of three 0.2–0.8 g/kg infusions according to their treatment schedule: in Weeks 0, 3 and 6 for patients on a three-weekly schedule, or in Weeks 0, 4 and 8 for patients on a four-weekly schedule. ITP patients could receive up to a maximum of 5 infusions for a maximum of 5 days: either as 0.8–1 g/kg given on Day 1, which could be repeated within 3 days, or 0.4 g/kg given daily for 2–5 days. Infusions were started at an initial rate of 1 ml/kg/h for 20 min. If well tolerated, the infusion rate could be gradually increased to a maximum of 8 ml/kg/h (through 2 ml/kg/h, 4 ml/kg/h, 6 ml/kg/h and 8 ml/kg/h) at 20–30 min intervals. If dosage and/or body weight prevented the patient from reaching maximum infusion rate, treatment was stopped at the corresponding infusion rate. The follow-up visit was held 30 ± 4 days after the last infusion.

Table 1
Inclusion and exclusion criteria for enrolment.

ID patients	ITP patients
Inclusion criteria	
1. Primary or secondary hypo--gammaglobulinaemia or agammaglobulinaemia.	1. Persistent ITP (3–12 months from diagnosis) and chronic ITP (lasting for >12 months).
2. Males or females aged 18–64 years (≥18 and ≤64 years).	2. Males or females aged 18–64 years (≥18 and ≤64 years).
3. Documented history of stable IVIg therapy for at least 6 months before study entry.	3. At least one previous treatment with immunoglobulin.
4. Written informed consent and consent to handle personal data.	4. Baseline platelet count <20 × 109/l.
	5. Written informed consent and consent to handle personal data.
Exclusion criteria	
1. No previous therapy with immunoglobulins.	1. No previous therapy with immunoglobulins.
2. Positivity for HIV, HCV, HBV, risky behaviour for blood-transmitted viral infections.	2. Positivity for HIV, HCV, HBV, risky behaviour for blood-transmitted viral infections.
3. Pregnant or breastfeeding women or women of childbearing age without adequate contraception.	3. Pregnant or breastfeeding women or women of childbearing age without adequate contraception.
4. Severe systemic conditions or associated conditions contraindicating immunoglobulins.	4. Severe systemic conditions or associated conditions contraindicating immunoglobulins.
5. Treatment with intravenous antibiotics within 1 week of inclusion in the study.	5. Proteinuria ≥3.5 g/24 h, serum protein levels <60 g/l or serum albumin levels <30 g/l.
6. Proteinuria ≥3.5 g/24 h, serum protein levels <60 g/l or serum albumin levels <30 g/l.	6. CKD or creatinine clearance <80 ml/min, (Cockroft formula).
7. CKD or creatinine clearance <80 ml/min (Cockroft formula).	7. Heart failure (NYHA III/IV), cardiomyopathy, congestive heart failure, severe hypertension.
8. Heart failure (NYHA III/IV), cardiomyopathy, congestive heart failure, severe hypertension, lymphoma, hypoalbuminaemia, protein-losing enteropathy (serum protein <60 g/l and serum albumin <30 g/l).	8. Thrombotic episodes within the last 12 months.
9. Positive thrombophilia test.	9. Any condition that in the Investigator's opinion could interfere with evaluation of study results.
10. Any condition that in the Investigator's opinion could interfere with evaluation of study results.	10. Incapable of giving informed consent (according to § 40 section 1, Sentence 3, Nr. 3 Letter a) of the German Medicinal Products Act (only for Germany).
11. Incapable of giving informed consent (according to § 40 section 1, Sentence 3, Nr. 3 Letter a) of the German Medicinal Products Act (only for Germany).	11. Participation in a clinical trial with another product within one month (30 days) of enrolment.
12. Participation in a clinical trial with another product within one month (30 days) of enrolment.	

2.5. Statistical analysis

The statistical analysis considered the following populations: the intention-to-treat (ITT) population (all patients enrolled in the study); the safety population (all patients receiving the first SD infusion); and the per-protocol (PP) population (safety population patients without