Safety and tolerability of intravenous immunoglobulin in chronic inflammatory demyelinating polyneuropathy: Results of the ProCID Study

Drug Safety

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Supplementary table 1 Related TEAEs per treatment group. n = number of patients; n' = number of infusions; N = number of events.

System organ class Preferred term	Treatment group									Total		
	0.5 g/kg (*n* = 35)			1.0 g/kg (*n* = 69)			2.0 g/kg (*n* = 38)			All patients (n = 142)		
	n (%)	n' (%)	N	n (%)	n' (%)	N	n (%)	n' (%)	N	n (%)	n' (%)	N
Nervous system disorders												
Headache	1 (2.9)	1 (0.4)	1	10 (14.5)	11 (2.3)	12	9 (23.7)	13 (4.8)	15	20 (14.1)	25 (2.5)	28
Dizziness	1 (2.9)	1 (0.4)	1				1 (2.6)	1 (0.4)	1	2 (1.4)	2 (0.2)	2
Somnolence	2 (5.7)	3 (1.3)	3				1 (2.6)	1 (0.4)	1	3 (2.1)	4 (0.4)	4
General disorders and administration site conditions												
Pyrexia	5 (14.3)	6 (2.6)	6	8 (11.6)	9 (1.9)	11	5 (13.2)	5 (1.9)	6	18 (12.7)	20 (2.0)	23
Chills	3 (8.6)	4 (1.7)	4	2 (2.9)	2 (0.4)	2	1 (2.6)	1 (0.4)	1	6 (4.2)	7 (0.7)	7
Asthenia							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Chest pain							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Influenza like illness				3 (4.4)	3 (0.6)	3				3 (2.1)	3 (0.3)	3
Chest discomfort							1 (2.6)	2 (0.7)	2	1 (0.7)	2 (0.2)	2
Gastrointestinal disorders												
Abdominal pain				1 (1.5)	1 (0.2)	1				1 (0.7)	1 (0.1)	1
Nausea	1 (2.9)	1 (0.4)	1	1 (1.5)	2 (0.4)	2	3 (7.9)	4 (1.5)	5	5 (3.5)	7 (0.7)	8
Vomiting				2 (2.9)	3 (0.6)	3	1 (2.6)	1 (0.4)	1	3 (2.1)	4 (0.4)	4
Diarrhoea							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Blood and lymphatic system disorders												
Leukopenia	1 (2.9)	2 (0.9)	2	2 (2.9)	2 (0.4)	2				3 (2.1)	4 (0.4)	4
Anaemia							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Respiratory, thoracic and mediastinal disorders												
Cough				1 (1.5)	1 (0.2)	1	1 (2.6)	1 (0.4)	1	2 (1.4)	2 (0.2)	2
Tachypnoea				1 (1.5)	1 (0.2)	4				1 (0.7)	1 (0.1)	4
Dyspnoea							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Cardiac disorders												
Tachycardia	1 (2.9)	1 (0.4)	1	2 (2.9)	2 (0.4)	4	1 (2.6)	1 (0.4)	1	4 (2.8)	4 (0.4)	6
Skin and subcutaneous tissue disorders												
Rash	1 (2.9)	1 (0.4)	1	1 (1.5)	1 (0.2)	1	1 (2.6)	5 (1.9)	5	3 (2.1)	7 (0.7)	7
Dermatitis	5 (14.3)	5 (2.2)	5	5 (7.3)	10 (2.1)	10	4 (10.5)	5 (1.9)	6	14 (9.9)	20 (2.0)	21
Skin exfoliation	1 (2.9)	1 (0.4)	1	2 (2.9)	2 (0.4)	3	1 (2.6)	1 (0.4)	1	4 (2.8)	4 (0.4)	5
Urticaria	3 (8.6)	4 (1.7)	4							3 (2.1)	4 (0.4)	4

