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ORIGINAL ARTICLE

The population-level costs of immunosuppression medications for the treatment of glomerulonephritis are increasing over time due to changing patterns of practice

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ABSTRACT

Background. Immunosuppression (IS) is the main treatment for most types of glomerulonephritis (GN). Quantifying the cost of IS is necessary to ensure equitable access to therapies and optimal health outcomes, but the real-world cost of IS treatment for GN is largely unknown. We examined temporal changes in the population-level IS medication costs for GN over a 14-year period in a large Canadian province.

Methods. We linked a provincial pathology database (containing all GN cases from 2000 to 2012) with renal and medication administrative databases to capture clinical characteristics and IS medications, with follow-up until 2013. The primary outcome (mean IS medication cost per treated patient each year) was evaluated for trends over time.

Results. The cohort included 2983 GN patients followed for a mean of 5.7 years. The yearly per-patient medication cost increased 6.8-fold from $205 to $1394 ($P < 0.001$), with significant increases of 3.5–11.7-fold in anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, focal segmental glomerulosclerosis, lupus nephritis, minimal change disease and membranous nephropathy ($P \leq 0.004$), but no change in immunoglobulin A (IgA) nephropathy. The cost of mycophenolate mofetil, calcineurin inhibitors and rituximab increased significantly ($P < 0.001$) such that in 2000 they accounted for 17.6% of medication costs and were used by 2.2% of patients, which increased to 94.5% and 44.6%, respectively, in 2013. The costs of azathioprine, cyclophosphamide and prednisone increased only slightly or decreased. Patterns of drug use and contribution to cost varied by type of GN.

Conclusions. These are the first population-level estimates of the IS treatment costs for GN, and demonstrate a striking increase due to changing practice patterns from older, cheaper medications to newer, more expensive therapies. These results provide important information to guide future health policy strategies and cost-effectiveness research in glomerular diseases.

Keywords: costs, glomerulonephritis, immunosuppression, medication, population-level

INTRODUCTION

Immunosuppressive (IS) therapies are the mainstay of treatment for glomerular diseases and improve both short- and long-term renal outcomes [1]. However, to date there has been minimal assessment of the medication costs for IS treatment for glomerulonephritis (GN). These are likely to be substantial as many IS medications are expensive and require prolonged administration over the chronic relapsing and remitting nature of most types of GN. Medication costs for patients with lupus nephritis are more than double that of lupus patients without nephritis, and is the single largest contributor to health-care resource utilization in lupus patients [2–4]. Furthermore, in health-care systems where individuals must pay for medications, high costs of IS medications contribute to non-adherence, which is associated with poor outcomes in GN patients [5–8]. Pharmaceutical costs continue to consume an increasing proportion of health-care expenses in most developed countries worldwide [9, 10]. Therefore, quantifying treatment costs in GN patients is critical to understanding health-care resource implications and patient outcomes in glomerular diseases.

Recent advances in the treatment of glomerular diseases have identified much needed therapies with improved efficacy and less toxicity, but have also focused predominantly on the use of more expensive IS medications. This includes replacing

cheaper medications such as azathioprine or cyclophosphamide with comparatively more expensive options such as mycophenolate mofetil (MMF) or calcineurin inhibitors (CNI) [11–17], and the use of expensive biologic therapies such as rituximab [18–23]. The impact of newer IS medications on temporal changes in treatment costs has been observed in renal transplantation, in which the cost of IS medications more than doubled in the period from 1998 to 2006, and is now the largest component of health-care expenses in transplantation [24, 25].

We hypothesize that the cost of IS treatment for GN has similarly increased over time due to a transition from older, cheaper medications to newer, more expensive therapies. We examined the population-level costs of IS medications for GN patients in a large Canadian province and temporal changes over a 14-year period from 2000 to 2013.

MATERIALS AND METHODS

Study design

This is a population-level retrospective cohort study that uses administrative health data in the province of British Columbia (BC), Canada. We included all adult patients in BC 18 years of age or older with a diagnosis of GN on a native-kidney biopsy between 1 January 2000 and 31 December 2012. We excluded types of GN that are not typically treated with IS medications, and patients with end-stage renal disease (ESRD) at the time of biopsy who did not receive any immunotherapy. The cohort was followed until 31 December 2013. Ethics approval was obtained from the University of British Columbia.

Data sources

All kidney biopsies in mainland BC within the study period were read by nephropathologists at a single centre (the BC Renal Pathology Laboratory in Vancouver). Biopsy details were recorded in a central pathology database including biopsy date, a unique patient identifier (personal health number), patient demographics and clinical characteristics and histologic diagnoses. We linked the pathology database to the BC Renal Agency and PharmaNet provincial administrative databases using the personal health number. The BC Renal Agency is a provincial health services organization that coordinates the care of all patients with kidney disease in BC. As of January 2000, the BC Renal Agency database captures all instances of dialysis or transplantation in the province, and all patients that are seen in multidisciplinary chronic kidney disease clinics. Once registered in the database, clinical characteristics, laboratory results, emigration status and mortality are automatically captured. PharmaNet is an administrative database managed by PharmaCare, which is the provincial government funding program for outpatient medications in BC. Community and outpatient hospital pharmacies have mandatory reporting to PharmaNet, and hence the database captures all medications, including IS, filled at such pharmacies in BC as of 1996.

