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Clinical and economic outcomes of a "high-touch" clinical management program for intravenous immunoglobulin therapy

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Objective: To compare clinical and economic outcomes of patients who received intravenous immunoglobulin (IVIG) therapies and were managed by a clinical management program vs the outcomes of matched controls using administrative claim data.

Methods: This retrospective cohort study used the PharMetrics Plus™ claim database between September 1, 2011 and June 30, 2014. Patients in the intervention group were from a "high-touch" IVIG clinical management program administered by a home infusion specialty pharmacy. A greedy propensity score matching algorithm was used to identify a control group from non-program patients. Generalized estimating equation models were employed to evaluate differences between cohorts who were followed for 1 year.

Results: Clinical outcomes were measured as infections and infusion-related adverse events. The proportion of patients who had serious bacterial infections was significantly lower (4.13% vs 7.75%, P=0.049) in the intervention group (n=242) compared to the control group (n=968). Other clinical outcomes assessed were not different between cohorts (P>0.050). The economic outcomes were measured as healthcare costs. The annual adjusted mean total health care costs of patients in the program were $26,522 lower compared to matched controls, representing a 20% lower cost ($109,476 vs $135,998, P=0.002). A major contribution to this difference ($17,269) was IVIG-related total outpatient cost (intervention vs control groups: $64,080 vs $81,349, P=0.001).

Conclusion: The patients in this high-touch IVIG clinical management program appeared to have comparable infections or adverse event rates and significantly lower total health costs compared to their matched controls.

Keywords: immunoglobulin, intravenous, management program, clinical outcomes, economic outcomes

Introduction

Intravenous immunoglobulin (IVIG) has been widely used as an antibody replacement or an "immunomodulatory agent" for indications in hematology, neurology, immunology, rheumatology, dermatology, nephrology, and ophthalmology.[1,2] While the clinical indications for using IVIG are expanding,[3–6] its administration may lead to considerable side effects and potential adverse events (AEs).[3] In addition, IVIG is expensive and thus requires judicious utilization. The annual cost of IVIG treatment has been estimated to exceed US$30,000 per patient depending on dosing, indications, and length of therapy.[7–10] Given the overall potential burden of Ig costs, considerations for cost containment are essential.

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Clinical outcomes

IVIG has been licensed by the US Food and Drug Administration for prevention of infection in various immunodeficiency diseases that cause susceptibility to recurrent, severe, or usual infections.[3,4] Infection rates were chosen as one of the primary clinical outcome measures for our study. AEs were also included, since IVIG administration often results in mild AEs and more rarely in severe AEs, though its safety profile is well established.[11–15]

Infections

In the US, about 25–30% of IVIG grams are used for the treatment of primary immunodeficiency disorder (PID), which is characterized by recurrent infections. Common variable immunodeficiency is the most common type of PID.[16–18] While there is extensive experience with the efficacy of IVIG in common variable immunodeficiency and related PID, there are increasing options for providing therapy, including dose, frequency, and site of care. IVIG therapy dose and residual "trough" IgG levels have been in aggregate correlated with infectious outcomes,[19–21] and current practice tends to focus upon individualizing the dosing approach to any given patient.

Adverse events

AEs are common in IVIG therapy. They can be classified as mild (eg, headache, flushing, shivering, itching, urticaria, anxiety, dizziness), moderate (eg, chest pain, wheezing, blood pressure fluctuations, mild reactions becoming worse), or severe (eg, severe headache, aseptic meningitis, renal dysfunction, anaphylaxis, thromboembolic event, moderate reaction persisting or becoming worse) reactions.[19–23] A number of studies in the US and other countries have examined the incidence of IVIG-related AEs.[3,19–21,23–27] The incidence rates varied widely across studies (21.4–44% of patients; 2.4–12.8% of infusions).[3,19–21,23–27] The majority of AEs reported were mild (non-severe).[3,19,24] Most mild reactions were able to be reversed by slowing or stopping the infusion for 15–30 minutes.[3] Severe AEs were rare: 0–1.3% of infusions or 0–3.6% of treatment courses.[19,21,23] Headache was reported as the most common type of AE in some studies,[23,25] and patients who received premedication had significantly reduced incidence of AEs (18.2% vs 29.3%, P=0.02).[24]

