

Letter to the Editor

Pharmacoeconomic advantages of subcutaneous versus intravenous immunoglobulin treatment in a Canadian pediatric center

To the Editor:

Although the data in the literature indicate that both subcutaneous (SC) and intravenous (IV) routes of administration of immunoglobulin (SC-Ig and IV-Ig) therapy are considered equivalent in terms of efficacy for patients with primary immunodeficiency,¹⁻³ the question of the cost effect of this treatment remains an important economics question. Some pharmacoeconomic studies that compared SC-Ig with IV-Ig therapy have been performed in various countries,⁴⁻⁶ but their conclusions were not unequivocal, and, as reviewed by Membe et al,⁷ those studies could not be transposed to the Canadian or US health system.

In 2007, when the Quebec government approved the use of SC-Ig, we offered our patients the choice between hospital-based IV-Ig and home-based SC-Ig, administered at equivalent doses. Most patients decided to switch to SC-Ig, allowing us to perform a retrospective pharmacoeconomic cohort study of 25 patients, in which we calculated expenditures for IV-Ig and then SC-Ig therapy over 2 consecutive years in the same cohort. Patients were eligible if they had been diagnosed with a primary immunodeficiency⁸ and received at least 1 year of uninterrupted IV-Ig before at least 1 year of uninterrupted SC-Ig. Because the literature clearly reported that both routes of administration were equivalent in terms of efficacy and safety,¹⁻³ a cost-minimization analysis was applied. Methods and allocation of unit costs for resource valuation from various sources are shown in Table E1 (see this article's Online Repository at www.jacionline.org) and patient characteristics in Table E2 (see this article's Online Repository at www.jacionline.org).

As shown in Table I, the time spent by parents in taking care of their children's treatment was significantly greater for IV-Ig than for SC-Ig. In addition, estimated time spent by nurses, technicians, and administrative assistants was higher for patients treated with IV-Ig. We found that the cost of medical resources and the cost of nonmedical resources were both significantly lower when patients were treated with SC-Ig ($P < .001$ and $P < .001$, respectively; Table II). In addition, the total cost (medical plus nonmedical costs) associated with SC-Ig was significantly lower than that associated with IV-Ig ($\$6,488 \pm \$4,571$ vs $\$10,761 \pm \$7,874$ per patient per year; $P < .001$, respectively; Table II). In this calculation, the cost of immunoglobulins was not taken into consideration, although they were quite similar for the different groups. Indeed, in Quebec (and in the rest of Canada), there is parity in the price per gram of SC-Ig and IV-Ig. The cost of immunoglobulins by itself accounted for about 48% and 66% of the total cost of IV-Ig and SC-Ig therapy, respectively. Interestingly, the total expenditures, which include the cost of immunoglobulins, were still significantly higher for the IV-Ig than for the SC-Ig route ($\$23,845 \pm \$13,245$ vs $\$19,044 \pm \$9,476$ per patient per year; $P < .001$, respectively) despite this high proportion of cost for immunoglobulins.

With respect to certain purchases such as pumps and infusion material that were covered by the hospital for IV-Ig and by the patients for SC-Ig, we adjusted our calculations for both a patient/parent perspective and a government/hospital one and found, as shown in Table II, that, all in all, the SC route remained less costly

than the IV route from either the patient perspective ($P < .001$) or the government perspective ($P < .001$).

We then performed a secondary analysis (sensitivity analysis) in which we considered only the loss of productivity for parents (ie, the number of hours parents declared to have spent away from their work to take care of their child), whereas for nurses we considered an estimated time that was based on an increased caseload of 5 patients per nurse instead of 2. On this basis, the total cost (medical plus nonmedical costs) was still significantly lower, as shown in Table E3 (see the Online Repository at www.jacionline.org), for SC-Ig compared with IV-Ig without or with including the cost of immunoglobulins ($P < .001$ and $P = .03$, respectively), thereby indicating that even considering this worst-case scenario (secondary analysis), the cost of SC-Ig therapy was significantly lower than that of IV-Ig therapy.

From a patients perspective with the use of this secondary analysis as described, costs for patients were still less for SC-Ig than for IV-Ig, although statistical significance was not reached ($P = .23$), whereas from a government perspective, costs were still significantly less for SC-Ig than for IV-Ig ($P < .001$), even if the cost of immunoglobulins was taken into account ($P = .03$; see Table E3 in this article's Online Repository at www.jacionline.org).

Interestingly, for the true cost of medications and medical consultations, no significant difference was observed between the 2 treatment groups (Table II). Expenditures related to the use of physicians were higher, although not statistically significant, for IV-Ig compared with SC-Ig, probably because patients treated with IV-Ig were charged for each monthly visit as opposed to every 4 to 6 months for those receiving SC-Ig. Costs for medications, which essentially comprised antibiotics, were similar for the 2 groups (Table II), suggesting that switching from IV-Ig to SC-Ig did not result in a higher number of infections. Moreover, the number of hospitalizations was similar for the 2 groups (data not shown).

