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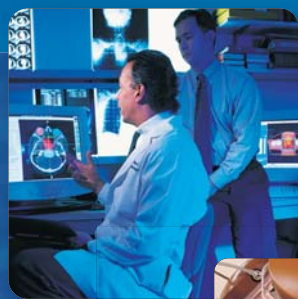
Agence canadienne  
des médicaments et des  
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## T E C H N O L O G Y   O V E R V I E W

**HTA**

Issue 36  
January 2008

Overview of Subcutaneous Versus  
Intravenous Immunoglobulin for  
Primary Immunodeficiencies: Systematic  
Review and Economic Analysis



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**Cite as:** Ho C, Membe S, Cimon K, Roifman C, Kanani A, Morrison A. *Overview of Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Analysis* [Technology overview number 36]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

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ISSN: 1203-9012 (print)  
ISSN: 1481-4501 (online)  
O0466 – January 2008

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**Canadian Agency for Drugs and Technologies in Health**

**Overview of Subcutaneous Versus Intravenous  
Immunoglobulin for Primary Immunodeficiencies:  
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January 2008

We thank Suzanne Morphet for her assistance in creating this overview from a longer report authored by Ho *et al.*

This overview is based on the Technology Report by CADTH: Ho C, Membe S, Cimon K, Roifman C, Kanani A, Morrison A. *Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Analysis*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008. Technology Report number 98.

## Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Evaluation

### Technology and Condition

Subcutaneous immunoglobulin (SCIg) and intravenous immunoglobulin (IVIg) for treatment of primary immunodeficiencies (PIDs).

### Issue

The use of IVIg for PIDs is well-established. SCiG is now available in Canada and offers potential advantages, such as home-based administration. Informed public policy requires an assessment of the clinical and cost-effectiveness of SCiG, relative to IViG.

### Methods and Results

A systematic clinical review identified one randomized controlled trial (RCT) and eight comparative observational studies comparing IViG and SCiG. A meta-analysis could not be conducted because of clinical heterogeneity between studies. The clinical evidence suggests similarities between SCiG and IViG in terms of most outcome measures, except quality of life (QoL), which was higher among SCiG patients. Cost-minimization and cost-utility analyses were performed to compare self-administered SCiG, hospital-based IViG, and hypothetical home-based IViG. Hospital-based IViG was associated with fewer quality-adjusted life-years (QALYs) than home-based IViG or SCiG (0.648 versus 0.659 and 0.675 respectively) and higher associated costs (C\$21,273 versus C\$19,433 and C\$20,065).

### Implications for Decision Making

- **Home-based options require less investment.** A switch from hospital IViG to SCiG or home IViG would save C\$700 to \$1000 per person yearly, given certain assumptions.
- **Home IViG is the least costly.** Home IViG yields the larger net gain from the avoidance of hospital and treatment or diagnostic charges. Compared to home IViG, SCiG is attractive, if decision makers are willing to pay C\$39,500 for a QALY. Information about the magnitude of initial investment, including training costs and comparative effectiveness, is needed to validate this.
- **Uncertainty remains regarding SCiG.** The comparison between IViG and SCiG is based on limited clinical and economic information. SCiG may be considered as a reasonable alternative for patients with contraindications to IViG and poor venous access. The widespread adoption of SCiG may be imprudent, until more information becomes available.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Ho C, Membe S, Cimon K, Roifman C, Kanani A, Morrison A. *Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Evaluation*

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# 1 Introduction

Primary immunodeficiencies (PIDs) refer to disorders that may occur when a person's immune system is functioning improperly. Instead of producing immunoglobulins (Igs) in the form of antibodies that neutralize and destroy harmful invaders, the immune system responds poorly or not at all, predisposing a person to repeated infections.

PIDs are characterized by low or undetectable levels of all five classes of Igs (IgG, IgM, IgA, IgD, and IgE). Some PIDs are congenital, while others manifest later in life. PIDs can be inherited. Agammaglobulinemia, for example, mainly affects males because it is an X-linked recessive trait. Inherited PIDs are classified by mode of inheritance and by whether the genetic defect affects T-cells, B-cells, or both. T-cells provide cellular immunity and protect against viral and fungal infections, while B-cells provide humoral immunity for protection against bacterial infections such as meningitis. Humoral immunodeficiencies are the largest group of PIDs and are relatively common. Isolated IgA deficiency, the most prevalent, becomes clinically evident at young adulthood and affects approximately one in 600 individuals in North America and Europe.

