West Middlesex University Hospital

Date of Search: 04/07/2016
Sources Searched: Medline, Embase, The Cochrane Library

Search History:
1. EMBASE; privigen.ti,ab; 102 results.
2. EMBASE; vigam.ti,ab; 18 results.
3. EMBASE; sandoglobulin.ti,ab; 155 results.
4. EMBASE; flebogamma.ti,ab; 65 results.
5. EMBASE; exp AUTOIMMUNE THROMBOCYTOPENIA/; 10534 results.
6. EMBASE; "immune thrombocytopenia".ti,ab; 3635 results.
7. EMBASE; 5 OR 6; 12493 results.
8. EMBASE; 2 OR 3 OR 4; 236 results.
9. EMBASE; 1 AND 7 AND 8; 1 results.
10. EMBASE; 7 AND 8; 10 results.
11. EMBASE; exp COMPARATIVE STUDY/; 1076784 results.
12. EMBASE; 1 OR 2 OR 3 OR 4; 325 results.
13. EMBASE; 7 AND 12; 20 results.
14. EMBASE; exp IMMUNOGLOBULIN/; 390864 results.
15. EMBASE; 7 AND 11 AND 14; 134 results.
16. EMBASE; *HUMAN IMMUNOGLOBULIN/; 572 results.
17. EMBASE; 7 AND 16; 24 results.
18. EMBASE; exp CLINICAL TRIAL/; 1096267 results.
19. EMBASE; 7 AND 14 AND 18; 463 results.
20. EMBASE; *IMMUNOGLOBULIN/; 37071 results.
21. EMBASE; 7 AND 20; 913 results.
22. EMBASE; 18 AND 21; 121 results.
23. EMBASE; 1 AND 7 AND 11; 2 results.
24. EMBASE; 3 AND 11; 6 results.
25. EMBASE; 2 AND 7; 2 results.
26. EMBASE; 4 AND 7; 1 results.
27. EMBASE; (intravenous AND (immunoglobulin* OR "Gamma Globulin")).ti; 5865 results.
28. EMBASE; 7 AND 27; 436 results.
29. EMBASE; 11 AND 28; 18 results.
30. EMBASE; exp IMMUNOGLOBULIN/iv [iv=Intravenous Drug Administration]; 27252 results.
31. EMBASE; 7 AND 30; 1869 results.
32. EMBASE; 18 AND 31; 282 results.
33. Medline; privigen.ti,ab; 28 results.
34. Medline; vigam.ti,ab; 7 results.
35. Medline; sandoglobulin.ti,ab; 137 results.
36. Medline; flebogamma.ti,ab; 30 results.
37. Medline; "immune thrombocytopenia".ti,ab; 2261 results.
38. Medline; exp PURPURA, THROMBOCYTOPENIC, IDIOPATHIC/; 5254 results.
39. Medline; 37 OR 38; 6580 results.
40. Medline; 33 AND 39; 1 results.
41. Medline; 33 OR 34 OR 35 OR 36; 198 results.

42. Medline; 39 AND 41; 4 results.
43. Medline; (intravenous AND (immunoglobulin* OR "Gamma Globulin")).ti; 4496 results.
44. Medline; exp IMMUNOGLOBULINS/; 788282 results.
45. Medline; 43 OR 44; 788673 results.
46. Medline; 39 AND 45; 2306 results.
47. Medline; compar*.ti,ab; 4043450 results.
49. Medline; "COMPARATIVE STUDY".af; 1757757 results.
50. Medline; 47 OR 49; 4895572 results.
51. Medline; 46 AND 50; 479 results.
52. Medline; 33 AND 35; 2 results.
53. Medline; 33 AND 34; 0 results.
54. Medline; 33 AND 36; 1 results.
55. Medline; IMMUNOGLOBULINS, INTRAVENOUS/; 10751 results.
56. Medline; 50 AND 55; 1950 results.
57. Medline; 39 AND 56; 144 results.
58. Medline; 39 AND 55; 691 results.
59. Medline; 58 [Limit to: (Document type Clinical Trial) and (Language English)]; 49 results.
60. EMBASE; 1 AND 2; 0 results.
61. EMBASE; 1 AND 3; 9 results.
62. EMBASE; 1 AND 4; 5 results.
63. EMBASE; exp HUMAN IMMUNOGLOBULIN/iv [iv=Intravenous Drug Administration]; 319 results.
64. EMBASE; 11 AND 63; 21 results.
65. EMBASE; "Carimune NF".ti,ab; 3 results.
66. EMBASE; Redimune.ti,ab; 2 results.
67. EMBASE; (product adj2 select*).ti,ab; 1466 results.
68. EMBASE; 7 AND 30 AND 67; 1 results.
69. EMBASE; 21 [Limit to: (Publication Types Review)]; 200 results.

Title: Quantitative Evidence of Wear-Off Effect at the End of the Intravenous IgG (IVIG) Dosing Cycle in Primary Immunodeficiency.