Definitions

The type of GN was taken from the pathology diagnosis in the BC Renal Pathology Laboratory database, and categorized as IgA nephropathy (IgAN), minimal change disease (MCD), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), ANCA vasculitis, lupus nephritis and 'other' (a complete list of included types of GN is provided in Supplementary Table S1). Laboratory data and blood pressures were taken as the closest value within 6 months of the biopsy date from either the BC Renal Agency or pathology databases. Estimated glomerular filtration rate (eGFR) was determined from provincially standardized creatinine measurements and the CKD-EPI formula [26, 27]. Proteinuria was taken from 24-h urine collections, but when these were not available urine albumin or protein-to-creatinine ratios were used to estimate daily protein excretion. ESRD status was obtained from the BC Renal Agency database and defined as either renal transplantation or chronic dialysis with duration >90 days (as per standardized administrative definitions in Canada [28]). Immune medications used to treat GN were taken from the PharmaNet database, which captures the amount of dispensed medications, including prednisone, intravenous and oral cyclophosphamide, azathioprine, MMF (mycophenolate mofetil and mycophenolate sodium), CNI (tacrolimus and cyclosporine) and rituximab. Hospital in-patient formularies are not covered by PharmaCare and hence do not report to PharmaNet. Intravenous cyclophosphamide for ANCA vasculitis and lupus nephritis is often given in outpatient hospital infusion centres, and due to the low cost of the drug it is frequently absorbed by the hospital in-patient formulary and hence may not be reliably captured in PharmaNet. Therefore, we developed an imputation algorithm based on the concurrent use of steroid and maintenance medications that have mandatory capture in PharmaNet, with positive and negative predictive values of 90% (see Supplementary Table S2). Intravenous cyclophosphamide was imputed in 73 patients (2.4% of the cohort). We performed a sensitivity analysis in which we varied the imputed dose by up to 100%, and there was no change in our results. More expensive intravenous medications given at outpatient infusion centres, such as rituximab, are not covered by hospital in-patient formularies, and therefore require funding from PharmaCare, resulting in reliable reporting to PharmaNet as it is required for cost reimbursement.

Statistical analysis

The primary outcome was the mean cost of IS medications per treated patient each year after kidney biopsy. Patients contributed person-time to the calculation of the primary outcome only during years after the kidney biopsy date in which they were actively treated with IS, but were followed until death, ESRD, emigration out of the province or 31 December 2013. Any use of IS medications during the study period and up to 6 months after the onset of chronic dialysis was considered to be attributable to the treatment of GN and hence included in the cost calculations. Drug exposure for >6 months after starting chronic dialysis was not included as it was assumed to be targeting extra-renal disease. Drug costs were determined based on dispensed quantities from PharmaNet and standardized provincial PharmaCare formulary pricing in 2016 Canadian dollars ($) (which is the maximum amount a pharmacy can charge for government-funded medications including co-pays

and deductibles, and which accounts for inflation and changing drug prices over time) [29, 30]. The mean cost per treated patient each year was the total cost of IS medications that year divided by the number of patients treated with any IS medication in the same year, and was analysed for monotonic increasing or decreasing trends over time using the non-parametric Mann–Kendall statistical test. Sensitivity analyses were performed in which lupus patients were stratified into proliferative classes (III, IV or mixed III/IV + V), pure Class V or other types of lupus-related glomerular disease to determine consistency of results across severity of disease; drug costs were stratified into those within 1 year compared with more than 1 year after biopsy to determine the impact of initial versus later treatments on medication costs. Crude incidence rates were calculated using estimates of the adult population (≥18 years) from BC Statistics [31].

All tests were two-sided with $P < 0.05$ considered statistically significant. Analyses and figures were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA) and R 3.3.0 (R Core Team 2014, Vienna, Austria).

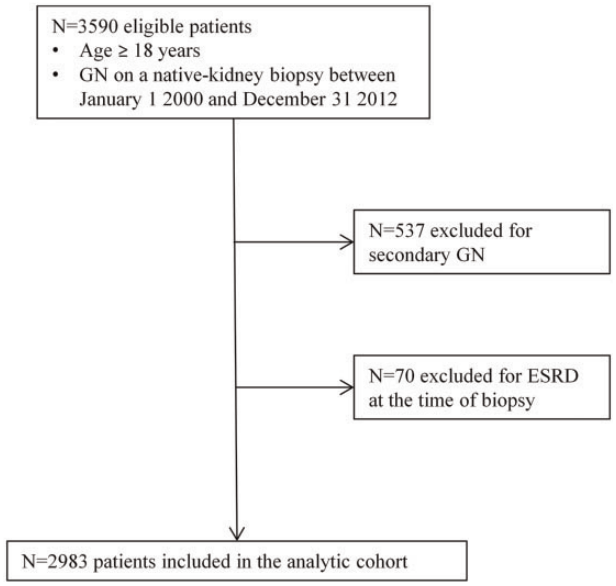

FIGURE 1: Derivation of the cohort.