Since the introduction of Ig replacement therapy, patients who might have died during childhood because of a congenital PID now lead relatively healthy lives.<sup>1</sup> Ig replacement therapy reduces the frequency and severity of infections. It can be administered intravenously or subcutaneously.<sup>2</sup> In Canada, the intravenous (IV) route is most common, whereas in some European centres, the subcutaneous (SC) route dominates.<sup>3-5</sup>

A review<sup>3</sup> found that intravenous immunoglobulin (IVIg) is used for 90 indications in Canada, but it has been approved for only six: primary immunodeficiency, hypogammaglobulinemia, idiopathic thrombocytopenia purpura, pediatric human immunodeficiency virus, bone marrow transplantation, and B-cell chronic lymphocytic leukemia.<sup>6</sup> Because most IV infusions are done in hospitals or clinics, the cost is high.

IVIg is generally well tolerated and considered to be safe,<sup>1,6</sup> although adverse events (AEs) range from mild fever and rash to rare episodes of severe anaphylaxis.<sup>7</sup> Products vary in their potential to cause AEs, depending partly on infusion rates and concentrations.<sup>8</sup> Outcomes can also be patient-specific. Some patients need indwelling central venous devices, which increase the risk of infection and complications.<sup>8,9</sup>

In contrast, subcutaneous immunoglobulin (SCIg) has several advantages: smaller doses given more often may better sustain Ig serum levels and decrease AEs; vascular access is unnecessary; and patients have more autonomy because they self-administer the Ig. Infusion takes between one and four hours. During this time, patients are mobile and can perform ordinary daily activities.<sup>10</sup> The disadvantages of SCIg include the need for frequent dosing, the slow response in serum Ig levels, the requirement for patients to be reliable, and necessity for patient education. Typically, patients or their parents complete between four and six training sessions at a hospital before they are ready to do self-infusion at home. SCIg is contraindicated for patients who tend to bleed or who have widespread skin problems.<sup>11</sup>

The method of preparing Ig products was developed over 50 years ago.<sup>12,13</sup> Using the classic Cohn cold alcohol fractionation process, plasma is collected from many donors and pooled to yield a fractionated serum of 95% to 99% IgG with traces of IgA, IgM, IgD, and IgE.<sup>18</sup> Manufacturers use a

variety of methods, starting with donor screening, to ensure that the final product is free of bacterial and viral contamination.<sup>8</sup>

IVIg costs between C\$51 and \$64 per gram. For an adult weighing 70kg, an infusion of 1 g/kg would cost approximately C\$4,000,<sup>14</sup> or C\$2,000 for a 500 mg/kg dose. The use of IVIg in Canada grew by approximately 115% between 1998 and 2005-2006, from 47 grams per 1,000 population to 101 grams.<sup>15</sup> The total cost in 2005-2006 was C\$196.1 million.<sup>15</sup> In Canada, SCIg is priced on par with IVIg.

<b>Table 1: IgG products licensed for use in Canada</b>						
<b>Product</b>	<b>Manufacturer</b>	<b>Route</b>	<b>Dosage Form</b>	<b>Strength</b>	<b>Dose for PID</b>	<b>Rate of Administration</b>
IGIVnex	Talecris Biotherapeutics; North Carolina, US	IV	Solution	10 g	100 to 600 mg/kg every 3 or 4 weeks	Initial rate 0.01 to 0.02 mL/kg body weight per minute for 30 minutes; may be increased to maximum of 0.14 mL/kg body weight per minute
Gamunex	Talecris Biotherapeutics; North Carolina, US	IV	Solution	10 g	100 to 600 mg/kg every 3 or 4 weeks	Initial rate 0.01 to 0.02 mL/kg body weight per minute for 30 minutes; may be increased to maximum of 0.14 mL/kg body weight per minute
Gammagard S/D	Baxter Corporation; Ontario, Canada	IV	Powder for 5% or 10% solution	0.5 g; 2.5 g; 5 g; 10 g	Monthly doses of $\geq 100$ mg/kg	5% solution: initial rate of 0.5 mL/kg/hour; may be increased to maximum of 4 mL/kg/hour. 10% solution: initial rate of 0.5 mL/kg/hour; may be increased to maximum of 8 mL/kg/hour
Iveegam	Baxter AG; Vienna, Austria	IV	Powder for 5% solution	5 g	Monthly doses of $\geq 200$ mg/kg, up to 500 mg/kg	Initial rate of 0.01 mL/kg/minute; may be increased to maximum of 0.08 mL/kg/hour
Vivaglobin	CSL Behring; Ontario, Canada	SC	Solution	160 mg	Weekly doses of 100 to 200 mg/kg body weight	Total volume of 15 mL per injection site at 20 mL/hour per site; infusion into multiple sites at least 2 inches apart when dose exceeds 15 mL

IgG=immunoglobulin type G; IV=intravenous; PID=primary immunodeficiency; SC=subcutaneous.