Pruritus							2 (5.3)	3 (1.1)	3	2 (1.4)	3 (0.3)	3
Erythema	1 (2.9)	2 (0.9)	2							1 (0.7)	2 (0.2)	2
Vascular disorders												
Hypertension	2 (5.7)	3 (1.3)	3	5 (7.3)	6 (1.2)	7				7 (4.9)	9 (0.9)	10
Hypotension	1 (2.9)	1 (0.4)	1							1 (0.7)	1 (0.1)	1
Investigations												
Blood lactate dehydrogenase increased				5 (7.3)	5 (1.0)	5				5 (3.5)	5 (0.5)	5
Transaminases increased	1 (2.9)	1 (0.4)	1	2 (2.9)	2 (0.4)	2				3 (2.1)	3 (0.3)	3
Alanine aminotransferase increased				2 (2.9)	3 (0.6)	3				2 (1.4)	3 (0.3)	3
Aspartate aminotransferase increased				2 (2.9)	3 (0.6)	3				2 (1.4)	3 (0.3)	3
Haemoglobin decreased				1 (1.5)	1 (0.2)	1				1 (0.7)	1 (0.1)	1
Infections and infestations												
Nasopharyngitis							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1
Renal and urinary disorders												
Micturition urgency							1 (2.6)	1 (0.4)	1	1 (0.7)	1 (0.1)	1

TEAE = treatment-emergent adverse event.

Supplementary table 2 Related TEAEs for daily doses below and above 78 g IVIg. n = number of patients; n' = number of infusions; N = number of events. The combined number of patients in both groups is higher than the number of randomised patients because different doses were administered during the loading and maintenance phases.

System organ class Preferred term	Actual daily dose					
	≤ 78g (*n* = 89)			> 78g (*n* = 80)		
	n (%)	n' (%)	N	n (%)	n' (%)	N
Any term	37 (41.6)	59 (11.2)	96	34 (42.5)	53 (11.6)	77
Nervous system disorders						
Headache	12 (13.5)	16 (3.0)	18	8 (10.0)	9 (2.0)	10
Dizziness	2 (2.3)	2 (0.4)	2			
Somnolence	3 (3.4)	4 (0.8)	4			
General disorders and administration site conditions						
Pyrexia	8 (9.0)	10 (1.9)	13	10 (12.5)	10 (2.2)	10
Chills	4 (5.6)	6 (1.1)	6	1 (1.3)	1 (0.2)	1
Asthenia	1 (1.1)	1 (0.2)	1			
Chest pain				1 (1.3)	1 (0.2)	1
Influenza like illness	2 (2.3)	2 (0.4)	2	1 (1.3)	1 (0.2)	1
Chest discomfort	1 (1.1)	2 (0.4)	2			
Gastrointestinal disorders						
Abdominal pain				1 (1.3)	1 (0.2)	1
Nausea	3 (3.4)	4 (0.8)	4	2 (2.5)	3 (0.7)	4
Vomiting	2 (2.3)	3 (0.6)	3	1 (1.3)	1 (0.2)	1
Diarrhoea	1 (1.1)	1 (0.2)	1			
Blood and lymphatic system disorders						
Leukopenia	2 (2.3)	3 (0.6)	3	1 (1.3)	1 (0.2)	1
Anaemia	1 (1.1)	1 (0.2)	1			
Respiratory, thoracic and mediastinal disorders						
Cough				2 (2.5)	2 (0.4)	2
Tachypnoea	1 (1.1)	1 (0.2)	4			
Dyspnoea	1 (1.1)	1 (0.2)	1			
Cardiac disorders						
Tachycardia	3 (3.4)	3 (0.6)	5	1 (1.3)	1 (0.2)	1
Skin and subcutaneous tissue disorders						
Rash	1 (1.1)	1 (0.2)	1	2 (2.5)	6 (1.3)	6
Dermatitis	6 (6.7)	7 (1.3)	8	8 (10.0)	13 (2.9)	13
Skin exfoliation	1 (1.1)	1 (0.2)	1	3 (3.8)	3 (0.7)	4
Urticaria	2 (2.3)	2 (0.4)	2	2 (2.5)	2 (0.4)	2
Pruritus	2 (2.3)	3 (0.6)	3			
Erythema	1 (1.1)	2 (0.4)	2			
Vascular disorders						
Hypertension	2 (2.3)	2 (0.4)	2	6 (7.5)	7 (1.5)	8
Hypotension	1 (1.1)	1 (0.2)	1			
Investigations						
Blood lactate dehydrogenase increased	2 (2.3)	2 (0.4)	2	3 (3.8)	3 (0.7)	3
Transaminases increased	2 (2.3)	2 (0.4)	2	1 (1.3)	1 (0.2)	1

Alanine aminotransferase increased				2 (2.5)	3 (0.7)	3
Aspartate aminotransferase increased				2 (2.5)	3 (0.7)	3
Haemoglobin decreased				1 (1.3)	1 (0.2)	1
Infections and infestations						
Nasopharyngitis	1 (1.1)	1 (0.2)	1			

IVIg = intravenous immunoglobulin; TEAE = treatment-emergent adverse event.