This retrospective study was performed within a single university-based hospital, which is less desirable than a prospective case-control study. However, by using each case as its own control provided considerable advantages, such as limiting selection bias, thereby making the 2 groups most comparable and also by eliminating inter-individual variability. Notwithstanding the small study sample size ($n = 25$), we found a statistically significant decrease, even in the secondary analysis, in both medical and nonmedical costs associated with switching from a hospital-based IV-Ig regime to that of a home-based SC-Ig regime. Furthermore, the results were consistent across the different payer perspectives whether it was the patient, the hospital, or the government. This is one of the first studies to address and encompass all of these various aspects. Another strong point is that most of our information was gathered from official, exhaustive, and computerized government sources, which minimized the need for cost estimates. Moreover, unlike other pharmacoeconomic studies,⁴⁻⁶ we observed that the cost differential was not related to any difference in the price of immunoglobulins, and, even when the price of immunoglobulins was not taken into account, the cost associated with SC-Ig treatment was significantly lower, suggesting that the observed differences were related to the other pharmacoeconomic factors.

TABLE I. Assessment of time per year and per patient spent by parents and care providers according to treatment

	IV, mean $\pm$ SD	SC, mean $\pm$ SD	SC-Ig minus IV-Ig, mean (95% CI)	P value (signed rank test)
Time (h) spent by parents (treatment supervision and administration and time spent in hospital visits)	160 $\pm$ 105	78 $\pm$ 40	-82 (-123 to -40)	<.001
Nurse (h)	60	7.5	-52.5	
Technician (h)	3	1	-2	
Administrative assistant (h)	3	1 1/3	-1 2/3	

TABLE II. Medical and nonmedical resource use and costs over the first year by dollars per patient

	IV, mean $\pm$ SD	SC, mean $\pm$ SD	SC-Ig minus IV-Ig, mean (95% CI)	P value (signed rank test)
Nonmedical resources				
(1) Travel expenses				
Transports (taxi, bus, metro, own car)	773 $\pm$ 921	193 $\pm$ 230	-580 (-865 to -295)	
Hotel	182 $\pm$ 476	46 $\pm$ 119	-137 (-284 to 11)	
Parking	63 $\pm$ 73	16 $\pm$ 18	-48 (-70 to -25)	
Total	1,019 $\pm$ 1,222	255 $\pm$ 305	-764 (-1,142 to -386)	<.001
(2) Time spent by parents (treatment supervision and administration and time-spent in hospital visits)	3,687 $\pm$ 2,430	1,807 $\pm$ 935	-1,880 (-2,840 to -920)	<.001
(3) Other resources (Emla cream)	<1	69 $\pm$ 126	69 (17 to 121)	.03
Total nonmedical resources (1) + (2) + (3)	4,706 $\pm$ 3,109	2,131 $\pm$ 976	-2,575 (-3,773 to -1,378)	<.001
Medical resources				
(4) Nurse, technician, administration (SJH)	1,867	273	-1,594	
(5) Pump, infusion materials	136	780	644	
(6) Medical services (consultations)	2,685 $\pm$ 5,508	1,918 $\pm$ 2,882	-767 (-2,853 to 1,318)	.14
(7) Pharmaceuticals	1,367 $\pm$ 3,630	1,387 $\pm$ 3,164	20 (-1,024 to 1,063)	.81
Total medical resources (4) + (5) + (6) + (7)	6,055 $\pm$ 6,197	4,358 $\pm$ 4,495	-1,698 (-3,242 to -153)	<.001
Total medical and nonmedical resources	10,761 $\pm$ 7,874	6,488 $\pm$ 4,571	-4,273 (-6,215 to -2,331)	<.001
Immunoglobulins	13,084 $\pm$ 9,225	12,556 $\pm$ 8,046	-528 (-1,716 to 660)	.36
Total medical and nonmedical resources + immunoglobulins	23,845 $\pm$ 13,245	19,044 $\pm$ 9,476	-4,801 (-7,419 to -2,183)	<.001
Cost according to perspective				
Patient perspective (1) + (2) + (3) + (5) (only for SC)	4,706 $\pm$ 3,109	2,911 $\pm$ 977	-1,795 (-2,993 to -598)	.05*
Government perspective (4) + (5) (only for IV) + (6) + (7)	6,055 $\pm$ 6,197	3,578 $\pm$ 4,495	-2,478 (-4,022 to -933)	.003

SJH, Ste-Justine Hospital.

*Four patients had to stay overnight in Montreal, and, when these patients were removed, the *P* value from the patient's perspective (SC vs IV) was not significant anymore ($\Delta = -\$345$, *P* = .24). However, the total medical and nonmedical resources without or with immunoglobulins were still significant, *P* = .011 and .021, respectively.

