

Appendix 3 — Safety of IVIG

General information

Condition summary

Safety of IVIG

Reference list:

- 252 Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med.* 1994 Aug 15;121(4):259-62.
- 165 Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003; 50(3):172-5.
- 245 Grillo JA, Gorson KC, Ropper AH, Lewis J, Weinstein R. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. *Neurology.* 2001 Nov 13;57(9):1699-701.
- 246 Caress JB, Cartwright MS, Donofrio PD, Peacock JE Jr. The clinical features of 16 cases of stroke associated with administration of IVIg. *Neurology.* 2003 Jun 10;60(11):1822-4.
- 247 Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. *Neurology.* 2003 Jun 10;60(11):1736-7.
- 248 Okuda D, Flaster M, Frey J, Sivakumar K. Arterial thrombosis induced by IVIg and its treatment with tPA. *Neurology.* 2003 Jun 10;60(11):1825-6.
- 251 Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med.* 1994 Aug 15;121(4):305-6.
- 253 Schmalldienst S, Mullner M, Goldammer A, Spitzauer S, Banyai S, Horl WH, Derfler K. Intravenous immunoglobulin application following immunoabsorption: benefit or risk in patients with autoimmune diseases? *Rheumatology (Oxford).* 2001 May;40(5):513-21.
- 254 Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. *Haematologica.* 1993 Nov-Dec;78(6 Suppl 2):35-40.
- 255 Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. *J Pediatr.* 1997 Feb;130(2):281-3.
- 24 Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. *QJM* 2000; 93(11):751-5.
- 257 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev.* 2003 Oct;17(4):241-51.
- 258 No authors listed. Renal insufficiency and failure associated with immune globulin intravenous therapy--United States, 1985-1998. *MMWR Morb Mortal Wkly Rep.* 1999 Jun 25;48(24):518-21.

- 259 Yap PL. Intravenous immunoglobulin and hepatitis C virus: an overview of transmission episodes with emphasis on manufacturing data. *Clin Ther.* 1996;18 Suppl B:43-58.
- 260 Berger M, Pinciario PJ. Safety, Efficacy, and Pharmacokinetics of Flebogamma(R) 5% [immune Globulin Intravenous (human)] for Replacement Therapy in Primary Immunodeficiency Diseases. *J Clin Immunol.* 2004 Jul;24(4):389-96.
- 256 Eibi MM
- 249 Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology.* 1994 Feb;44(2):223-6.

Types of study:	7 uncontrolled studies
Total sample size:	512
Quality:	Low
Result:	Varied from no adverse events, to mild adverse events (4-42.7%) to severe adverse events (3.5-8%)
Adverse events:	
Conclusion:	Conflicting results, generally appear to be few adverse events except in certain subpopulations
Category:	

Condition studies: Safety of IVIG

252 Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med. 1994 Aug 15;121(4):259-62.

Study design: Other Length of follow-up: N/A

Sample size: 54 Population:

Intervention: high-dose (2 g/kg) IVIG

Comparison / control: N/A

Outcome(s) measured: aseptic meningitis, associated risk factors, penetration of serum IgG into the cerebrospinal fluid, and clearance of cerebrospinal fluid IgG

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups:	6/54 patients (11%; 95% CI, 4% to 23%) developed aseptic meningitis within 24 hours after completion of the infusions; Cerebrospinal fluid showed pleocytosis in 4 patients, eosinophilia in 3 patients, and IgG elevation in all patients	Control / comparison group(s):
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P-value: See Col 29, 31

Adverse events: Symptoms, lasting 3 to 5 days, included severe headache, meningismus, photophobia, and fever

Conclusions / Comments: High rate of aseptic meningitis associated with high-dose IVIG. More likely to occur with history of migraine, appears not to be related to type of preparation or infusion rate. Could be related to IgG itself, stabilising products, cytokine release triggered by IVIG, cerebrovascular sensitivity in those with migraine.

Condition studies: **Safety of IVIG**

165 Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. Eur Neurol 2003; 50(3):172-5.