RESULTS

Description of the cohort

There were 2983 patients in the cohort, including 347 (11.6%) with ANCA vasculitis, 491 (16.5%) with FSGS, 756 (25.3%) with IgAN, 362 (12.1%) with lupus nephritis, 199 (6.7%) with MCD and 407 (13.6%) with MN. Derivation of the cohort is shown in Figure 1, and a description of the cohort is provided in Table 1. There were (mean ± SD) 229.5 (±26.2) cases of GN biopsied each year, corresponding to an incidence rate of 8.14 (±0.82) per 100 000 population per year. The cohort had a mean age of 50.4 (±17.1) years, and 51.5% were male. The mean duration of follow-up was 5.7 (±4.1) years, with a total of 17 039 person-years of observation, during which 689 patients (23.1%) progressed to ESRD after a mean of 2.57 (±2.92) years after biopsy. A total of 1828 patients (61.3%) used IS medications at any time during follow-up with a median treatment duration of 2.0 years (interquartile range 1, 4), including 1768 patients (59.3%) treated with prednisone, 589 (19.8%) with cyclophosphamide, 483 (16.2%) with azathioprine, 373 (12.5%) with MMF, 257 (8.6%) with a CNI and 38 (1.3%) with rituximab.

Per-patient IS medication costs for all GN

The mean per-patient costs for all IS medications are shown in Figure 2 and summarized in Supplementary Table S3. For all types of GN combined, the yearly medication costs increased 6.8-fold from $205 per patient in 2000 to $1394 per patient in 2013 ($P < 0.001$). Significant increases in yearly per-patient IS medication costs were observed in ANCA vasculitis (3.5-fold from $403 to $1398, $P = 0.003$), FSGS (7.6-fold from $210 to $1,596, $P = 0.001$), lupus nephritis (9.0-fold from $171 to $1544, $P < 0.001$), MCD (10.0-fold from $121 to $1216, $P = 0.004$) and MN (11.7-fold from $170 to $1991, $P < 0.001$). An exception was IgAN, in which the medication cost per patient did not significantly change from $158 in 2000 to $221 in 2013 ($P = 0.08$).

The costs per year for each individual type of IS medication are shown in Figure 3 and Supplementary Table S3, and the percentages of treated patients that used each type of IS medication are shown in Table 2. The largest changes were seen in the medication costs of MMF, CNI and rituximab, all of which increased substantially from 2000 to 2013 ($0–$26 to $417–$455 per patient per year, $P < 0.001$). These three types of IS medications were used by only 2.2% of patients and constituted only 17.6% of the total yearly per-patient medication cost in 2000. By 2013, there was a dramatic increase in use, such that 44.6% of patients were treated with MMF, CNI or rituximab, and these three medications contributed 94.5% of the total yearly per-patient medication cost. The mean per-patient medication cost of azathioprine increased only slightly from 2000 to 2013 ($12–$32 per patient per year, $P < 0.001$), whereas the costs of prednisone and cyclophosphamide decreased ($32–$125 to $22 per patient per year, $P = 0.002$ and <0.001, respectively).

Per-patient IS medication costs for each type of GN

The contribution of individual types of IS to increasing yearly per-patient medication costs varied by type of GN (see Figure 4 and Table 2). In IgAN, prednisone was used in the majority (89.3–100%) of treated patients, and the yearly per-patient medication costs for prednisone did not change over time ($P = 0.06$). In MN, there was a significant increase in the yearly per-patient medication costs for CNI ($P < 0.001$) and MMF ($P = 0.001$), with a significant decrease in the cost of cyclophosphamide ($P = 0.007$). From 2000 to 2002, cyclophosphamide contributed the majority (71.8–77.1%) of the mean yearly per-patient cost of IS medications, and was used in 37.5–59.4% of patients with MN. In comparison, from 2011 to 2013 cyclophosphamide was used less often (15.7–26.1% of patients) and contributed only 2.6–8.5% of the yearly medication costs, with CNI and MMF instead being used in 35.2–47.2% and 7.1–11.4% of patients, respectively, and contributing the