Citation: Journal of clinical immunology, Apr 2016, vol. 36, no. 3, p. 210-219, 1573-2592 (April 2016)

Author(s): Rojavin, Mikhail A, Hubsch, Alphonse, Lawo, John-Philip

Abstract: Intravenous IgG (IVIG) treatment wear-off is commonly experienced by patients, who report increased susceptibility to infection, and decreased quality of life towards the end of their 3- or 4-week dosing cycle, when serum IgG levels approach their trough. We quantified IVIG wear-off in terms of treatment efficacy and patient well-being. Data were collected from patients enrolled in three Phase III trials of Sandoglobulin® NF Liquid or Privigen®, treated every 3- or 4- weeks. Pooled analyses of raw patient data compared the rate of infection and other clinical outcomes during the course of the dosing cycle. Subjective symptoms of wear-off were quantified by comparing patient-reported overall well-being scores. The probability of a first infection in the final week of the IVIG cycle was 1.26 (95 % confidence intervals [CI]: 0.76-2.11; p = 0.3621) and 1.55 (95 % CI: 1.04-2.32; p = 0.0314) times higher than in the first week, for patients on a 3-week cycle and 4-week dosing cycles, respectively. Wear-off, as manifested by a decrease in overall well-being, was experienced in 10 % of all cycles and reported at least once by 61 % of the patients on a 3-week cycle, and 43 % of those on a 4-week cycle. These findings confirm the existence of decreased efficacy (treatment wear-off) towards the end of a 3-4 week IVIG dosing cycle, and provide a quantifiable evaluation to a phenomenon typically reported anecdotally. For patients experiencing wear-off, increasing the IgG dose or shortening the dosing interval and/or a switch to SCIG may be beneficial.

Source: Medline

Full Text:
Available from *Springer Link Journals* in Journal of Clinical Immunology

---

Title: Immunoglobulin replacement therapy: A twenty-year review and current update

Citation: International Archives of Allergy and Immunology, August 2014, vol./is. 164/2(151-166), 1018-2438;1423-0097 (August 2014)

Author(s): Saeedian M., Randhawa I.

Language: English

Abstract: Objective: The expansion of immunoglobulin replacement to multiple disease entities marks a decade-long advancement in immune therapy. Parallel to its extension, the characteristics and composition of immunoglobulin products have diversified. The aim of this study was to summarize a 20-year comprehensive literature review of currently commercially available immunoglobulin products, particularly examining individual product properties in a comparative format. Data Sources/Study Selections: The literature review was performed using PubMed and Ovid, screening a time span of 2 decades. Both authors reviewed the obtained articles for acceptable quality, and the selection was narrowed down based on criteria for randomized clinical and therapeutic trials. Results: Product-specific characteristics in terms of purification strategy, stabilizers, composition, and viral inactivation were found among the immunoglobulin products investigated. Such differing characteristics manifest in their variable clinical safety and efficacy as assessed by the comparative product analysis. In subgroups of patients, subcutaneous immunoglobulin therapy may be an alternative to intravenous immunoglobulin (IVIG) therapy with an equal efficacy and a lower number of systemic adverse events. Conclusion: Only few comprehensive clinical synopses are available to clearly demonstrate the differences in IVIG products despite the widespread clinical use of the therapy. This review defines significant characteristics of individual immunoglobulin products, noting important differences in product development and application and allowing informed clinical decisions to match a product with patients' risk factors and comorbidity. This balanced approach to gammaglobulin replacement therapy is imperative to produce the highest clinical efficacy and lowest number of adverse events. © 2014 S. Karger AG, Basel.

Publication Type: Journal: Review

Source: EMBASE

Full Text:
Available from *ProQuest* in International Archives of Allergy and Immunology

---

Title: Quantification of the wear-off effect towards the end of the intravenous immunoglobulin infusion interval: Pooled data analysis

Citation: Journal of Allergy and Clinical Immunology, February 2014, vol./is. 133/2 SUPPL. 1(AB179), 0091-6749 (February 2014)

Author(s): Lawo J.-P., Hubsch A., Rojavin M.

Language: English

Abstract: RATIONALE: Some patients with primary immunodeficiencies (PID) report increased frequencies of infections and/or fatigue at the end of their intravenous IgG (IVIG) dosing cycle. This study aimed to quantify the "wear-off" effect by analyzing efficacy endpoints throughout 3- or 4-weekly IVIG dosing cycles. METHODS: The database included 132 patients (7482 data points) from Phase III trials of Sandoglobulin NF Liquid or Privigen. A binomial regression model for repeated measurements was used to compare infection probabilities during each week of the cycle. The compound symmetry correlation structure was used to account for within-subject correlation. To account for incubation periods of infections starting early after infusion, a 3-day shifted time interval analysis was performed.As thiswas a retrospective analysis for hypothesis generation, no adjustment of p-values due to multiplicity was performed. RESULTS: The probability of infection increased significantly inWeek 4 compared toWeek 1 of the 4-weekly cycle (ratio 1.55; p=0.031). Although the same effect was observed for the 3-weekly cycle, the difference was not statistically significant (ratio 1.27; p=0.362). With shifted time intervals, the number of days with infection increased moderately, but statistically significantly, at the end of both dosing cycles (3-weekly: ratio 1.13, p=0.047; 4-weekly: ratio 1.13, p<0.001). No signs of wear-off were seen for days of hospitalization or absence from school/work. CONCLUSIONS: This analysis provides additional evidence for the existence of a "wear-off" effect in patients with PID. Possible ways of reducing the increased infection risk are shorter IVIG infusion intervals, increased IVIG dose and/or switch to subcutaneous therapy.