Importantly, none of our patients had any desire to switch back to hospital-based IV-Ig therapy (patients were questioned about this issue at every visit). Studies have found that treatment at home provides patients and their families with a better quality of life as related to several aspects, including treatment independence and convenience, mental health, school and social functioning, and family activities.^{9,10} Thus, once patients switch from IV-Ig to SC-Ig, they are unlikely to switch back; hence, the pharmacoeconomic effect would be for the long term.

Given that both treatment options are equally effective and safe,¹⁻³ the financial arguments for SC-Ig are appealing with greater expected benefits at less cost. This is particularly relevant in Quebec where the study was performed but could easily be applicable to most health care systems in the Western world. In several societies, most medical expenses are covered or reimbursed by the government, whereas in others the same expenses would be handled by private insurance or the individual directly. Our data show that, no matter what the circumstances, there are appreciable economic incentives in favor of home-based SC-Ig treatment.

As stated in our study, the dose of SC-Ig was equivalent to the dose of IV-Ig, as is done in Europe,¹¹ whereas US recommendations lean toward a 37% higher dose of SC-Ig.¹² If the latter dosage had been used, it would have led to a 37% increase in the cost of immunoglobulins for the SC-Ig group, which in our model would have resulted in the matching of total expenditures for both treatments. The savings from other medical and nonmedical expenses, in turn, would still have offset this, as we have shown. This is especially relevant because the price of the product itself, which constitutes the bulk of the cost, is likely to change in the future. The benefits from the patient's perspective would also remain, facilitating their tolerability of the treatment and easing the burden for families, which in terms of macroeconomics and health care policies are still of the outmost importance.

With the current efforts to improve efficiency in health care delivery and resource management, this type of pharmacoeconomic study could become an example of how to realistically transform a costly therapy for a chronic illness into a more economical and patient-oriented alternative, especially considering the lasting monetary effect on the health care system, which should be substantial.

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TABLE E1. Allocation of unit costs for resource valuation

Type of utilization	Mode of evaluation	Unit cost (\$Can)	Sources for unit cost
Medical resources			
Nurse, technician	Estimated time per patient	28.75 per hour*	CHU Ste-Justine
Administrative assistant	Estimated time per patient	19.20 per hour	CHU Ste-Justine
Immunoglobulin product	Real cost, calculated for each patient by reviewing chart	57 per gram of immunoglobulin	Héma-Québec
Dispensing by blood bank	Estimated time	28.75 per hour*	CHU Ste-Justine
Pump	Real cost, 1 per patient	136	CHU Ste-Justine
Infusion materials	Estimated cost	3.94 (Burethrol), 3.49 (infusion tubing), 3.50 (Jelco per unit)	CHU Ste-Justine
Preparation of infusion materials	Estimated time per patient	28.75 per hour*	CHU Ste-Justine
Pharmaceuticals	Real cost, obtained for each patient		Government (RAMQ)
Pediatric consultations	Real cost, obtained for each patient		Government (RAMQ)
Other medical services	Real cost, obtained for each patient		Government (RAMQ)
Nonmedical resources			
Travel by private car	Questionnaire for each patient	0.47 per km†	CAA
Travel by public transport	Questionnaire for each patient	3.00 per trip	STM
Travel by taxis	Questionnaire for each patient	3.30 + 1.70 per km, per trip	Montreal, City Hall
Parking	Questionnaire for each patient	12.00 per day	CHU Ste-Justine
Hotel	Questionnaire for each patient	120.00 per night	CHU Ste-Justine
Loss of productivity‡	Questionnaire for each patient	23.10 per hour	Statistics Canada§

Demographics and clinical data were acquired by a retrospective chart review. Medical direct treatment costs and economic data were captured from a number of sources and through questionnaires specifically developed for the study. The study was approved by the Ethics Committee of Ste-Justine Hospital and the "Commission d'Accès à l'Information du Québec" to obtain authorization for database access and linkage to patient information. All patients signed informed consents before study entry. Information on resource utilization and costs was retrieved from 2 provincial government health care databases: RAMQ (Régime de l'Assurance Maladie du Québec) and Med-Echo. The RAMQ database collects data on outpatient prescription drugs dispensed by community pharmacies (drug identification number, dispensing date, dose, treatment duration, and quantity of drug dispensed), in-patient and out-patient physician visits (date of visit, specialty of the physician, and ICD9 diagnostic code). The Med-Echo database maintained by the Ministry of Health and Social Services of Quebec (MSSS) provides information on all hospital admissions in Quebec (date of admission, length of stay, primary discharge diagnosis). CAA, Canadian Automobile Association; RAMQ, Régie de l'Assurance Maladie du Québec; STM, Société de Transport de Montréal.