Economic outcomes

Few studies have examined economic outcomes associated with Ig therapy, despite the increasing focus on management of health care cost.[10,28,29] One study in the US found that the annual costs of IVIG therapies for treating chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy were >$50,000 per patient,[10] and annual mean costs for treating a cohort of mucous membrane pemphigoid, ocular cicatricial pemphigoid, bullous pemphigoid, and pemphigus vulgaris patients with IVIG were $65,190 ($37,271–$118,232) in another US study.[29] Ig drug costs have been identified as the main cost drivers of IVIG therapy in several studies from various countries (Canada, Italy, and Germany).[28,30–32]

Ig clinical management

Given the current focus on evidence-based medicine and health care cost containment, appropriate clinical management to assure the safe and effective administration of IVIG products is desirable. Accordingly, a "high-touch" clinical management program for patients with IVIG therapy was developed by a US home infusion and specialty pharmacy. The program provided IVIG infusion in a patient's home or at ambulatory infusion suites. It consisted of a comprehensive care model that included a pre-infusion risk assessment by a pharmacist, infusion monitoring by an Ig-specialized registered nurse (RN), regular clinical follow-up with a patient by a pharmacist that was communicated to physicians for expedient resolution of any clinical issues, and financial consultations.

Site of care

Few studies in the US have compared site of care (ie, place of service), such as hospital inpatient, hospital outpatient, physician office, community infusion center, and patient home. Small studies comparing two care sites have identified no differences in infection or related clinical outcomes, although some differences in quality of life and cost have emerged.[33,34] Further understanding of the clinical and economic advantages and disadvantages of all available sites of care is needed. Regardless of site of care, expert clinical practice is essential to ensure safe administration of IVIG[3,20,35] and avoid adverse reactions.[20]

Study objective

This study evaluated a national home infusion specialty pharmacy clinical management program on economic and clinical outcomes of IVIG patients. We hypothesized that AEs and infection rates, as well health costs, could be lower through this patient management model compared to the outcomes of other care models.

Ethics approval

This research was approved by Quorum IRB (28495/1) with a waiver of informed consent, as well as a complete waiver of Health Insurance Portability and Accountability Act authorization.

Materials and methods

We conducted a retrospective cohort study to compare the clinical and economic outcomes of patients who received IVIG and managed by an Ig clinical management program with matched controls in the PharMetrics Plus (PMTX+) database, a US-based administrative claims database with adjudicated medical and pharmacy claims for more than 150 million unique enrollees since 2006.

Ig clinical management model

This IVIG patient care model provided individualized patient care and clinical management by qualified health care professionals. These services included the following:

- pre-infusion clinical evaluation – evaluation for comorbidities affecting the risk of adverse drug reactions (ADRs), coordination with the prescribing clinician for individualized infusion plans to avoid ADRs and patient education to address concerns proactively
- clinical management of infusion by RNs – individualized infusion rate protocols with clinical monitoring before, during, and after infusion; patient education regarding Ig; expectations of treatment; and potential AEs
- regular clinical follow-up with a patient by a pharmacist that was communicated to the prescribing clinician – minimally quarterly contact (always after the first visit, a monthly option is also provided) to assess adherence and ADR management, disease-specific patient-reported outcome measures (quarterly report), and dose adjustment

The care team also provided patient consultation on insurance coverage and financial assistance.

Data source and study population

The data used in this study was from the PMTX+ database, from which the dependent outcomes and covariables for both intervention and control groups were derived. This database is a large longitudinal repository of adjudicated medical and pharmacy claims of more than 150 million unique, commercially insured members throughout the US since 2006.

The same inclusion and exclusion criteria were used for the intervention and control groups. Included in the study were patients who had received at least one claim (prescription or administration procedure) for IVIG therapy between September 1, 2011 and June 30, 2013, had continuous eligibility in the PMTX+ database for a minimum of 6 months prior to and 12 months after the date they had received the first IVIG therapy in the study period (the index date), and had at least four IVIG claims in the 12-month post-index period and one claim of IVIG during or after month 6. Both intervention and control cohorts excluded patients who were administered intramuscular immunoglobulin or subcutaneous immunoglobulin during the period, who had incomplete or invalid data records, or if they were prescribed products that can be administered subcutaneously or intravenously (ie, Gammagard liquid, Gamunex-C, and Gammaked), unless they had an administration code (ie, J1561, J1569) observed within 7 days of the claim date. All inclusion and exclusion criteria can be found in Table S1.