Publication Type: Journal: Conference Abstract

Source: EMBASE

Title: Safety and efficacy of Gammaplex® in idiopathic thrombocytopenic purpura (ClinicalTrials.gov--NCT00504075).

Citation: PloS one, Jan 2014, vol. 9, no. 6, p. e96600., 1932-6203 (2014)

Author(s): Dash, Clive H, Gillanders, Kate R, Stratford Bobbitt, Margaret E, Gascoigne, Ernie W, Leach, Samantha J

Abstract: This multicentre, open-label study investigated the safety and efficacy of Gammaplex, a 5% Intravenous Immunoglobulin (IVIg), in patients with idiopathic (immune) thrombocytopenic purpura (ITP). Patients were between the ages of 6 and 70 years; had ITP for at least six months and had a platelet count ≤ 20 × 10(9)/L. Eligible patients were dosed with 1 g/kg of Gammaplex on two consecutive days, followed by assessment of safety and efficacy on Days 3, 5, 9, 14, 21, 32 and 90. Response was defined as the increase in platelet count to a threshold of ≥ 50 × 10(9)/L on or before Day 9 after the first dose of Gammaplex. All 35 patients received at least one infusion of Gammaplex. Twenty-nine (83%) patients responded to Gammaplex, similar to the historical control, with a 95% lower one-sided confidence interval of 68.9%. Median duration of response was 10.0 days, with an overall reduction in bleeding episodes. Gammaplex provided supranormal concentrations of total IgG; mean peak concentration (Cmax) of 45.3 g/L (4.53 g/dL), with a mean half-life of 28.5 days. Fifteen patients reported 63 Adverse Drug Reactions (ADRs); the most common were headache (10 patients), vomiting (6 patients) and pyrexia (5 patients). Five of these ADRs were considered serious, one patient had three concurrent Serious Adverse Events (SAEs); these were

vomiting, dehydration and headache. Two other patients each had one SAE (headache). There were no unexpected Adverse Events (AEs) or thromboembolic episodes and no significant changes in vital signs, biochemical, haematological and virology results. Gammaplex achieved a very high concentration of serum IgG but was well-tolerated and effective in the treatment of ITP with a similar degree of efficacy to the pre-determined historical control group and the pre-set statistical criteria. ClinicalTrials.gov NCT00504075 Clinical Trials Registry India 000016.

Source: Medline

Full Text:
Available from *National Library of Medicine* in PLoS ONE
Available from *ProQuest* in PLoS One
Available from *National Library of Medicine* in PLoS ONE
Available from *Allen Press* in PLoS One

Title: Should therapeutic immunoglobulin be considered a generic product? An evidence-based approach

Citation: Journal of Allergy and Clinical Immunology: In Practice, November 2013, vol./is. 1/6(567-572), 2213-2198 (November 2013)

Author(s): Misbah S.A.

Language: English

Abstract: The increasing therapeutic use of intravenous immunoglobulin (IVIG) for an expanding range of indications, from immunodeficiency to autoimmune disease coupled with the availability of multiple products has prompted debate on whether IVIG products should be considered to be generic. Although the manufacturing process and associated excipients for individual products varies, all currently licensed IVIG products are composed predominantly of IgG (>95%) and comply with the quality standards of regulatory agencies. Because these products have a licence for a common group of indications, does that mean that all of them are equally efficacious in the treatment of the same disease? In vitro data and published evidence of head-to-head trials of IVIG in primary antibody deficiency, immune thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy suggest that different IVIG products are likely to be equally efficacious in terms of clinical efficacy. Consequently, it would be reasonable to consider IVIG products to be generic in terms of clinical outcomes. However, the lack of significant differences in clinical efficacy should not be used to justify frequent product changes on financial or nonclinical grounds because of the increased risk of adverse effects and difficulty in tracking a suspect product in the event of a future outbreak of IVIG-associated viral transmission. © 2013 American Academy of Allergy, Asthma & Immunology.

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *ProQuest* in Journal of Allergy and Clinical Immunology. In Practice

---

Title: IVIG trademark head to head analysis of adverse events in 1394 intravenous immunoglobulin replacement treatments

Citation: Journal of Allergy and Clinical Immunology, February 2013, vol./is. 131/2 SUPPL. 1(AB70), 0091-6749 (February 2013)

Author(s): Larrauri B.J., Romero D.F., Juri M.C., Malbran A.