Supplementary table 3 Related adverse events per loading and maintenance dose. n = number of patients; n' = number of infusions; N = number of events.

System organ class Preferred term	Loading dose						Maintenance dose					
	2.0 g/kg (*n* = 141)			0.5 g/kg (*n* = 34)			1.0 g/kg (*n* = 66)			2.0 g/kg (n = 34)		
	n (%)	n' (%)	N	n (%)	n' (%)	N	n (%)	n' (%)	N	n (%)	n' (%)	N
Nervous system disorders												
Headache	15 (10.6)	15 (10.6)	18				3 (4.6)	3 (0.8)	3	5 (14.7)	7 (3.0)	7
Dizziness	1 (0.7)	1 (0.7)	1	1 (2.9)	1 (0.6)	1						
Somnolence	2 (1.4)	2 (1.4)	2	1 (2.9)	1 (0.6)	1				1 (2.9)	1 (0.4)	1
General disorders and administration site conditions												
Pyrexia	14 (9.9)	14 (9.9)	17	2 (5.9)	3 (1.7)	3	3 (4.6)	3 (0.8)	3			
Chills	5 (3.6)	5 (3.6)	5	1 (2.9)	2 (1.1)	2						
Asthenia	1 (0.7)	1 (0.7)	1									
Chest pain	1 (0.7)	1 (0.7)	1				1 (1.5)	1 (0.3)	1			
Influenza like illness	2 (1.4)	2 (1.4)	2							1 (2.9)	1 (0.4)	1
Chest discomfort	1 (0.7)	1 (0.7)	1									
Gastrointestinal disorders												
Abdominal pain							1 (1.5)	1 (0.3)	1			
Nausea	4 (2.8)	4 (2.8)	5				1 (1.5)	1 (0.3)	1	2 (5.9)	2 (0.9)	2
Vomiting	3 (2.1)	3 (2.1)	3				1 (1.5)	1 (0.3)	1			
Diarrhoea	1 (0.7)	1 (0.7)	1									
Blood and lymphatic system disorders												
Leukopenia	1 (0.7)	1 (0.7)	1	1 (2.9)	2 (1.1)	2	1 (1.5)	1 (0.3)	1			
Anaemia	1 (0.7)	1 (0.7)	1									
Respiratory, thoracic and mediastinal disorders												
Cough	2 (1.4)	2 (1.4)	2									
Tachypnoea	1 (0.7)	1 (0.7)	4									
Dyspnoea										1 (2.9)	1 (0.4)	1
Cardiac disorders												
Tachycardia	3 (2.1)	3 (2.1)	5							1 (2.9)	1 (0.4)	1

Skin and subcutaneous tissue disorders												
Rash				1 (2.9)	1 (0.6)	1	1 (1.5)	1 (0.3)	1	1 (2.9)	5 (2.2)	5
Dermatitis	5 (3.6)	5 (3.6)	5	2 (5.9)	2 (1.1)	2	4 (6.1)	8 (2.0)	8	3 (8.8)	4 (1.7)	5
Skin exfoliation				1 (2.9)	1 (0.6)	1	2 (3.0)	2 (0.5)	3	1 (2.9)	1 (0.4)	1
Urticaria	3 (2.1)	3 (2.1)	3	1 (2.9)	1 (0.6)	1						
Pruritus	1 (0.7)	1 (0.7)	1							2 (5.9)	2 (0.9)	2
Erythema				1 (2.9)	2 (1.1)	2						
Vascular disorders												
Hypertension	4 (2.8)	4 (2.8)	5	2 (5.9)	2 (1.1)	2	2 (3.0)	3 (0.8)	3			
Hypotension	1 (0.7)	1 (0.7)	1									
Investigations												
Blood lactate dehydrogenase increased	1 (0.7)	1 (0.7)	1				4 (6.1)	4 (1.0)	4			
Transaminases increased	1 (0.7)	1 (0.7)	1	1 (2.9)	1 (0.6)	1	1 (1.5)	1 (0.3)	1			
Alanine aminotransferase increased	1 (0.7)	1 (0.7)	1				2 (3.0)	2 (0.5)	2			
Aspartate aminotransferase increased	1 (0.7)	1 (0.7)	1				2 (3.0)	2 (0.5)	2			
Haemoglobin decreased							1 (1.5)	1 (0.3)	1			
Infections and infestations												
Nasopharyngitis										1 (2.9)	1 (0.4)	1