## 2 Objectives

The objectives are to compare the clinical and cost-effectiveness of SCIg with IVIg, and to determine the impact of Ig therapy for patients with PIDs on provincial health care budgets.

## 3 Methods

Using the Ovid interface, we searched the following databases for controlled trials, systematic reviews, and economic studies in English: MedLine (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), BIOSIS Previews (1985-1989 and 1989 to present), CINAHL (1982 to present). We ran parallel searches on the Health Economic Evaluations Database (HEED) and The Cochrane Library. Supplemental searches aimed to find:

- economic comparisons between IVIg or SCIg and other drugs
- other conditions that depend on the chronic use of Ig
- guidelines on the delivery of Igs for PID patients.

We found grey literature by searching the World Wide Web and by reviewing the web sites of health technology assessment and related agencies, professional associations, and specialized databases. This was supplemented by hand searching the bibliographies of key papers and abstracts from conference proceedings, and by contacting experts, including the manufacturers of Ig products.

Two reviewers independently screened studies; first by title and abstract, then by full text if they were deemed to be relevant. Clinical studies were included if they were randomized controlled trials (RCTs) or comparative observational studies (prospective or retrospective) on adults or children with PIDs, and compared SCIg with IVIg. Primary outcomes needed to include the number and severity of infections, while secondary outcomes included serum IgG levels, AEs, and days lost from work or school.

Full and partial economic studies were included if they compared SCIg with IVIg in adults or children with PIDs and reported outcomes, including the costs associated with quality-adjusted life-years (QALYs), life-years saved, and health care resources used. Disagreement between reviewers was resolved by discussion until consensus was reached.

Two reviewers (two for clinical studies and two for economic studies) independently extracted outcome data. For clinical studies, extracted information included details on the trial, publication, patients, intervention, outcomes related to clinical benefit, and outcomes related to harm. For economic studies, extracted data included publication characteristics, type of evaluation, and results from base-case analysis and sensitivity analyses. Reviewers compared data and resolved any disagreements by discussion.

To assess the quality of included clinical studies, we modified the Hailey<sup>16</sup> and Jadad<sup>17</sup> assessment scales to produce a scale from one to 15 that assessed randomization, blinding, and withdrawals. Poor quality studies scored between one and five, and high quality studies scored between 11.5 and 15.

## 4 Results

### *Clinical Review*

We included nine clinical reports with a total of more than 500 patients. One was an RCT,<sup>18</sup> six were prospective studies,<sup>19-24</sup> one was a retrospective study,<sup>25</sup> and one was a survey.<sup>26</sup> Two studies were conducted in Canada and the US,<sup>22,23</sup> and seven were based in Europe.<sup>18-20,24,25,27,28</sup> Four of the European studies had the same first author.<sup>19-21,25</sup> Industry sponsored six studies.<sup>18-20,22,23,26</sup> Five

studies focused on adult patients,<sup>18,21,22,25,26</sup> while four included adults and children.<sup>19,20,23,24</sup> One study was of high quality.<sup>19</sup> The rest ranged from poor to good.

Outcome data from the nine studies were grouped into eight categories. Three studies compared the number of patients with infections<sup>18,24,26</sup> and two of those reported the severity of infections. The RCT<sup>18</sup> reported no significant differences in number or severity between IVIg and SCIg patients. Pac *et al*<sup>24</sup> reported 34 respiratory tract infections during 12 months of IVIg therapy, including 10 serious ones. By comparison, there were 17 respiratory tract infections in 12 months of SCIg therapy, two of which were serious. The third study reporting on the number of infections<sup>26</sup> found a statistically significant reduction in the number of infections after patients switched from six months of IVIg therapy to six months of SCIg therapy ( $p = 0.021$ ).