Language: English

Abstract: RATIONALE: Different intravenous immunoglobulin (IVIG) manufacturers use different strategies for product isolation, sterilization and stabilization, so they may have different rates of adverse effects. We conducted a retrospective and prospective, head to head analysis, of immediate adverse events (IAE) among seven different IVIG trademarks. METHODS: We analyzed 1394 IVIG monthly infusions (1030 retrospective and 364 prospective) in 28 hipogammaglobulinemic patients, mean 49.8654.8, median32.5 (range 2-214). Seven IVIG trademarks provided by health insurances were studied. In 22 (1.6%) infusions trademark was not available. We define as immediate adverse event those occurring within 48 hrs of infusion. Prospectively, we recorded velocity of administration in gr/hr. RESULTS: Patients received a median of 2 (1-6) different IVIG. Fifty six (4%) IAE were recorded with a median of 1 (0-9) per patient. Nineteen out of 28 patients (67.9%) have an IAE that was recorded in 6.0% of 449 KiovigTM (Baxter) infusions, in 0.5% of 371 EndobulinTM (Immuno), 6.1% of 228 UNCTM (Cordoba University), in 4.5% of 112 PurissimusTM (Purissimus SA), in 1% of 99 SandoglobulinTM (Sandoz), 5.1% of 98 FlebogammaTM (Grifols), and 0% of 15 PrivigenTM (CSL Behring). IAE were mild in 36.4%, moderate in 61.8% and severe in 1.8%. Infusions were stopped 9 times. Retrospectively, KiovigTM had performed significantly worst than EndobulinTM, 11/255 vs. 2/371, p<0.001. Prospectively, IAE presented at a mean velocity of infusion of 9.0464.63 gr/hr compared to 10.5664.63 gr/hr, p<0.10. CONCLUSIONS: Different IVIG preparations have different rates of adverse events that should be taken into account to select the best.

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *ProQuest* in Journal of Allergy and Clinical Immunology

---

Title: Increased frequency of infections at the end of the intravenous immunoglobulin dosing cycle: Effect characterization from three phase III studies

Citation: Journal of Clinical Immunology, September 2012, vol./is. 32/(S353), 0271-9142 (September 2012)

Author(s): Bexon M., Baggish J.S., Rojavin M.A., Berger M., Zenker O.

Language: English

Abstract: Introduction: Anecdotal reports suggest that some patients with primary immunodeficiencies (PIs) may experience diminished protection from infection ("wear-off" effect) toward the end of their intravenous immunoglobulin (IVIG) dosing cycle, but this phenomenon has not been studied objectively. Objective: We evaluated the incidence of infection in each week of the IVIG dosing cycle in different licensing trials in PI patients as an objective measure of "wear-off" effect. Methods: Three Phase III trials of Sandoglobulin NF Liquid or Privigen (CSL Behring, Marburg,

Germany) were included in a pooled analysis. Kaplan-Meier estimates were used to analyze the time to first infection following infusion. Results: A total of 2123 infusions in 177 patients were analyzed (4-week dosing cycle, 1543 infusions; 3-week dosing cycle, 580 infusions). The median equivalent weekly doses in the efficacy phase were 125.5 mg/kg (Sandoglobulin NF Liquid, NCT00168012), 117.8 mg/kg (Privigen, NCT00168025), and 128.2 mg/kg (Privigen, NCT00322556). The probability of first infection in patients on a 4-week cycle was 0.033, 0.027, 0.025, and 0.046 for Weeks 1-4, respectively; in patients on a 3-week cycle, it was 0.076, 0.042, and 0.081 for Weeks 1-3, respectively. Thus, the probability of first infection increased during the last week compared to the preceding week(s). Conclusions: In PI patients receiving IVIG therapy, the frequency of infection varies by week, with the highest frequency of infections at the end of 3- or 4-week dosing cycles. This may be indicative of a "wear-off" effect, reflecting the immunoglobulin serum concentration profile associated with intravenous administration, which is characterized by pronounced peak and trough levels.

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *Springer Link Journals* in Journal of Clinical Immunology
Available from *ProQuest* in Journal of Clinical Immunology

Title: Direct medical costs of liquid intravenous immunoglobulins in children, adolescents, and adults in Spain

Citation: Journal of Clinical Pharmacology, April 2012, vol./is. 52/4(566-575), 0091-2700;1552-4604 (April 2012)

Author(s): Darba J., Restovic G., Kaskens L., De Agustin T.

Language: English

Abstract: The aim of this study was to determine health care resource utilization and direct medical costs in Spanish patients treated with intravenous immunoglobulins (IVIGs) in 2009. Cost-of-illness analyses were performed to estimate direct medical costs of patients treated with IVIGs. Prevalence data were obtained from the Spanish Primary Immunodeficiency registry. A semi-structured questionnaire was used to collect data on health care resource utilization and patient distribution. Drug, administration, and premedication costs were considered from the payer's perspective. Separate analyses were conducted for children and adolescents versus adults. The numbers of children and adolescents with replacement therapy were 724, with immunomodulation 243, and with allogeneic bone marrow transplantation 30. The numbers of adult patients were, respectively, 3450, 1134, and 172. Mean annual costs for children and adolescents were 6293 with Privigen, 6292 with Kiovig, 6939 with Flebogamma, and 6559 with Octagamocta. For adults, estimations were 17 106 with Privigen, 17 103 with Kiovig, 18 077 with Flebogamma, and 17 423 with Octagamocta. Direct medical costs for IVIGs were approximately 91.8 million . Drug costs represented 94% of total costs. The choice for a certain IVIG treatment depends on individual patient characteristics and cost considerations. © 2012 The Author(s).