*Source: registered nurse (RN), Fédération interprofessionnelle du Québec (FIQ).

†Flat rate of \$0.47 per km (http://www.caa.ca/documents/CAA_Driving_Costs_Brochure_2010.pdf as of July 21, 2010).

‡The costs of lost productivity were estimated by multiplying the amount of lost time reported by the average daily wage for Canadian employees in 2010. The expenditures of assistance from relatives and paid assistance were estimated with the average hourly wage for employees in Canada.

§Average wages (men and women) from Statistics Canada as of July 2010.

TABLE E2. Patient characteristics (n = 25)

	Value
Age at initial diagnosis (y), mean $\pm$ SD [median]	6.5 $\pm$ 4.0 [5]
Age at index date* (y), mean $\pm$ SD [median]	11.7 $\pm$ 4.4 [13]
Sex (male), no. (%)	10 (40)
Weight* (kg), mean $\pm$ SD [median]	35.7 $\pm$ 16.6 [36]
No. of months since start of immunoglobulin therapy, mean $\pm$ SD [median]	42.9 $\pm$ 41.8 [24]

Patients had the following diagnoses: 18, common variable immunodeficiency (CVID); 4, combined immunodeficiency (CID); 1, Di George syndrome; 2, X-linked lymphoproliferative syndrome (XLP) with a CVID-like phenotype.

*Defined as date of switch to SC-Ig therapy.

TABLE E3. Secondary analysis of medical and nonmedical resource costs over the first year, \$CAN per patient

	IV, mean $\pm$ SD	SC, mean $\pm$ SD	SC-Ig minus IV-Ig, mean (95% CI)	P value (signed rank test)
Nonmedical resources				
(1) Travel expenses				
Transports (taxi, bus, metro, own car)	773 $\pm$ 921	193 $\pm$ 230	−580 (−865 to −295)	
Hotel	182 $\pm$ 476	46 $\pm$ 119	−137 (−284 to 11)	
Parking	63 $\pm$ 73	16 $\pm$ 18	−48 (−70 to −25)	
Totals	1,019 $\pm$ 1,222	255 $\pm$ 305	−764 (−1142 to −386)	<.001
(2) Loss of productivity*	1,120 $\pm$ 3,119†	16 $\pm$ 80†	−1204 (−2494 to 87)	.06†
(3) Other resources (Emla cream)	<1	69 $\pm$ 126	69 (17 to 121)	.03
Total nonmedical resources (1) + (2) + (3)	2,239 $\pm$ 3,767†	340 $\pm$ 341†	−1899 (−3388 to −409)†	<.001†
Medical resources				
(4) Nurse, technician, administration‡ (SJH)	832†	95†	−737†	
(5) Pump, infusion materials	136	780	+644	
(6) Medical services (consultations)	2,685 $\pm$ 5,508	1,918 $\pm$ 2,882	−767 (−2853 to 1318)	.14
(7) Pharmaceuticals	1,367 $\pm$ 3,630	1,387 $\pm$ 3,164	20 (−1024 to 1063)	.81
Total medical resources (4) + (5) + (6) + (7)	5,020 $\pm$ 6,197†	4,180 $\pm$ 4,495†	−841 (−2385 to 704)†	.021†
Total medical and nonmedical resources	7,259 $\pm$ 8,242†	4,520 $\pm$ 4,644†	−2739 (−5021 to −458)†	<.001†
Immunoglobulins	13,084 $\pm$ 9,225	12,556 $\pm$ 8,046	−528 (−1716 to 660)	.36
Total medical and nonmedical resources + immunoglobulins	20,343 $\pm$ 13,351†	17,075 $\pm$ 9,164†	−3267 (−6055 to −480)†	.03†
Cost according to perspective				
Patient perspective (1) + (2) + (3) + (5) (only for SC)	2,239 $\pm$ 3,767†	1,120 $\pm$ 341†	−1119 (−2608 to 371)†	.23†
Government perspective (4) + (5) (only for IV) + (6) + (7)	5,020 $\pm$ 6,197†	3,400 $\pm$ 4,495†	−1621 (−3165 to −76)†	<.001†

In this secondary analysis we based the loss of productivity for parents on the number of hours parents declared to have spent away from their work to take care of their child, whereas for nurses we considered an estimated time that was based on an increased caseload of 5 patients per nurse instead of 2, which both decreased the monetary difference between hospital and home-based care.

SJH, Ste-Justine Hospital.

*Loss of productivity per year for parents was evaluated as 52 $\pm$ 135 hours versus 1 $\pm$ 3 hours for IV-Ig and SC-Ig, respectively.

†Numerical differences between this table and Table II.

‡The estimated time spent by nurses per patient per year was 24 hours for IV-Ig (mainly watching over patients) versus 1.5 hours for SC-Ig (mainly in teaching patients how to administer their treatment).