Table 1. Description of the cohort

	All GN	ANCA vasculitis	FSGS	IgAN	Lupus nephritis	MCD	MN	Other GN
Total number of patients, *n* (% of total)	2983 (100)	347 (11.6)	491 (16.5)	756 (25.3)	362 (12.1)	199 (6.7)	407 (13.6)	421 (14.1)
Age at biopsy (years)	50.4 (17.1)	52.3 (15.2)	51.8 (17.0)	44.6 (14.2)	38.2 (12.8)	49.6 (19.2)	56.5 (15.4)	54.8 (16.9)
Male sex	1537 (51.5)	162 (46.7)	285 (58)	466 (61.6)	59 (16.3)	108 (54.3)	230 (56.5)	227 (53.9)
Laboratory data at biopsy								
Creatinine (μmol/L)	191 (171.4)	296.1 (188.5)	188.3 (120.7)	170.8 (150.6)	122.7 (108.8)	129.2 (101.5)	119.4 (95.1)	282.2 (250.9)
eGFR (mL/min/1.73 m^2)	54.8 (35.8)	26.9 (22.3)	48.2 (32.2)	58.5 (32.1)	75.1 (36.8)	72.9 (35.7)	73.2 (32.7)	39.6 (32.2)
Albumin (g/L)	32 (8.6)	32.3 (6.6)	34.2 (8.5)	37.5 (6.5)	30.0 (7.6)	24.7 (10.0)	25.6 (8.1)	30.9 (7.8)
Proteinuria (g/day)	3.9 (4.0)	1.6 (1.7)	4.4 (3.8)	2.3 (2.3)	3.0 (2.8)	6.7 (5.2)	7.1 (5.3)	3.6 (3.8)
MAP at biopsy (mmHg)	99.2 (15.8)	95.9 (14.6)	101.5 (16.3)	100.7 (15.3)	96.6 (17.2)	96.2 (17.2)	96.5 (15.4)	100.6 (14.8)
Duration of follow-up (years)	5.7 (4.1)	4.6 (4.0)	5.7 (3.9)	5.9 (4.1)	6.8 (4.0)	7.1 (4.0)	6.1 (4.0)	4.4 (3.9)
Total patient-years of follow-up	17 039	1591	2806	4428	2463	1404	2476	1871
Progression to ESRD, *n* (%)	689 (23.1)	88 (25.4)	180 (36.7)	179 (23.7)	48 (13.3)	9 (4.5)	49 (12)	136 (32.3)
Time from biopsy to ESRD (years)	2.57 (2.92)	1.61 (2.79)	3.52 (2.95)	3.7 (2.82)	2.87 (3.29)	2.51 (4.03)	3.39 (3.27)	1.35 (2.07)
Number of biopsies per year	229.5 (26.2)	26.7 (6.8)	37.8 (9.7)	58.2 (10.1)	27.9 (5.3)	15.3 (2.8)	31.3 (9.8)	32.4 (10.3)
Incidence rate (per 100 000 population per year)	8.14 (0.82)	0.94 (0.21)	1.36 (0.4)	2.06 (0.32)	1.00 (0.23)	0.54 (0.1)	1.11 (0.3)	1.14 (0.32)

Data presented as mean (SD) or count (percentage). MAP, mean arterial blood pressure.

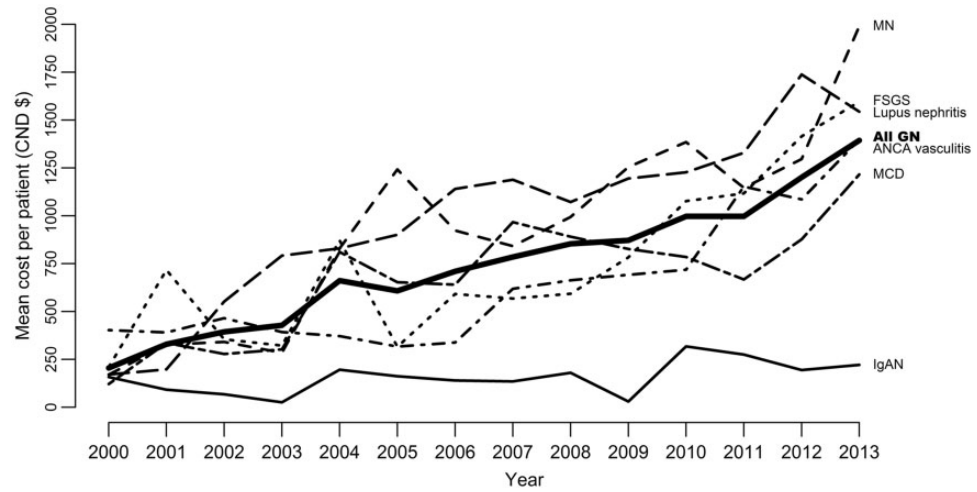

FIGURE 2: The mean cost of IS medications per treated patient each year amongst different types of GN. Costs are in 2016 Canadian dollars.

majority (64.6–91.8%) of the yearly medication costs. Rituximab was used only in 2013, but constituted 31.4% of per-patient medication costs and was used in only 3.4% of patients.