The intervention group was identified by linking patients from the national home infusion specialty pharmacy to the PMTX+ database. All patients at the national home infusion specialty pharmacy were managed by the Ig clinical management program, which was administered across multiple locations in the US. None of the patients opted out unless their claims could not be identified in the databases.

All patients were categorized by whether they had an IVIG-treatable autoimmune disease, a non-IVIG-treatable autoimmune disease, or a non-autoimmune disease (Table S2). Within each autoimmune-disease category, the control group was selected from patients who were not in the program and matched to the intervention group using a 1:4 greedy propensity score without replacement.[36] Covariates in the propensity score model were age at index date, sex, proximity to immunology centers of excellence (Table S3), geographic region, Charlson Comorbidity Index score, and 6-month pre-index total health care costs (Table 1).

Clinical outcomes

Primary clinical outcomes included infection and infusion-related AE rates. Infections were categorized into three groups: serious bacterial infections (SBIs), other infections, and all infections (both SBIs and other infections).[14,15,37–41] AEs were categorized into four groups: common AEs, serious AEs, and mild, less common AEs (both subjective and objective) (Table S3). Infections and AEs were reported as both patient counts by events of interest and as rates (number of events per patient per year).

Economic outcomes

The primary economic outcome was direct medical costs per person during the study period (12 months post-index date). Total health care costs and segregated cost categories, inpatient, emergency center, outpatient, and total pharmacy claims were reported. All patients in the cohort were included for calculating total health care cost. The allowed amount of the claim was used to determine direct costs, which was defined as the amount the health plan allowed for a particular service, and included both the plan amount paid and member liability (ie, copayment, deductible, and coinsurance). These fully adjudicated claims

Table 1 Baseline characteristics of study population before and after propensity score matching

Characteristics	Before					After				
	Intervention		Control		*P*	Intervention		Control		*P*
	n=274		n=4,010			n=242		n=968		
Age (years), mean (95% CI)	47	(45.1–48.9)	47.5	(47–48.1)	0.631	46.4	(44.4–48.5)	48.3	(47.3–49.4)	0.112
Age group (years), n (%)					0.011					0.653
0–18	22	8%	497	12.4%		22	9.1%	70	7.2%	
19–30	21	7.7%	244	6.1%		19	7.9%	68	7%	
31–54	123	44.9%	1,475	36.8%		107	44.2%	421	43.5%	
≥55	108	39.4%	1,794	44.7%		94	38.8%	409	42.3%	
Male, n (%)	126	46%	1,799	44.9%	0.718	110	45.5%	436	45%	0.908
Census region, n (%)					<0.0001					0.968
Northeast	147	53.6%	816	20.3%		115	47.5%	449	46.4%	
Midwest	49	17.9%	1,304	32.5%		49	20.2%	191	19.7%	
South	62	22.6%	1,596	39.8%		62	25.6%	263	27.2%	
West	16	5.8%	294	7.3%		16	6.6%	65	6.7%	
Proximity to centers, n (%)	217	79.2%	2,432	60.6%	<0.0001	185	76.4%	761	78.6%	0.465
Autoimmune disease, n (%)					0.002					1.000
IVIG-treatable	169	66.5%	2,067	55.3%		145	63%	580	63%	
Not IVIG-treatable	11	4.3%	218	5.8%		11	4.8%	44	4.8%	
Not autoimmune immunodeficiency[a]	74	29.1%	1,456	38.9%		74	32.2%	296	32.2%	
CCI scores, n (%)					0.003					0.748
0	94	34.3%	1,032	25.7%		81	33.5%	339	35%	
1–2	122	44.5%	1784	44.5%		108	44.6%	414	42.8%	
3–4	36	13.1%	768	19.2%		31	12.8%	141	14.6%	
≥5	22	8%	426	10.6%		22	9.1%	74	7.6%	
6-month pre-index total health care costs, mean US$ (95% CI)	47,961	(38,310–57,612)	53,731	(50,805–56,657)	0.324	48,552	(38,051–59,053)	52,339	(46,190–58,487)	0.578
Categorical costs, n (%)					0.224					0.828
≤$15,000	72	26.3%	1,120	27.9%		63	26%	253	26.1%	
>$15,000–≤$30,000	76	27.7%	988	24.6%		64	26.4%	247	25.5%	
>$30,000–≤$60,000	74	27%	963	24%		68	28.1%	255	26.3%	
>$60,000	52	19%	939	23.4%		47	19.4%	213	22%	

Note: [a]Including common variable immunodeficiency.
Abbreviations: CCI, Charlson Comorbidity Index; IVIG, intravenous immunoglobulin.

were inflation-adjusted to 2014 prices using the medical care component of the US Consumer Price Index for all urban consumers. When appropriate, costs that were considered directly related to the drug or administration of the drug were broken down based on Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT), or National Drug Codes. Specifically, Ig-related costs were reported for total allowable costs and total outpatient costs (based on HCPCS/CPT codes). Inpatient/outpatients costs were capped at five times the standard deviation (SD), in order to mitigate outlier effects for both intervention and control groups.