Study design: Case-series **Length of follow-up:** No length of follow up was recorded

Sample size: 117 **Population:**

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: Adverse effects including; headaches, DVT

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: 42.7% showed adverse events **Control / comparison group(s):** N/A

P-value:

Adverse events: Majority of patients presented with minor adverse effects, mostly asymptomatic laboratory changes including; Rash or mild headache; DVT complications

Conclusions / Comments: Side effects generally absent or minor. Patients with pre-existing disorders (eg heart or renal insufficiency, or immobilisation) may be at higher risk for complications

Condition studies: Safety of IVIG

245 Grillo JA, Gorson KC, Ropper AH, Lewis J, Weinstein R. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. Neurology. 2001 Nov 13;57(9):1699-701.

Study design: Case-series Length of follow-up: No length of follow up was recorded

Sample size: 50 patients with neuromuscular disorders Population:

Intervention: Rapid infusion of IVIG

Comparison / control: N/A

Outcome(s) measured: Adverse effects

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups:	There were 89 adverse events after 341 rapid infusions (26%), 3.5% of which were considered to be major (requiring hospitalization - chest pain, myocardial infarction, congestive heart failure, severe headache, pleurisy, tranfusion-related acute lung injury, allergic reaction) and 22.5% minor (mild or moderate headache, malaise, nausea, myalgia, hypertension, fever, chills, pedal edema, slight dyspnea).	Control / comparison group(s):	N/A
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P-value:

Adverse events:

Conclusions / Comments: Rate of adverse events slightly higher (26%) than for conventional-infusion regimens at slower rates.

Condition studies: Safety of IVIG

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Caress JB, Cartwright MS, Donofrio PD, Peacock JE Jr. The clinical features of 16 cases of stroke associated with administration of IVIg. *Neurology*. 2003 Jun 10;60(11):1822-4.

Study design: Case-series **Length of follow-up:** No length of follow up was recorded

Sample size: 16 stroke patients **Population:**

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: Adverse effects

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: 14 of the strokes occurred within 24 hours of an infusion; 9 patients had multifocal infarctions. **Control / comparison group(s):** N/A

P-value:

Adverse events: strokes, multifocal infarctions

Conclusions / Comments: Exclude due to small numbers and risk factors

Condition studies: Safety of IVIG

247 Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology. 2003 Jun 10;60(11):1736-7.

Study design: Other Length of follow-up: N/A

Sample size: N/A Population:

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: Adverse effects

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: N/A Control / comparison group(s): N/A

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies: Safety of IVIG

248 Okuda D, Flaster M, Frey J, Sivakumar K. Arterial thrombosis induced by IVIg and its treatment with tPA. Neurology. 2003 Jun 10;60(11):1825-6.

Study design: Case-series Length of follow-up: No length of follow up was recorded

Sample size: 4 patients who developed cerebral and peripheral arterial thrombosis after treatment with IV immunoglobulin Population:

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: Use of tissue plasminogen activator

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: No sufficient information is provided Control / comparison group(s): N/A

P-value:

Adverse events:

Conclusions / Comments: Exclude - small sample

Condition studies: Safety of IVIG

251 Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med. 1994 Aug 15;121(4):305-6.

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention:

Comparison / control: N/A

Outcome(s) measured:

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: N/A Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies: Safety of IVIG

253 Schmalldienst S, Mullner M, Goldammer A, Spitzauer S, Banyai S, Horl WH, Derfler K. Intravenous immunoglobulin application following immunoadsorption: benefit or risk in patients with autoimmune diseases? Rheumatology (Oxford). 2001 May;40(5):513-21.

Study design: RCT Length of follow-up:

Sample size: 35 Population:

Intervention: n=17 combined immunoadsorption and intravenous immunoglobulins

Comparison / control: n=18 control immunoadsorption alone

Outcome(s) measured: infection rates, adverse effects

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups:	1.3 infections per patient-year	Control / comparison group(s):	0.9 infections per patient-year
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P-value:

Adverse events: in patients in whom circulating immunoglobulins had been depleted was associated with a high incidence of serious side-effects

Conclusions / Comments: Exclude - not relevant to safety, looks at benefit of IVIG after immunoadsorption (outside the scope of this review)

Condition studies: Safety of IVIG

254 Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica. 1993 Nov-Dec;78(6 Suppl 2):35-40.