Publication Type: Journal: Article

Source: EMBASE

Title: Rapid clearance of L-proline after intravenous and subcutaneous infusion with L-proline-stabilized immunoglobulin replacement products

Citation: Journal of Clinical Immunology, September 2011, vol./is. 31/(S50-S51), 0271-9142 (September 2011)

Author(s): Hagan J.B., Robak T., Church J.A., Rojavin M., Wasserman R.L.

Language: English

Abstract: Introduction: L-Proline (proline) is a naturally occurring amino acid found in many foods (average daily intake =5.2 g) and has been used safely for many years as a component of parenteral nutrition. Two immunoglobulin replacement products, Privigen (immune globulin intravenous [IVIg; human], 10% liquid, CSL Behring) and Hizentra (immune globulin subcutaneous [SCIg; human], 20% liquid, CSL Behring), used to treat patients with primary immunodeficiency (PID) and immune thrombocytopenic purpura (ITP; Privigen only), use proline (250 mmol/L at pH 4.8) as a stabilizer to minimize IgG dimerization, aggregation, and denaturation. In preclinical studies, no toxicity was observed following proline administration at daily doses 5-fold and 25-fold higher than the content of proline in normal human doses of Privigen and Hizentra, respectively. However, the labeled contraindication in patients with hyperprolinemia, an extremely rare genetic condition characterized by persistently elevated plasma proline and neurologic defects, led us to examine the potential accumulation of exogenously administered proline in patients with normal proline metabolism. Objective: To determine the potential for proline accumulation in subjects treated with Privigen or Hizentra. Methods: Proline pharmacokinetics was assessed as part of 2 prospective, open-label, multicenter, single-arm, phase 3 efficacy and safety studies of: 1) Privigen administered via IV infusion pump (1,000 mg IgG/kg body weight) on 2 consecutive days in subjects 12-65 years old with chronic ITP and 2) Hizentra administered weekly via SC infusion in subjects 7-75 years old with PID. The latter comprised a 12-week washin/washout period and a 12-month efficacy period. During week 28 (mean dose range=223-231 mg/kg body weight), proline serum concentration was measured predose, and then 2 hours, 1 day, 3 days, and 7 days postdose. In the Privigen study, proline serum concentration was measured predose and postdose on days 0-1 and on days 3 and 7. Results: Before dosing, mean serum proline levels were within the normal range for adults in both studies (Privigen= 223 mumol/L; Hizentra=228 mumol/L). In the Privigen study, serum proline levels increased immediately after the first infusion (mean=3,064 mumol/L), were near baseline levels (mean=577 mumol/L) before administration of the second dose, and had returned to baseline values (mean=250 mumol/L) by 2 days after the second dose (postdose day 3; Table). In the Hizentra study, mean serum proline level increased to almost twice the baseline value 2 hours after infusion (mean= 415 mumol/L) and returned to baseline values (mean= 236 mumol/L) within 1 day (Table). No treatment-related serious adverse events (SAEs) were reported in the Hizentra study, and 1 treatment-related SAE (aseptic meningitis) was reported in the Privigen study. Conclusions: Serum proline does not accumulate in subjects with normal proline metabolism and is rapidly cleared from circulation after infusion of proline-containing immunoglobulin products.

Publication Type: Journal: Conference Abstract

Source: EMBASE

Full Text:
Available from *Springer Link Journals* in Journal of Clinical Immunology
Available from *ProQuest* in Journal of Clinical Immunology

Title: Information for healthcare providers on general features of IGIV with emphasis on differences between commercially available products

Citation: Autoimmunity Reviews, June 2010, vol./is. 9/8(553-559), 1568-9972 (June 2010)

Author(s): Gurcan H.M., Keskin D.B., Ahmed A.R.

Language: English

Abstract: Objective: Intravenous immunoglobulin (IGIV) has provided an essential replacement therapy for primary and secondary immunodeficiencies patients and prophylaxis of infectious diseases in them. It is also used in several autoimmune and chronic inflammatory disorders. An overview of IGIV with information on several commercially available IGIV products is discussed. Data Sources: Medline databases and literature provided by the manufacturer for each product presented in the manuscript. Study Selection: From the vast body of information on IGIV, only those studies were selected that were pertinent to general features of IGIV (as presented below) or information provided by the manufacturer that facilitated comparing one product to the other. Data Extraction: Data was extracted on production, and purification procedures, removal of infectious agents, physical and biochemical properties and issues of safety. Data was extracted only for products available in the US. Data Synthesis: IGIV is prepared using pooled plasma. The purification of IGIV is a complex and multi-step process. There is a reciprocal relationship between the purity of IgG in the product and the recovery rate from the total plasma. It is quite possible that some of the biological mediators of the inflammatory and immune systems may be present in trace amounts. Screening and removal of blood borne pathogens is necessary and there are several different techniques available. The specifics of the administration are often variable and no consistent pattern or protocol has been used. When limited dosages are required IGIV may be administered subcutaneously. The side effects associated with IGIV are usually mild and self-limiting. Conclusion: There are differences in products produced by different manufacturers. The current data does not provide sufficient detail or information to be able to make specific recommendations for the use of a given commercial preparation in a specific disease state. The use of IGIV is associated with certain common and uncommon side effects. The identification of risk factors that might predispose a patient to developing them have been studied and reported. In choosing a IGIV preparation the user may avoid features that may predispose to certain side effects. Equally important is monitoring of patients during and after the IGIV therapy. © 2010 Elsevier B.V. All rights reserved.