Statistical analyses

We compared baseline characteristics between the two groups using χ^2 or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Categorical measures were reported as the number of cases and percentage of total patients observed in each category, and both mean and SD/confidence intervals (CIs) were reported for continuous variables. Clinical and economic outcomes were analyzed using generalized estimation equation (GEE) models with log-link, negative-binomial distributions. The unstructured correlation matrix was applied or compound symmetry used if the model did not converge. For the clinical model, the adjusted event rate was reported and the models adjusted for program-management model, number of Ig administrations, place of service (eg, hospital, home, clinic), diabetes (yes/no), and renal disease (yes/no). The program-management variable adjusted for changes in how the program was administered over the 3-year study period across the US. For example, the frequency of clinical assessments increased for the intervention group over time. For the economic model, adjusted mean costs used were adjusted by program management model, place of service, and number of Ig administrations. The proportion of patients with AEs was compared between intervention and control groups using χ^2 or Fisher's exact test. Unadjusted results were

presented if the GEE model did not converge. All analyses were performed at a patient level using SAS 9.2 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

Results

To evaluate the impact of this "high-touch" clinical management program, both clinical and economic outcomes were compared between patients within the program and their matched controls. Prior to propensity score matching, there were 274 and 4,010 eligible patients in the intervention and control groups, respectively. Before matching, patient geographic distribution and access to immunology expertise centers were significantly different between the two groups, whereas no significant differences were found for age, sex, or autoimmune disease status. After propensity score matching, the 242 and 968 patients remaining in the intervention and control groups, respectively, had similar baseline characteristics across all domains, including cost prior to intervention (Table 1).

After the intervention, there were a few differences worth noting. While most AE and infection outcomes were not statistically significantly different, the proportion of patients who had SBIs was significantly lower in the intervention group compared to the matched controls (4.13% vs 7.75%, $P=0.05$). The SBI rate (events per patient per year) was also much lower among managed patients and close to significance (0.12 vs 0.45, $P=0.07$; Table 2).

Considerably lower cost was achieved for managed patients (Table 3). The annual mean total allowable cost of patients in the clinical management program was $26,522 (20%) lower compared to the annual mean cost of matched controls ($P=0.002$), with the difference in mean Ig-related total allowable costs $17,495 (annual mean cost of intervention vs control groups $64,332 vs $81,827, $P=0.001$). A major contribution to this difference ($17,269) was Ig-related total outpatient cost (intervention vs control groups: $64,080 vs $81,349, $P=0.001$). Though not statistically significant, annual differences in total mean inpatient and pharmacy costs were $5,356 and $1,517, respectively. In contrast, the total emergency center care costs were slightly higher for patients in the IVIG clinical management program, but the difference was not significant ($P=0.107$).

Discussion

IVIG is standard therapy for many immunologic diseases. In recent years, alternative sites of care for IVIG infusion

Table 2 Infection and adverse event rates of comparison groups

Clinical outcomes	Rates (events/patient/year)[a]			Proportion of patients (% of patients)		
	Intervention (n=242)	Control (n=968)	*P*	Intervention (n=242)	Control (n=968)	*P*
Infections						
All	2.71	2.06	0.274	54.13%	53.2%	0.795
Serious bacterial	0.12	0.45	0.066	4.13%	7.75%	0.049
Other	2.52	1.85	0.241	52.89%	50.31%	0.472
Adverse events						
Common	0.02	0.03	0.776	1.65%	2.69%	0.355
Serious	0.02[b]	0.01[b]	NA	1.65%	0.62%	0.12
Mild, less common (subjective)	0.04	0.03	0.333	3.72%	4.13%	0.771
Mild, less common (objective)	NA	NA	NA	9.92%	7.23%	0.163

Notes: [a]Rates are means after adjustment of program management model, number of Ig administrations, site of care, diabetes (yes/no), and renal disease (yes/no) by the GEE regression model; [b]unadjusted means, since the GEE model did not converge.
Abbreviations: GEE, generalized estimation equation; NA, not applicable.