In FSGS, there was a significant decrease in the per-patient medication costs of prednisone ($P = 0.03$) and cyclophosphamide ($P = 0.04$), with increasing costs of CNI ($P < 0.001$) and MMF ($P < 0.001$). From 2000 to 2002, prednisone was used in 90.3–94.1% and cyclophosphamide in 8.3–23.5% of patients, which reduced to 70.8% and 2.8% respectively by 2013. By comparison, the use of CNI and MMF increased such that by 2013 MMF was used in 12.5% and CNI in 40.3% of patients and collectively contributed the majority (85.3%) of the mean yearly per-patient medication costs. Rituximab medication costs increased in the last 2 years of follow-up but did not reach statistical significance ($P = 0.19$), contributing 11.7–13% of the per-patient medication costs and being used in only 1.2–1.4%

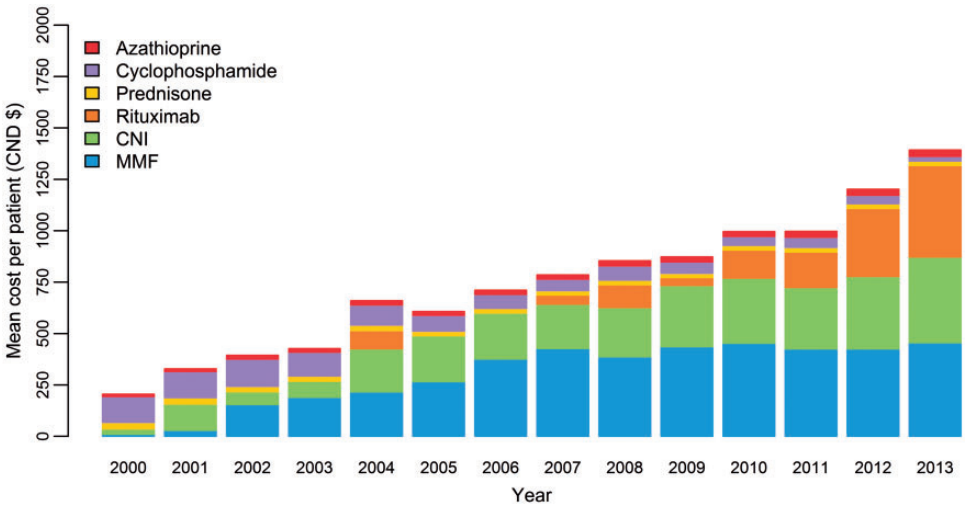

FIGURE 3: Amongst all GN patients, the mean cost per treated patient each year for different types of IS medications. Costs are in 2016 Canadian dollars.

of patients. The results for MCD were similar to FSGS (data not shown).

In ANCA vasculitis, throughout the entire duration of follow-up there was a significant decrease in the mean per-patient yearly medication cost of cyclophosphamide ($P < 0.001$) and an increase in the cost of MMF ($P < 0.001$), with a significant increase in the cost of rituximab ($P < 0.001$) from 2007 onwards. During the period from 2000 to 2002, cyclophosphamide was used in 64.9–83.3% of patients and constituted the majority (76.2–90.3%) of the per-patient medication costs each year, with rituximab not being used at all. In comparison, from 2011 to 2013 rituximab was used to treat a minority of patients (4.1–7.9%) but contributed 61.9–72.7% of the yearly per-patient medication costs. In 2000, MMF was not used at all, but this increased during the follow-up period such that by 2013 it was used to treat 10.9% of patients and contributed 16.4% of the yearly per-patient medication costs.

In lupus nephritis, the cost of MMF increased substantially over the entire follow-up period ($P < 0.001$), as did the percentage of patients treated with MMF (from 3.3% to 55.3%) and the contribution to the mean yearly per-patient medication costs (from 17.6% up to 68.3%). In parallel, the medication cost of cyclophosphamide decreased significantly ($P < 0.001$). In 2000, cyclophosphamide was used to treat 13.3% of lupus nephritis patients and contributed 48.2% of the mean yearly per-patient medication cost, compared with only 2 and 0.5%, respectively, in 2013. The per-patient medication costs of rituximab increased significantly ($P = 0.003$), such that from 2011 to 2013 despite rituximab being used in only 1.5–3.5% of lupus nephritis patients, it constituted 12.6–25% of the mean yearly per-patient medication costs.

Sensitivity analyses

Over the study period, the medication costs per treated patient increased significantly for both IS medications given within the first year of biopsy ($205–$767, $P = 0.001$), and those given >1 year after biopsy ($203 to $1360, $P < 0.001$). Amongst those with lupus nephritis, the per-patient medication costs increased significantly in those with Class III or IV (±V) disease ($209 to $1592, $P < 0.001$), pure Class V disease ($118 to $1002, $P = 0.016$) or other types of renal lupus ($48 to $1831, $P < 0.001$).