Publication Type: Journal: Review

Source: EMBASE

Title: Evidence for the use of intravenous immunoglobulins - A review of the literature

Citation: Clinical Reviews in Allergy and Immunology, April 2010, vol./is. 38/2-3(201-269), 1080-0549 (April 2010)

Author(s): Kivity S., Katz U., Daniel N., Nussinovitch U., Papageorgiou N., Shoenfeld Y.

Language: English

Abstract: Intravenous immunoglobulins (IVIg) were first introduced in the middle of the twentieth century for the treatment of primary immunodeficiencies. In 1981, Paul Imbach noticed an improvement of immune-mediated thrombocytopenia, in patients receiving IVIg for immunodeficiencies. This opened a new era for the treatment of autoimmune conditions with IVIg. Since then, IVIg has become an important treatment option in a wide spectrum of diseases, including autoimmune and acute inflammatory conditions, most of them off-label (not included in the US Food and Drug Administration recommendation). A panel of immunologists and internists with experience in IVIg therapy reviewed the medical literature for published data concerning treatment with IVIg. The quality of evidence was assessed, and a summary of the available relevant literature in each disease was given. To our knowledge, this is the first all-inclusive comprehensive review, developed to assist the clinician when considering the use of IVIg in autoimmune diseases, immune deficiencies, and other conditions. © Humana Press Inc. 2009.

Publication Type: Journal: Review

Source: EMBASE

Full Text:
Available from *Springer Link Journals* in Clinical Reviews in Allergy and Immunology
Available from *ProQuest* in Clinical Reviews in Allergy and Immunology

---

Title: The Use of Immunoglobulin Therapy for Patients With Primary Immune Deficiency: An Evidence-Based Practice Guideline

Citation: Transfusion Medicine Reviews, January 2010, vol./is. 24/SUPPL. 1(S28-S50), 0887-7963 (January 2010)

Author(s): Shehata N., Palda V., Bowen T., Haddad E., Issekutz T.B., Mazer B., Schellenberg R., Warrington R., Easton D., Anderson D., Hume H.

Language: English

Abstract: The standard treatment for patients with primary antibody deficiency is immunoglobulin (IG), but the care of these patients is complex. These guidelines, initiated by the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products, have been developed to facilitate and standardize the care of these patients by the various physician specialties that are responsible for their care. A panel of national expert immunologists and methodologists developed salient clinical questions; and a systematic, expert, and bibliography literature search up to July 2008 was conducted. One thousand eighty-seven citations were retrieved, and 102 reports were used in the preparation of this guideline. The recommendations provide guidance (1) on the complexity of the treatment of these patients; (2) the established benefits of IG on morbidity and mortality; (3) dosage, routes of administration, and management of reactions; (4) the various IG formulations available; (5) vaccination of these patients; and (6) research priorities. © 2010 Elsevier Inc. All rights reserved.

Publication Type: Journal: Article

Source: EMBASE

Title: Relevant criteria for selecting an intravenous immunoglobulin preparation for clinical use

Citation: BioDrugs, 2010, vol./is. 24/4(211-223), 1173-8804;1179-190X (2010)

Author(s): Cherin P., Cabane J.

Language: English

Abstract: Over the past several decades, the use of intravenous human normal immunoglobulin (IVIg) products in a diverse range of immunodeficiency, inflammatory and infectious disorders has increased significantly. Newer manufacturing processes have increased the yield of intact IVIg molecules and have also improved the tolerability and safety of these products, including reducing the transmission risk of blood-borne diseases. While there are no appreciable differences between the numerous commercially available IVIg products in terms of efficacy, different manufacturing processes and the final composition of IVIg products have resulted in different safety and tolerability profiles. The tolerability profile of different IVIg products may be idiosyncratic for individual patients and may not be predictable, based on product characteristics. Consequently, patients receiving an IVIg product should be carefully monitored at initial exposure, and switching of products should be avoided. To achieve the best outcomes in patients requiring IVIg therapy, treatment should be tailored to the patients needs. The riskbenefit profile of an IVIg in relation to patient risk factors and the underlying immune deficiency, or autoimmune or inflammatory disorder should be considered when deciding on the most appropriate therapy. © 2010 Adis Data Information BV. All rights reserved.