Table 3 Total allowable costs (US$) of comparison groups

Total allowable costs[a]	Intervention (n=242) [A] Mean (95% CI)		Control (n=968) [B] Mean (95% CI)		*P*	Mean difference, [A] – [B]
Total costs	$109,476	($98,568–$121,592)	$135,998	($121,766–$151,893)	0.002	$26,522
Ig-related	$64,332	($57,926–$71,447)	$81,827	($73,127–$91,562)	0.001	$17,495
Total inpatient costs	$8,781	($5,171–$14,912)	$14,137	($7,767–$25,732)	0.236	$5,356
Total EC costs	$992	($558–$1,764)	$482	($293–$793)	0.107	$510
Total outpatient costs	$93,865	($84,858–$103,827)	$108,561	($97,899–$120,384)	0.026	$14,696
Ig-related	$64,080	($57,656–$71,219)	$81,349	($72,646–$91,094)	0.001	$17,269
Total pharmacy costs	$6,666	($5,313–$8,363)	$8,183	($6,287–$10,651)	0.189	$1,517

Note: [a]Mean costs per patient per year are means after adjustment of program management model, site of care, and number of Ig administrations by regression model.
Abbreviation: EC, emergency center.

have emerged, including infusion in a patient's home or at an ambulatory infusion suite, compared to more traditional sites of care, such as a hospital or a physician's office.[6,42]

Due to the complexity of immunoglobulin administration and its known potential for causing AEs, safety is a major concern, especially in settings outside hospitals or hospital infusion centers. While IVIG infusion is clinically complex, several studies have demonstrated the safety of administration of IVIG at home or in ambulatory infusion settings.[26,43–45] Providers and physicians continue to develop and optimize clinical care models to provide the best outcomes while minimizing health care expenditures. The results of this study suggested that a clinical care model drives comparable clinical outcomes when compared to a diverse population receiving IVIG. AE rates and non-serious infection rates in the intervention group were comparable, while SBI rates and the proportion of patients who had SBIs were either significantly lower or very close to being significantly lower in the intervention group. This may be attributable to the individualized infusion services provided by the Ig-trained RNs and pharmacists in this care model. It was difficult to compare our findings with AE rates stated in the existing literature, due to differences in Ig dosages, diversity of diagnoses, and the scope and definition of AEs and infections. When one considers AE rates in licensing materials (package inserts) from IVIG products, those identified in the present work were generally in line with existing/expected experience.[34] The major exception was common, mild AEs, which were low in both populations, but this could have been due to differences in reporting these occurrences in a trial study vs real-world practice.

This study also revealed lower direct health care expenditure in the intervention group compared to the control group. The majority of the difference in total adjusted allowable cost between the two groups was in Ig-related outpatient costs ($17,269, 65% of cost difference). The IVIG treatment cost variations in this study and two other US studies cited in the introduction session could be attributed to cost inflation, place of service, disease scope, and dosage range of Ig therapies. Even when Ig-related costs were removed, cost differences remained in the intervention group when compared to controls. This difference could be ascribed to lower medication costs related to site of care; in other words, the same drug is reimbursed differently across sites of care.[46,47] With the rising demand for accessible high-quality care at lower overall cost, this patient-centered clinical management model may show the ability to help achieve these goals in IVIG treatment.

Limitations

Many of the limitations in this study were similar to many other retrospective observational studies using administrative claims data. For instance, the population of patients selected for one particular treatment over another may have different characteristics (channeling bias). The medical billing codes used to indicate diagnoses and procedures may be subject to non-clinical influences. Some of these differences can often be measured (such as age and autoimmune disease status), and thus were controlled for in this study. Others were unknown or not measurable. In addition, this study was unable to specify if any clinical care model was applied to any patient in the control group. Because our study period covered 3 years, changes in the program model were inevitable, although we tried to control for such changes by adding the program management model variable to our regression models. While there was careful matching of the intervention and control groups in the pre-intervention period, the comparison may be skewed by physicians maintaining more fragile patients at inpatient and outpatient settings for treatment, which would lead to a bias in health care-related expenses in the control group. That said, we controlled for pre-intervention costs via propensity score matching. Importantly, the cost advantage of this care model was maintained, even when the differing drug cost was removed as a factor. Future studies could and perhaps should focus more specifically upon comparing specific care models within individual sites of care. This, however, represents a first step in generating the motivation for these questions.