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention: IVIG

Comparison / control:

Outcome(s) measured: adverse reactions

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Major adverse reactions included aseptic meningitis (14 cases), hemolytic anemia (8 cases) and renal dysfunction (12 cases)

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies: Safety of IVIG

255 Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. J Pediatr. 1997 Feb;130(2):281-3.

Study design: Case-series **Length of follow-up:**

Sample size: 38 children with acute immune thrombocytopenic purpura (ITP) **Population:**

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: incidence, associated morbidity, and impact on health care charges of neurologic complications

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: 13/38 (34%) had transient neurologic complications, manifested by severe headache, nausea, and, rarely, aseptic meningitis

Control / comparison group(s):

P-value:

Adverse events: 12 patients were hospitalized longer than was required for their ITP alone

Conclusions / Comments: Frequency of significant acute side effects with IVIG may be higher than previously suggested, may substantially increase costs of treatment

Condition studies: Safety of IVIG

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Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. QJM 2000; 93(11):751-5.

Study design: Cohort Length of follow-up:

Sample size: 119 Population: Variety of indications - thrombocytopaenia, SLE, neruopathy, Guillain-Barre syndrome, infections

Intervention: IVIG (Vigam and Sandoglobulin)

Comparison / control:

Outcome(s) measured: Renal function

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Renal function deteriorated in 8 patients (6.7%) and no renal recovery occurred in 2 (1.7%). The 3 patients with the most severe renal failure received Vigam IVIG.

Control / comparison group(s):

P-value:

Adverse events: IVIG associated with renal impairment that may be irreversible (max incidence 6.7%)

Conclusions / Comments: Results suggest that any preparation of IVIG can cause renal impairment, therefore, IVIG should not be used with other potential nephrotoxins, renal function should be checked before and after administration of IVIG, especially in patients with pre-existing renal disease, and serum creatinine should be measured 4-5 days after starting high-dose IVIG therapy.

Condition studies: Safety of IVIG

257 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003 Oct;17(4):241-51.

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

258 No authors listed. Renal insufficiency and failure associated with immune globulin intravenous therapy--United States, 1985-1998. MMWR Morb Mortal Wkly Rep. 1999 Jun 25;48(24):518-21.

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review/report on the epidemiology of IGIV-associated RAEs in the United States

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

259 Yap PL. Intravenous immunoglobulin and hepatitis C virus: an overview of transmission episodes with emphasis on manufacturing data. Clin Ther. 1996;18 Suppl B:43-58.

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

260 Berger M, Pinciaro PJ. Safety, Efficacy, and Pharmacokinetics of Flebogamma(R) 5% [immune Globulin Intravenous (human)] for Replacement Therapy in Primary Immunodeficiency Diseases. J Clin Immunol. 2004 Jul;24(4):389-96.

Study design: cohort **Length of follow-up:** 12 months

Sample size: 51 (aged 14-74) **Population:** Subjects aged 14 and older, minimum weight of 27 kg, with well-defined primary immunodeficiency.

Intervention: IVIG (Flebogamma) with well-defined primary immunodeficiency diseases at a dose of 300-600 mg/kg every 21-28 days

Comparison / control: N/A

Outcome(s) measured: safety, efficacy, and pharmacokinetics of Flebogamma(R)

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: The calculated serious infection rate for the intent-to-treat population was 0.061/subject/year. The incidence of adverse events considered potentially related to Flebogamma(R) 5%, and occurring during or within 72 h after completing the infusion was approximately 8%.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Flebogamma(R) 5% is efficacious, safe, and well-tolerated, and does not put subjects at increased risk of adverse events other than those that could be reasonably expected in primary immunodeficient subjects who are receiving any immune globulin product.

Condition studies: Safety of IVIG

256 Eibi MM

Study design: Other Length of follow-up:

Sample size: N/A Population:

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

249 Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994 Feb;44(2):223-6.

Study design: Case-series Length of follow-up:

Sample size: 13 patients (5 with amyotrophic lateral sclerosis [ALS], 8 with IgM paraproteinemic polyneuropathy) Population:

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: measured serum viscosity

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Serum viscosity increased after IVIg in all the patients by 0.1 to 1.0 centipoise; Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - small sample