Three studies compared length of infections. One<sup>18</sup> found no difference between patients receiving IVIg and those on SCIg. The other two reported shorter hospital stays with SCIg<sup>21</sup> or less total time on antibiotic therapy with SCIg.<sup>24</sup> All four studies that compared serum trough levels of Ig found them to be higher in patients on SCIg treatment.<sup>18,19,21,24</sup> One study reported on statistical significance and found the difference between therapies to be statistically significant (i.e.,  $p < 0.001$  for children and adults).<sup>19</sup> One study<sup>18</sup> compared the number of days lost from work or school and found them to be the same (12 days) for each treatment. Four studies compared the rates of AEs between IVIg and SCIg treatments, but no statistically significant differences were reported.<sup>18,21,24,25</sup> Three studies<sup>18,21,25</sup> reported a higher rate of systemic AEs with IVIg, and one reported no difference.<sup>24</sup> Results were inconclusive for infusion reaction between treatments. One trial reported on withdrawals due to AEs.<sup>18</sup> Not one of the nine patients on IVIg therapy withdrew, but three of 13 patients on SCIg therapy did. The statistical significance was not reported. Three trials compared the quality of life (QoL) between patients on IVIg and SCIg. Different scales and questionnaires were used to measure QoL, but the results were similar. One<sup>26</sup> found patients on SCIg were more satisfied than those on IVIg ( $p < 0.001$ ). Another<sup>22</sup> found that most patients preferred SC over IV therapy, or home therapy over hospital therapy, regardless of whether it was IV or SC. The third study found that children and adults who previously received IVIg in hospitals reported better health-related QoL after switching to SCIg ( $p < 0.05$ ).

## **Economic Review**

For economic studies, we included two cost analyses<sup>25,29</sup> and two cost-minimization analyses (CMAs)<sup>30,31</sup> from the perspective of the health care systems in Sweden, Germany, UK, and France. Three studies involved children and adults.<sup>25,30,31</sup> The fourth did not specify the study population. The results indicated that self-administered SCIg is cost-saving compared with hospital-based IVIg. All four studies assumed that IVIg and SCIg were equally safe and effective. Because this could not be derived from any of the reviewed studies, questions can be raised about the validity of the findings.

# **5 Economic Evaluation**

## **Methods**

A review of the literature and interviews with clinical experts identified cost items that are relevant to the Canadian public health care payer, including Ig costs, treatment or diagnostic charges by nurses or physicians, hospital charges, costs of infusion pumps, and costs of infusion materials. It was not possible to combine the clinical data statistically or perform any meta-analyses because of

insufficient data and variations in the reporting of outcomes. As a result, we performed an economic analysis with two scenarios, based on different assumptions about the effectiveness of Ig therapy.

- Scenario A was a CMA, assuming that SCIg is as effective as IVIg.
- Scenario B was a cost-utility analysis (CUA) accounting for differences in effectiveness [i.e., number and severity of infections or severe adverse events (SAEs)].

A budget impact analysis (BIA) was performed from the public health care payer's perspective. Where sufficient cost data and effectiveness estimates for children were obtained, we performed separate analyses for them.

## **Assumptions**

Our baseline assumption was that PID patients are at equal levels of risk and irrespective of their specific disease complications, have three alternatives for receiving Ig:

- IVIg in hospital
- IVIg at home
- SCIg at home.

Because SCIg has just been introduced in Canada, the short- or medium-term costs associated with the training and monitoring of patients receiving home-based interventions are not known with certainty. Therefore, we assumed zero costs due to the initial learning process and production distribution for patients receiving self-administered SCIg and home-based IVIg.

## **Results**

### **a) Scenario A: Cost-minimization Analysis**

The base case results from the CMA show that for each treatment arm and patient subgroup, therapy prices account for more than 85% of the total cost of therapy. For child and adult patients, the respective incremental cost of SCIg and home IVIg when compared to hospital IVIg is about C\$1,400 and about C\$1,900 per patient per year when only direct costs are considered. When indirect costs are included, the respective incremental cost is about C\$2,000 and C\$2,700.

The results of a sensitivity analysis show that for adults and children, the yearly incremental cost differences between SCIg and hospital-based IVIg are more responsive to hospital charges, treatment costs, infusion pumps, and infusion materials. Overall, the cost differences are not driven by the per gram price of IVIg and SCIg, because they are assumed to be within the same range.

### **b) Scenario B: Simple Cost-utility Model**

Base case results show that SCIg is the most cost-effective intervention when compared to home-based IVIg, with an incremental cost-effectiveness ratio (ICER) of C\$39,500/quality-adjusted life year (QALY), based on a threshold ICER of C\$50,000/QALY. SCIg produces more QALYs (0.675 versus 0.659 home-based IVIg, and 0.648 hospital-based IVIg). Hospital-based IVIg is more costly (C\$21,273 versus C\$20,065 SCIg, and C\$19,433 home-based IVIg). The ICER between SCIg and hospital-based IVIg suggests that the latter is not cost-effective (i.e., dominated).

One-way sensitivity analyses were performed to examine the effects of variation in the three key parameters (i.e., utility of infection, utility of hospital recovery due to infection, and hospital and physician or nurse costs). The results were responsive to changes in utility of infection (in numbers and severity of infections) and utility of hospital recovery. SCIg therapy dominated hospital-based

IVIg even when hospital charges, and physician and nurse costs for hospital IVIg were lowered by 50%.