Implications for clinical care and future research

In aggregate, though there were a few notable clinical benefits, clinical outcomes were similar between patients in this care model and the matched control group, which likely represented various types of care models. However, given the significant economic advantage shown here, the provision of therapy at home using this type of care model should be a consideration for patients, providers, and payers. Since it was difficult to draw strong conclusions from this initial study, further research will be needed to identify exactly which type of patients may benefit most and exactly what advantages this robust clinical care model may offer in comparison with other programs. Appreciating that the site of care decision for patients is complex, we are hopeful that research will help identify how to utilize advantages and avoid disadvantages to achieve the best clinical outcomes and cost savings for patients.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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Disclosure

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Supplementary materials

Table S1 Study population attrition

Criterion	Intervention		Control	
	n	%	n	%
Patients received IVIG during 6-month pre-index period (September 1, 2011 to June 30, 2013)	595	100%	11,918	100%
AND met continuous enrollment in PMTX+ database for a minimum of 6 months prior to index date	435	73.1%	9,206	77.2%
AND met continuous enrollment criteria in PMTX+ database for a minimum of 12 months after index date	354	59.5%	6,599	55.4%
AND with at least four claims of index IG in 12-month post-index period	312	52.4%	5,017	42.1%
AND with one claim of index IVIG on or after month 6 (ie, after day 150 from index)	282	47.4%	4,190	35.2%
AND without IMIG (exclusion criteria)	282	47.4%	4,190	35.2%
AND not receiving both SCIG and IVIG during 12-month post-index period	274	46.1%	4,048	34%
AND with complete data and valid data	274	46.1%	4,010	33.6%
Post 1:4 propensity score matching	242	40.7%	968	8.1%

Abbreviations: IVIG, intravenous Ig; PMTX, PharMetrics; IMIG, intramuscular immunoglobulin; SCIG, subcutaneous immunoglobulin.

Table S2 Classification of autoimmune disease covariates

	ICD9-CM	IVIG-treatable autoimmune disease	Not IVIG-treatable autoimmune disease	Not autoimmune disease
Common variable immunodeficiency	279.0X			Yes
Immunodeficiency diseases	279.1X, 279.2, 279.3			Yes
Behçet's syndrome	136.1	Yes		
Post-polio syndrome	138	Yes		
Autoimmune cytopenia	238.7	Yes		
Hashimoto's thyroiditis and thyroiditis with hyperthyroidism	245.2	Yes		
Autoimmune diabetes mellitus	250.01, 250.03	Yes		
Autoimmune disease not elsewhere classified	279.4X (not 279.41)	Yes		
Graft-versus-host disease	279.5	Yes		
Hemolytic anemia, autoimmune	283	Yes		
Autoimmune hemophilia	286.52	Yes		
Henoch–Schönlein purpura	287	Yes		
Idiopathic thrombocytopenic purpura	287.31	Yes		
Post-transfusion purpura	287.41	Yes		
Autoimmune neutropenia	288.09	Yes		
Macrophage-activation syndrome	288.4	Yes		
Acute disseminated encephalomyelitis, autoimmune encephalopathy, limbic encephalitis, Rasmussen's syndrome, demyelinating brain-stem encephalitis	323.81	Yes		
Alzheimer's disease	331	Yes		
Stiff-person syndrome	333.91	Yes		
Cerebellar ataxia, opsoclonus–myoclonus syndrome, post-infectious, paraneoplastic cerebellar degeneration	334.2, 334.3	Yes		
Paraproteinemic neuropathy	337.00, 337.09,356.8	Yes		
IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy	337.1	Yes		
Multiple sclerosis, relapsing–remitting	340	Yes		
Epilepsy, intractable childhood	345.61	Yes		
Narcolepsy with cataplexy	347.01	Yes		
Lumbosacral or brachial plexitis	353.0, 353.1	Yes		
Chronic demyelinating polyneuropathy	356.4	Yes		
Guillain–Barré syndrome	357	Yes		
Multifocal motor neuropathy	357.89	Yes		
Myasthenia gravis	358	Yes		
Lambert–Eaton myasthenic syndrome	358.3	Yes		
Necrotizing autoimmune myopathy	359.81	Yes		

(*Continued*)

Table S2 (*Continued*)