Publication Type: Journal: Review

Source: EMBASE

Full Text:
Available from *ProQuest* in BioDrugs

Title: Intravenous immunoglobulins-understanding properties and mechanisms

Citation: Clinical and Experimental Immunology, December 2009, vol./is. 158/SUPPL. 1(2-13), 0009-9104;1365-2249 (December 2009)

Author(s): Durandy A., Kaveri S.V., Kuijpers T.W., Basta M., Miescher S., Ravetch J.V., Rieben R.

Language: English

Abstract: High-dose intravenous immunoglobulin (IVIg) preparations are used currently for the treatment of autoimmune or inflammatory diseases. Despite numerous studies demonstrating efficacy, the precise mode of action of IVIg remains unclear. Paradoxically, IgG can exert both pro- and anti-inflammatory activities, depending on its concentration. The proinflammatory activity of low-dose IVIg requires complement activation or binding of the Fc fragment of IgG to IgG-specific receptors (FcgammaR) on innate immune effector cells. In contrast, when administered in high concentrations, IVIg has anti-inflammatory properties. How this anti-inflammatory effect is mediated has not yet been elucidated fully, and several mutually non-exclusive mechanisms have been proposed. This paper represents the proceedings of a session entitled 'IVIg - Understanding properties and mechanisms' at the 6th International Immunoglobulin Symposium that was held in

Interlaken on 26-28 March 2009. The presentations addressed how IgG may affect the cellular compartment, evidence for IVIg-mediated scavenging of complement fragments, the role of the dimeric fraction of IVIg, the anti-inflammatory properties of the minor fraction of sialylated IgG molecules, and the genetic organization and variation in FcgammaRs. These findings demonstrate the considerable progress that has been made in understanding the mechanisms of action of IVIgs, and may influence future perspectives in the field of Ig therapy. © 2009 British Society for Immunology.

Publication Type: Journal: Review

Source: EMBASE

Full Text:
Available from *John Wiley and Sons* in Clinical and Experimental Immunology
Available from *Wiley-Blackwell Free Backfiles NHS* in Clinical and Experimental Immunology
Available from *John Wiley and Sons* in Clinical and Experimental Immunology
Available from *Ingenta* in Clinical and Experimental Immunology
Available from *National Library of Medicine* in Clinical and Experimental Immunology
Available from *John Wiley and Sons* in Clinical and Experimental Immunology

---

Title: Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders

Citation: Annals of Pharmacotherapy, May 2007, vol./is. 41/5(812-823), 1060-0280 (May 2007)

Author(s): Gurcan H.M., Ahmed A.R.

Language: English

Abstract: OBJECTIVE: TO determine the efficacy of various intravenous immunoglobulin (IVIG) protocols used in the treatment of autoimmune and chronic inflammatory disorders. DATA SOURCES: Literature retrieval was accessed through MEDLINE (November 1984-March 2007) and a search was conducted using the term intravenous immunoglobulin. References cited in the selected articles were also reviewed. STUDY SELECTION AND DATA EXTRACTION: Inclusion criteria for studies were (1) English language, (2) randomized controlled trials, (3) defined protocols, (4) a minimum of 15 patients, and (5) objective criteria provided to assess clinical outcomes and course. DATA SYNTHESIS: The therapeutic efficacy of IVIG therapy is well established, and defined protocols exist for treatment of Kawasaki disease, immune thrombocytopenic purpura, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and autoimmune mucocutaneous blistering diseases. In the absence of a defined protocol, studies have demonstrated that IVIG therapy is effective in the treatment of myasthenia gravis, dermatomyositis, stiff person syndrome, antineutrophil cytoplasmic antibody positive systemic vasculitides, Graves' ophthalmopathy, and certain forms of systemic lupus erythematosus. It might also be of benefit in some patients with relapsing-remitting multiple sclerosis. The outcomes are variable in these studies. In toxic epidermal necrolysis and Stevens-Johnson syndrome, use of IVIG has dramatically influenced clinical response and reduced mortality. CONCLUSIONS: The cumulative evidence suggests that the clinical outcomes observed are significantly influenced by the use of a defined protocol. There is a need for multicenter trials approved by the Food and Drug Administration to better define the role of IVIG in many disease states. Such studies would be able to establish the indications for use, optimal dose, frequency of infusions, duration of therapy, and need for gradual

withdrawal versus sudden cessation. Defined protocols resulting from the study of a large cohort of patients often convince insurance companies to create policies that provide access to IVIG therapy.

Publication Type: Journal: Article

Source: EMBASE

Title: IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life.