Supplementary table 4 Selected reports relating to high-dose IVIg in a variety of diseases.

Publication	Disease area	Report type	N	IVIg treatment	Safety findings
Cherin P et al. (1991) [1]	Chronic refractory polymyositis and dermatomyositis	Single-centre report	20	IVIg was administered monthly in one of two ways: 1 g/kg/day during 2 days for 13 patients and 0.4 g/kg/day during 5 days for 7 patients. 14 patients received between 3 and 6 infusions, 2 patients received 1 infusion, and 4 patients had 12 IVIg infusions.	• No premature discontinuation of IVIg because of lack of tolerance. • 16 patients experienced no side effects with IVIg. • Side effects were observed in 4 patients: headaches (1 patient), fever with shivering and sweating (2 patients), and delirium (1 patient). These adverse reactions disappeared spontaneously after discontinuation of the infusion and did not reoccur during subsequent IVIg infusions.
Dalakas MC et al. (1993) [2]	Dermatomyositis	Double-blind, placebo controlled, cross-over report	15	IVIg 2 g/kg (over 2 days) per month for 3 months or placebo. After 3 months patients were crossed over. Total of 12 patients received IVIg.	• In general, IVIg infusion were well tolerated. • 2 patients had recurrent headache with IVIg infusion necessitating treatment but stated benefit outweighed adverse event.
Harman KE et al. (1999) [3]	Autoimmune blistering diseases	Case series	14	IVIg 2 g/kg (over 5 days) for variable durations.	• Side effects occurred in 8 of the 14 patients and included tachycardia (3 patients), hypertension (4 patients), headache (3 patients), and myalgia (2 patients). These responded to slowing the rate of infusion and did not prevent continued treatment.
Engineer L et al. (2000) [4]	Pemphigus vulgaris	Retrospective analysis	21	1.2–2 g/kg per cycle over 3–5 consecutive days for variable durations (1 patient received 39 g daily over 3-5 days).	• No significant side effects were observed in any of the 21 patients during the follow-up.
Levy Y et al. (2000) [5]	Systemic sclerosis	Case series	3	6 monthly IVIg infusion cycles (2 g/kg over 5 days). 2 patients received 6 cycles as planned and 1 patient received 3 cycles.	• No adverse events were reported for the 2 patients who completed 6 IVIg cycles. • The third patient who received 3 cycles developed renal failure and died of sepsis, which was considered unlikely to be related to IVIg.
Dalakas MC et al. (2001) [6]	Stiff-person syndrome	Randomised trial report	16	IVIg 2 g/kg (over 2 days) per month for 3 months.	• No comment on safety. • 1 patient withdrew due to severe blistering rash after each infusion.
Vo AA et al. (2008) [7]	Renal transplantation	Single-centre report	20	IVIg given twice (2 g/kg) on day 0 and day 30.	• No infusion-related side effects.
Attarian S et al. (2010) [8]	Chronic ataxic neuropathy associated with anti-GD1b IgM antibodies	Retrospective, uncontrolled, single-centre report	13	Twenty-four 2 g/kg IVIg were performed on average (range 3 to 100 infusions) per patient at a rate of one 3- to 5-day infusion every 4 to 8 weeks. Lower doses as part of maintenance infusion were not used.	• No specific safety reported.

Nair V et al. (2012) [9]	Kidney transplant candidates	Case series	15	1 g/kg dosing twice a month for 4 months (or until transplantation if earlier).	• No specific safety reported. • 13 of 15 patients received the full 8 g/kg dose; one patient experienced extreme restlessness during treatments resulting in the termination of therapy after 5.5 g/kg and another patient received 4 g/kg and then was transplanted.

IVIg = intravenous immunoglobulin.

Supplementary references

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