	ICD9-CM	IVIG-treatable autoimmune disease	Not IVIG-treatable autoimmune disease	Not autoimmune disease
Uveitis, autoimmune	360.19	Yes		
Grave's ophthalmopathy (thyrotoxic exophthalmos)	376.21	Yes		
Autoimmune optic neuropathy	377.49, 377.30	Yes		
Brown–Vialetto–van Laere syndrome	389.1	Yes		
Cerebral infarctions with antiphospholipid antibodies	434.01, 434.11, 434.91	Yes		
Polyarteritis nodosa	446	Yes		
Kawasaki disease	446.1	Yes		
Thrombotic thrombocytopenic purpura	446.6	Yes		
Antineutrophil antibody syndrome	447.6	Yes		
Inflammatory bowel disease	555.0, 555.1, 555.2, 555.9	Yes		
Autoimmune chronic active hepatitis	571.42	Yes		
Antiphospholipid antibody syndrome in pregnancy	649.3	Yes		
Pemphigus foliaceus, pemphigus vulgaris, pemphigus, paraneoplastic	694.4	Yes		
Bullous pemphigoid	694.5	Yes		
Cicatricial pemphigoid	694.6	Yes		
Scleromyxedema	701.8	Yes		
Chronic urticaria	708.1, 708.8	Yes		
Systemic lupus	710	Yes		
Systemic sclerosis (scleroderma)	710.1	Yes		
Sjögren's syndrome (sicca syndrome)	710.2	Yes		
Dermatomyositis	710.3	Yes		
Polymyositis	710.4	Yes		
Mixed connective-tissue disease	710.8	Yes		
Unspecified diffuse connective-tissue disease	710.9	Yes		
Rheumatoid arthritis, severe	714	Yes		
Felty's syndrome	714.1	Yes		
Juvenile idiopathic arthritis	714.3	Yes		
Juvenile idiopathic arthritis	714.31	Yes		
HTLV1-associated myelopathy	721.1, 721.4, 721.91	Yes		
Acute idiopathic dysautonomia	742.8	Yes		
Chronic bullous disease of childhood, epidermolysis bullosa acquisita	757.39	Yes		
Fetomaternal alloimmune thrombocytopenia	776.1	Yes		
Sarcoidosis	135		Yes	
Grave's disease	242		Yes	
Addison's disease, autoimmune	255.41		Yes	
Autoimmune polyglandular syndrome, type I	258.01		Yes	
Autoimmune polyglandular syndrome, type II	258.02, 258.03		Yes	
Pernicious anemia	281		Yes	
Encephalomyelitis	323.9		Yes	
Retinopathy	362.1		Yes	
Thromboangiitis obliterans	443.1		Yes	
Churg–Strauss disease, Wegener's granulomatosis	446.4		Yes	
Temporal arteritis	446.5		Yes	
Takayasu's arteritis	446.7		Yes	
Autoimmune chronic active hepatitis	571.49		Yes	
Primary biliary sclerosis	571.6		Yes	
Sclerosing cholangitis	576.1		Yes	
Gluten-sensitive enteropathy	579		Yes	
Infertility, immunomediated	628.8		Yes	
Pemphigoid gestationis	646.8		Yes	
Dermatitis herpetiformis	694.2		Yes	
Linear IgA disease	694.8		Yes	
Erythema nodosa	695.2		Yes	

(*Continued*)

Table S2 (*Continued*)

	ICD9-CM	IVIG-treatable autoimmune disease	Not IVIG-treatable autoimmune disease	Not autoimmune disease
Psoriasis	696.1		Yes	
Alopecia, autoimmune	704		Yes	
Vitiligo	709.01		Yes	
Other rheumatoid arthritis with visceral or systemic involvement	714.2		Yes	
Rheumatoid lung	714.81		Yes	
Other specified inflammatory polyarthropathies	714.89		Yes	
Unspecified inflammatory polyarthropathy	714.9		Yes	
Ankylosing spondylitis	720		Yes	

Abbreviations: HTLV1, Human T-lymphotropic virus 1; IVIG, intravenous immunoglobulin.