We performed a threshold analysis to determine the extent to which the per patient total cost of SCIg and disutility of the number and severity of infections have to increase for SCIg to be non-cost-effective. The results show that a 7% increase in the per gram price of SCIg (plus additional yearly fixed costs such as those for infusion pumps, materials, and monitoring) results in SCIg being non-cost-effective, based on a threshold ICER of C\$50,000/QALY. A similar effect was observed from an increase of disutility of number and severity of infections from 0.46 to 0.32.

### ***Budget Impact***

The results of the budget impact analysis show that the Canadian health care system would save C\$9 million a year if 75% of PID patients switch from hospital-based IVIg to SCIg. This translates to an average saving of approximately C\$700 per patient, assuming a PID prevalence rate of 0.0004. The health care system would save more (approximately C\$13 million or C\$1,000 per patient) if 75% of patients switch from hospital-based IVIg to home-based IVIg.

## **6 Health System Implications**

Before decision makers act on any findings from this report, the cost-effectiveness position of home-based IVIg needs further investigation. Home-based IVIg is potentially cost-saving, because it yields the larger net gain from the avoidance of hospital and treatment or diagnostic charges. A better understanding of PIDs in Canada is also needed regarding its prevalence and the population of patients who are suitable for home-based IVIg. Furthermore, if switching patients to home-based IVIg is to be considered, it is imperative to know the magnitude of the initial investment needed to make the switch.

Compared with hospital-based IVIg, SCIg is the more cost-saving. With some uncertainty, it seems to be cost-effective based on a willingness-to-pay threshold of C\$50,000/QALY. Therefore, it could be gradually established as an alternative for patients who are willing to adopt the therapy and are clinically suitable.

### ***Limitations***

Our study is limited by several factors. The clinical data were insufficient and inconclusive. High quality, well-designed studies with randomization, larger patient populations, better patient selection, and the reporting of primary and secondary outcomes are needed.

Our economic analyses should be interpreted cautiously because they are limited by three factors. First, little is known about the use of health care resources in SCIg therapy because it is new to the Canadian health care system. For example, SCIg can be administered using a scalp-vein needle and syringe directly. This technique obviates the need for expensive infusion pumps and kits, and reduces the time lost because of treatment. This technique was not studied in our model because we did not identify a scientific study that focused on it.

Second, although the CMA shows that home IVIg is the least expensive Ig route, more investigation is needed. We assumed that patients have equal levels of Ig and can receive Ig by either route. Some

patients, however, may be unsuitable for home-based IVIg. Also, our calculations underestimated the costs of home-based IVIg, because we did not take into account the initial investment (training costs, product distribution, and storage costs) needed to switch from hospital- to home-based IVIg. Such uncertainties call for more research on home-based IVIg.

Third, the validity of the CUA results was compromised by the use of uncertain estimates of comparative clinical effectiveness and a lack of key estimates for the construction of a full economic model. Most probability estimates of the paths applied to the cost-utility model were derived through consultation with an expert, whereas some utility estimates were adopted from clinical studies that compared IVIg with no treatment. In addition, the absence of mortality estimates for each treatment required that Ig mortality rates be applied uniformly to each treatment arm. This may have contributed to the small differences that were observed in effectiveness between the treatments.

## 7 Conclusions

Given the current limited clinical evidence, SCIg cannot be considered to be a replacement for IVIg in practice. SCIg may be considered to be a reasonable alternative for patients with contraindications to IVIg or with a preference for home-based treatment. The use of Ig in Canada requires stricter controls, because it is used in more than 80 off-label indications, many with limited evidence of efficacy.

If the clinical evidence for SCIg can be confirmed, however, the economic arguments regarding SCIg are appealing. Compared with hospital-based IVIg, SCIg dominates (greater expected benefits at less expected costs). In comparison with home-based IVIg, it seems to be the most cost-effective intervention, with an ICER of C\$39,500/QALY, which is deemed to be cost-effective if it is based on a willingness-to-pay threshold of C\$50,000/QALY. There is uncertainty about the cost and comparative clinical effectiveness of SCIg. The cost-effectiveness position of SCIg is likely to change with the availability of:

- Canadian prices for infusion pumps and kits
- information about a less expensive method of administering SCIg
- reliable comparative estimates of mortality rates among interventions
- reliable comparative utility estimates for infections.

Until a reliable, comparative clinical and cost-effectiveness study can be undertaken, the challenge for Canadian decision makers may be to gradually establish SCIg as an alternative for patients who are willing and clinically suitable to switch to it.

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