DISCUSSION

We used a large population-level cohort of all patients with biopsy-proven GN to describe temporal changes in the cost of IS medications for glomerular diseases within the current era. This is the first study to quantify the real-world medication costs of immunotherapy for GN, and demonstrates a 6.8-fold increase in per-patient treatment costs from 2000 to 2013. This was due to both the widespread more frequent use of newer and more expensive medications such as MMF and CNI instead of cheaper alternatives such as cyclophosphamide or prednisone, and due to a small proportion of GN patients that were treated with disproportionately expensive therapies such as rituximab.

We observed that patterns of drug use contributing to rising medication costs over time differed by type of GN and paralleled evolving literature in the field. For example, the increasing medication cost of treating MN was due to the more frequent use of CNI over the entire duration of follow-up instead of cyclophosphamide, and to the recent use of rituximab. This parallels the publication of clinical trials in the late 1990s advocating the use of CNI and the recent literature on the efficacy of rituximab [15, 16, 18–20]. A similar pattern was observed in FSGS [32–35]. The use of MMF for the treatment of lupus nephritis steadily increased as of 2000 with a parallel reduction in the use of cyclophosphamide, which mirrors the early publications from 2000 to 2005 and the Aspreva Lupus Management Study (ALMS) trial in 2009 suggesting that MMF is equivalent to cyclophosphamide for induction therapy [11, 12, 36]. Rituximab use in ANCA vasculitis increased dramatically after 2010, which corresponds to the Rituximab in ANCA-Associated Vasculitis (RAVE) trial and rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) trial trials demonstrating the efficacy of rituximab for induction

Table 2. The percentage of treated patients each year that used each type of IS medication

Year	2000	2001	2002	2011	2012	2013
All GN						
Azathioprine	18.9	15.8	22	26.3	23.0	24.3
Cyclophosphamide	28.9	31.1	28.9	11.6	9.8	7.1
Prednisone	97.8	93.8	89.0	81.6	82.2	78.0
Rituximab	0	0	0	1.2	2.2	3.5
CNI	1.1	5.1	3.7	12.1	14.2	16.5
MMF	1.1	5.1	11	24.3	22.7	24.6
MN						
Azathioprine	12.5	5.3	12.5	9.1	7.1	7.9
Cyclophosphamide	37.5	52.6	59.4	26.1	19.4	15.7
Prednisone	100	94.7	81.3	71.6	71.4	68.5
Rituximab	0	0	0	0	0	3.4
CNI	0	0	3.1	35.2	42.9	47.2
MMF	0	5.3	6.3	11.4	7.1	9.0
FSGS						
Azathioprine	0	4.2	9.7	9.7	3.7	9.7
Cyclophosphamide	23.5	8.3	12.9	6.9	3.7	2.8
Prednisone	94.1	91.7	90.3	79.2	84	70.8
Rituximab	0	0	0	0	1.2	1.4
CNI	5.9	25.0	12.9	31.9	35.8	40.3
MMF	0	4.2	0	12.5	12.3	12.5
ANCA vasculitis						
Azathioprine	0	16.7	35.1	58.8	47.5	58.4
Cyclophosphamide	73.3	83.3	64.9	29.9	30.3	14.9
Prednisone	100.0	93.3	81.1	78.4	82.0	72.3
Rituximab	0	0	0	4.1	4.9	7.9
CNI	0	0	0	0	0.8	1.0
MMF	0	0	2.7	12.4	9.0	10.9
Lupus nephritis						
Azathioprine	40.0	30.4	33.8	34.4	31.0	28.6
Cyclophosphamide	13.3	10.7	13.0	2.1	2.0	2.0
Prednisone	100.0	96.4	89.6	87.2	83.3	80.4
Rituximab	0	0	0	1.5	3.0	3.5
CNI	0	1.8	2.6	3.1	3.4	4.5
MMF	3.3	10.7	28.6	55.9	56.7	55.3
IgAN						
Azathioprine	50.0	11.1	6.7	10.4	12.9	11.9
Cyclophosphamide	25.0	11.1	13.3	3.0	3.5	4.8
Prednisone	100.0	100.0	100.0	89.6	89.4	89.3
Rituximab	0	0	0	1.5	1.2	1.2
CNI	0	0	0	1.5	2.4	1.2
MMF	0	0	0	4.5	5.9	4.8

Values are represented in percentages. For ease of presentation, data are shown for the years 2000–02 and 2011–13 only; however, monotonic trends persisted in between. The results for MCD are similar to those for FSGS.

therapy [21, 22]. Conversely, the medication costs for IgAN did not change over time, likely because steroids remain the only sufficiently studied therapy to warrant a kidney disease improving global outcomes (KDIGO) guideline recommendation for the majority of patients [1, 37]. These patterns suggest that the increasing medication costs for treating glomerular diseases reflect the dissemination of published literature into clinical practice, and underscore the need for comprehensive cost-effectiveness analysis as future research identifies more effective and less toxic therapies that will almost certainly be more expensive.