Citation: Thrombosis and haemostasis, Apr 2004, vol. 91, no. 4, p. 771-778, 0340-6245 (April 2004)

Author(s): Bussel, James B, Eldor, Amiram, Kelton, John G, Varon, David, Brenner, Benjamin, Gillis, Shmuel, Angiolillo, Anne, Kulkarni, Roshni, Abshire, Thomas C, Kelleher, Jack, IGIV-C in ITP Study Group

Abstract: The general safety and efficacy of intravenous immunoglobulin (IGIV) as treatment for idiopathic thrombocytopenic purpura (ITP) has been well-studied. The current study compares the safety and efficacy of a novel IGIV (IGIV-C; Gamunex, 10%) with a licensed solvent/detergent-treated product (IGIV-S/D; GamimuneN, 10%) in treatment of ITP. Ninety-seven pediatric and adult patients with acute and chronic ITP were treated in a multi-center, prospective, randomized, double-blind parallel group, non-inferiority trial at 26 international sites. Baseline data (age, duration of ITP, platelet counts, previous treatment) were comparable between groups. Patients were treated with 1 g/kg/day of IGIV-C or IGIV-S/D for 2 days. The primary end-point, proportion of patients whose platelet counts increased from >/=20 x 10(9)/L to >/=50 x 10(9)/L within 7 days after dosing, was achieved by 35/39 (90%) and 35/42 (83%) of patients treated with IGIV-C and IGIV-S/D, respectively. A secondary endpoint, maintaining platelet counts >/=50 x 10(9)/L for >/=7 days, was achieved by 29/39 (74%) of IGIV-C and 25/42 (60%) IGIV-S/D treated patients. Compared with IGIV-S/D, fewer patients treated with IGIV-C received corticosteroids beyond day 7 (p = 0.02). Efficacy was independent of the presence of isoantibodies or blood type, supporting mechanisms of effect different from anti-D treatments. Adverse events were generally mild and occurred with similar frequency in each group. Viral safety monitoring for HIV, HCV, HBV and Parvovirus B19 showed no seroconversions on study. In conclusion, IGIV-C is as safe and efficacious as IGIV-S/D in treatment of ITP.

Source: Medline

Title: Efficacy, tolerability, safety and pharmacokinetics of a nanofiltered intravenous immunoglobulin: Studies in patients with immune thrombocytopenic purpura and primary immunodeficiencies

Citation: Vox Sanguinis, January 2003, vol./is. 84/1(45-53), 0042-9007 (January 2003)

Author(s): Wolf H.H., Davies S.V., Borte M., Caulier M.T., Williams P.E., Bernuth H.V., Egner W., Sklenar I., Adams C., Spath P., Morell A., Andresen I.

Language: English

Abstract: Background and Objectives: A nanofiltration step with the capacity to reduce bloodborne pathogens was introduced into the manufacturing process of intravenous immunoglobulin (IVIG). In order to demonstrate the efficacy, safety and pharmacokinetics of the modified product, we conducted Phase II/III studies comparing the nanofiltered IVIG (IVIG-N) with its parent product, Sandoglobulin, in patients with chronic immune thrombocytopenic purpura (ITP) and primary immunodeficiencies (PID). Materials and Methods: Patients with ITP (n = 27) with platelet counts of < 20 x 10⁹/l were treated with Sandoglobulin or IVIG-N infusions at a dose of 0.4 g/kg body weight on five consecutive days. The primary efficacy end-point was the number of patients with an increase in platelet counts to > 50 x 10⁹/l. Secondary end-points were time to and duration of response, and regression of bleeding. Patients with PID (n = 36) were treated for 6 months with Sandoglobulin or IVIG-N at doses of 0.2-0.8 g/kg, infused at 3- or 4-week intervals. The primary end-point was the number of days absent from school/work. Secondary end-points were hospitalization, use of antibiotics and feeling of well-being. In both studies, tolerability was assessed by recording of adverse events and laboratory determinations. Viral safety was ascertained by serology supplemented with nucleic acid detection methods. Pharmacokinetics were analysed in patients with PID using serum concentration-time data for immunoglobulin G (IgG), and IgG antibodies to hepatitis B surface antigen (anti-HBsAg). Results: In the ITP study, the primary end-point was met by 12/16 patients on IVIG-N and by 10/10 patients on Sandoglobulin (P = 0.123). A shift towards lesser bleeding intensity was seen in both groups. In the PID study, seven of 18 patients on IVIG-N and six of 16 patients on Sandoglobulin missed days at work/school, with monthly mean absences of 0.4 and 0.5 days (P = 0.805). The feeling of well-being was comparable in both groups. In the ITP study, adverse events with a causal relationship to medication were suspected in six patients on IVIG-N and in seven on Sandoglobulin. In the PID study, three patients on IVIG-N and two on Sandoglobulin experienced possible drug-related adverse events. In both studies, serological and polymerase chain reaction (PCR) tests gave evidence for virus safety. Pharmacokinetics showed constant peak and trough serum IgG levels in all patients, indicating almost steady-state conditions for both formulations. The overall half-life (t<inf>1/2</inf>) for total IgG was 33 +/- 17 days in the IVIG-N arm and 25 +/- 16 days in the Sandoglobulin arm; for anti-HBsAg t<inf>1/2</inf>, values were 17 +/- 7 and 17 +/- 9 days, respectively. Conclusions: IVIG-N is efficacious, well tolerated and safe in patients with ITP and PID. Its pharmacokinetic properties were comparable to those of Sandoglobulin.

Publication Type: Journal: Article

Source: EMBASE

Full Text:
Available from *John Wiley and Sons* in Vox Sanguinis
Available from *John Wiley and Sons* in Vox Sanguinis