Table S3 Clinical outcomes

Clinical outcome	Diagnosis	ICD9-CM
Serious bacterial infections	Bacterial pneumonia	482.XX
	Visceral abscess	324.X, 478.24. 513.0, 567.22, 567.38, 572.0, 590.2
	Septicemia	995.91,995.92,038.xx,790.7, 785.52
	Bacterial meningitis	320.X, 321.X,322.X,047.X, 003.21, 036.0
	Osteomyelitis/septic arthritis	711.0X, 730.0X
Other infections	Conjunctivitis	372.00, 372.05, 372.3,372.03
	Acute bronchitis	466
	Acute otitis	382.0, 382.0X, 382.4, 382.9.
	Pyoderma/cellulitis/subcutaneous abscess	686.XX, 682.XX
	Mastoiditis	383.XX
	Sinusitis	461.X, 473.X
	URI (added on February 1, 2015	465.8, 465.9
Common AEs	Abdominal pain	789.XX, 789.6
	Fever/pyrexia	780.60, 780.62, 780.66
	Nausea	787.02
	Asthenia/other malaise and fatigue	780.79
	Headache/acute migraine	784.0, 339.00, 339.01, 339.43, 339.85, and 346.XX with the exceptions of 346.40, 346.41, 346.42, 346.43;
	Myalgia	729.1
	Rash/local reaction: burning or itching	782.1
Serious rare AEs	Anaphylaxis/anaphylactoid reaction/anaphylactic shock	995.0, 999.41, 999.49
	Pulmonary edema	518.4
	Embolism	444.X,415.19, 445.x
	Seizure	345.0X, 345.1X, 345.2X, 345.3X, 345.4X, 345.5X, 345.8X, 345.9X, 780.39
	Aseptic meningitis	322.9
	Transfusion-related acute lung injury	518.7
	"Serum sickness"	999.51,999.59
	Acute renal failure/anuria/ renal tubular necrosis/blood creatinine increased/blood urea increase	584.XX
	Thrombotic complications	453.9
	Dermatitis, bullous/exfoliative/epidermal	694
	Hepatitis/acute hepatitis (uninfectious)/hepatic dysfunction/hepatic failure/hepatocellular damage/jaundice	573.3,070.XX
	Neurodegeneration	294.1
	Neurological illness	357.9 and 348.9
Mild, less common AEs (subjective)	Anxiety	300.00,300.09
	Arthralgia	719.4X
	Asthma/bronchospasm (wheezing)	519.11, 493.01, 493.02, 493.11, 493.12, 493.21, 493.22, 493.91, 493.92

(*Continued*)

Table S3 (*Continued*)

Clinical outcome	Diagnosis	ICD9-CM
	Chest pain	786.5
	Chills	780.64
	Cyanosis/hypoxia	799.02, 782.5
	Acute diarrhea	787.91
	Dizziness	780.4
	Dysgeusia	781.1
	Dyspnea	786.05
	Peripheral edema	782.3
	Emesis	787.0, 787.01, 787.03, 787.04
	Fainting	780.2
	Flushing	782.62
	Back pain	724.2, 724.5
	Pain	338.1, 338.19
	Palpitation	R00.2
	Tremor	333.1
	Urticaria	708.0, 708.1, 708.8, and 708.9
	Vertigo	780.4
	Rigors/shivering	780.99
	Acrodynia	985
	Colitis/enterocolitis	555.XX, 558.2, 558.3, 558.9
	Eczematous dermatitis	692.9, 693.0
	Sleep disturbance	780.5X
	Local reaction – swelling	782.2, 782.8
	Erythema multiforme	695.10, 695.11, 695.12, 695.19
	Uveitis	360.11, 360.12
	Cutaneous vasculitis (in type II mixed cryoglobulinemia)	709.8
Mild, less common	Hyperglycemia (glucose-containing products only)	790.29
AEs (objective)	Hypotension	458.XX
	Hypertension	401.X,405.X,997.91
	Leucopenia/neutropenia/pancytopenia	288.03, 284.01, 284.09. 284.81, 284.9, 288.03, 288.5
	Tachycardia/sinus tachycardia/SVT/arrhythmia (cardiac, any type)	785.0, 785.1, 427.XX
	Complement consumption associated with an eczematous cutaneous reaction	693
	Fluid overload	276.61,276.69
	Hyponatremia/hypernatremia	276.0, 276.1
	Hematuria	599.7X
	Coombs positivity (hemolytic anemia)/hemolysis/hemolytic anemia	283.XX, 790.01
	Nonspecific elevation of levels of transaminase or LDH	790.4

Abbreviations: URI, Upper respiratory infections; AEs, adverse events; SVT, supraventricular tachycardia; LDH, lactic acid dehydrogenase.