This is the first study to systematically describe the population-level medication costs of treating glomerular diseases. A substantial strength of our analysis is that we captured all newly biopsied patients in an entire province, thereby generating a population cohort without the selection bias affecting research-based registries that are more typically used in GN research. This type of data is essential for the development of evidence-based health policy for the treatment of GN, and has significant implications for government or private payers of health services for GN patients, that will need to consider both the widespread conversion from cheaper to more expensive treatment options and the use of disproportionately expensive therapies in a relatively small number of patients. Our results suggests that cost-containment efforts will need to anticipate changes in patterns of practice resulting from evolving published literature and that health policy makers will need to additionally consider the quality of evidence that influences treatment decisions. In kidney transplantation, the increasing cost of IS treatment over time is largely due to the use of biologic induction therapies, which is supported by a Grade 1B recommendation in the KDIGO guidelines [24, 38]. In comparison, there is a known deficiency of randomized trials in GN such that 78% of the KDIGO GN guideline recommendations are based on low or very low quality of evidence (Grades C–D) [1, 39]. Our finding that MMF has replaced cyclophosphamide in the majority of patients with lupus nephritis, thus contributing to a 9-fold increase in medication costs, may be justified by a high grade (1B) guideline recommendation and the desire to avoid alkylating-agent toxicity in a younger, mostly female population [1]. Conversely, the more frequent use of CNI and MMF instead of steroids for the treatment of FSGS is supported by only weak (Grade 2C–D) guideline recommendations, and may reflect previously described suboptimal dissemination of GN guidelines into clinical practice and, therefore, may be amenable to health policy intervention [1, 40]. For example, our results suggest that the RAVE and RITUXVAS trials correspond to a small shift in prescribing practices in ANCA vasculitis affecting only 7.9% of patients, but that resulted in rituximab contributing 72.7% towards a 3.5-fold increase in the yearly per-patient medication costs for vasculitis [21, 22]. As a result, the BC Renal Agency implemented a policy regulating rituximab for use only in patients with a contraindication to cyclophosphamide, which is supported by a Grade 1B KDIGO guideline recommendation (www.bcrenalagency.ca) [1].

When considering the health policy implications of our results, it is important to contextualize the rising costs of IS treatment for GN with the economic implications of disease progression to ESRD and the impact on quality of life. A prior study demonstrated that 83–86% of nephrologists describe negative impacts on patient care that result from having poor access to funding for IS medications for GN [40]. This suggests that part of the current 16.3–22% of ESRD in USA and Canada that is due to GN may result from poor access to IS treatments capable of reducing the risk of renal function decline [28, 41]. As such, future health policy decisions to improve access to IS therapies for GN will need to weigh the increasing medication costs against the potential for significant health-care cost savings that result from delaying or preventing progression to ESRD. Our results demonstrate that despite increasing medication costs to $1394 per treated GN patient in 2013, this represents only a small fraction of the cost of haemodialysis.

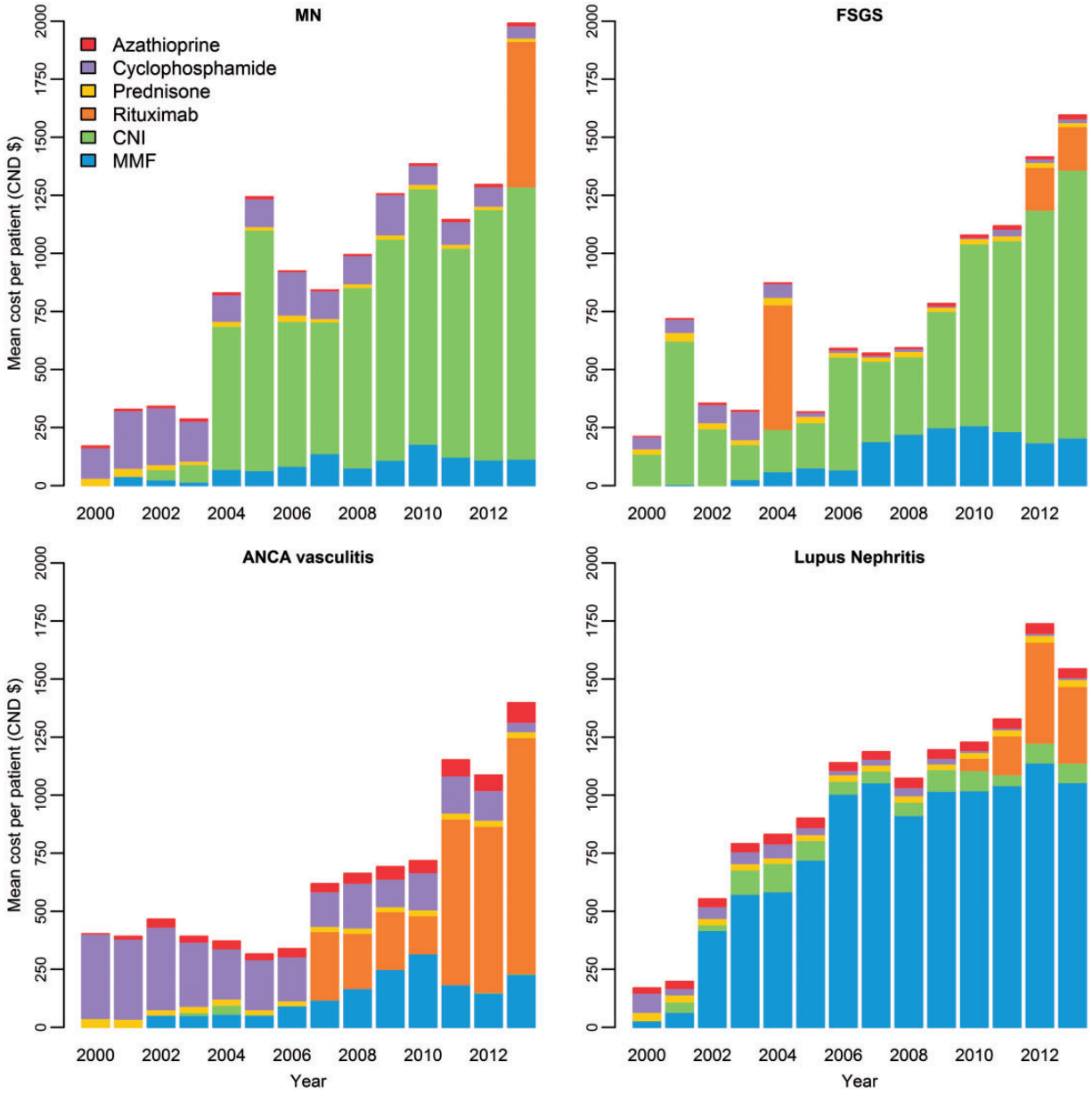

FIGURE 4: The mean cost per treated patient each year for different types of IS medications, in those with MN, FSGS, ANCA vasculitis and lupus nephritis. Costs are in 2016 Canadian dollars.

Although we did not perform a formal cost-effectiveness analysis, this does suggest that from a health services provider point of view even a minimum delay in the progression to ESRD would be worth the increasing costs of treatment. Furthermore, IS therapies that reduce disease activity in GN may be associated with improved patient-reported outcomes and quality of life [42]. This underscores the need for future clinical trials and observational studies to not only consider surrogate outcomes such as changes in proteinuria and eGFR as have been recently advocated [43–45], but to also quantify the anticipated delay in progression to ESRD and improvement in quality of life in order to inform cost-effectiveness analyses that can evaluate the cost versus benefit of newer, more expensive therapies.

There are several limitations to consider when interpreting our results. We attributed all IS exposure up to 6 months after the onset of ESRD to the treatment of GN, which we cannot differentiate from IS treatment for other indications or for extra-renal manifestations of systemic diseases such as lupus. However, our results for lupus nephritis were unchanged when restricted to more severe classes of disease (III, IV or V) in which treatment is commonly dictated by the presence of nephritis, suggesting minimal bias from the treatment of extra-renal lupus. The dose of intravenous cyclophosphamide was imputed in a small minority (2.4%) of the cohort. Due to the inexpensive drug cost for this medication, our results did not change in sensitivity analyses in which we varied the imputed dose by up to 100%. We do not have data on medications used during hospital admissions; however, because IS medications are usually continued after discharge, their outpatient use is captured in our dataset. As such, there is likely minimal impact on our cost calculations. This was an incident, and not prevalent cohort. Consequently, the earlier follow-up period may not have

captured patients on longer-term treatment during which more expensive therapies may have been preferentially given. This is unlikely to have substantially influenced our results because the median duration of treatment for each patient was only 2.0 years, and as such this limitation would not explain our findings that treatment costs continued to increase throughout the entire follow-up period, and medication costs within the first year and more than 1 year after biopsy both increased significantly over time. Our results do not constitute a formal evaluation of the cost effectiveness of different IS regimens for the treatment of GN, which would need to additionally consider adverse events, patient outcomes and other treatment-related costs not captured in this analysis. Future cost-effectiveness research will be required to determine a minimum delay in progression to ESRD or improvement in other health outcomes as a result of IS treatment that would justify increasing medication costs. Finally, our absolute per-patient treatment costs may not generalize to other jurisdictions with different funding models and drug costs. However, we believe that the relative changes in costs over time are likely to be applicable in similar health-care systems.

In conclusion, we describe for the first time the real-world population-level medication cost of IS treatment for glomerular diseases, and have demonstrated a striking increase in medication costs due to the more frequent use of newer, more expensive therapies such as MMF and CNI instead of older, cheaper alternatives, and due to a small minority of GN patients being treated with disproportionately expensive immunotherapies such as rituximab. Our results provide important information to guide future health policy efforts that ensure cost-effective treatment strategies in glomerular diseases.

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SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

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