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International variation in medication prescription rates among elderly patients with inflammatory bowel disease☆

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Abstract

Background and aims: The elderly represent a growing demographic of patients with IBD. No study has previously described variations in care or medication prescriptions in senior patients with IBD. We compared prescription rates among elderly patients with IBD in four countries using health administrative data.
Methods: Databases from the United States (US), United Kingdom (UK), Denmark and Canada were queried. Variation in prescription rates between countries was assessed in patients ≥65 y with prevalent IBD who had ≥1 prescription for an IBD-related medication in a given

Abbreviations: ASA, aminosalicylates; CD, Crohn's disease; DIN, Drug Identification Number; GPRD, General Practice Research Database; IBD, inflammatory bowel disease; MP, mercaptopurine; ODB, Ontario Drug Database; SASP, sulfasalazine; TR, Thompson Reuters; UC, ulcerative colitis; UK, United Kingdom; US, United States.

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quarter between 2004 and 2009. Patients were identified using previously-reported, validated algorithms. Country-specific rates were compared in each quarter using Fisher's exact test.

Results: In patients with Crohn's disease, Canada and US had higher prescription rates for oral 5-ASA ($P<0.0001$ in all quarters) and infliximab ($P<0.05$ in 22/24 quarters), while the US had higher rates of thiopurine usage ($P<0.05$ in 23/24 quarters). Canada had greater rates of methotrexate prescriptions ($P<0.05$ in 21/24 quarters analyzed). In patients with ulcerative colitis (UC), rates of oral steroid usage was lowest in the US ($P<0.05$ in 22/24 quarters) and oral 5-ASA use was highest in the US and Canada ($P<0.0001$ in all quarters). Canada and Denmark used more rectal therapy than the US. Infliximab usage in UC was significantly higher in the US and Canada after 2006.

Conclusions: Significant variation in medication prescription rates exists among countries. Future research should assess whether these differences were associated with disparities in outcomes and health care costs.

1. Introduction

Low fertility and mortality rates are contributing heavily to the aging of populations in developed nations. Countries with the highest percentage of elderly individuals include the United States (US), Canada, and the European countries.[1] The aging population has a huge impact on costs of health care delivery. For example, in Canada alone in 2005, individuals 65 and older accounted for 13.7% of the population, but 60% of all acute care service spending. It is therefore important to study and optimize health care delivery to the elderly.[2] Individuals with inflammatory bowel disease (IBD) represent a chronic disease population with a growing elderly component. Up to 1/3 of new cases of Crohn's disease (CD) occur in elderly patients,[3] and those with long-standing IBD are aging, accounting for a large segment of elderly individuals living with IBD. Little is known about the therapies used internationally in the treatment of IBD in the elderly. A recent study of US hospital discharges showed that geriatric IBD patients accounted for a disproportionate number of admissions; 25% of all IBD-related hospitalizations in 2004.[4] These admissions were associated with substantial morbidity and increased mortality when compared to younger patients. As therapeutic agents have significant implications in both cost and outcomes in IBD, it is important to study prescribing patterns in the elderly and of interest to compare practice patterns internationally.

While variations in care are ubiquitous in medical practice, they can suggest variation in provider or patient preference, regional differences in clinical practice guidelines, as well as system-level differences such as financial reimbursement and insurance policies.[5] Additionally, identification of care variation may facilitate observational and health services research to better understand healthcare utilization, and drug safety in future studies. Previous description of care variations in children with IBD has prompted a quality improvement movement which has positively impacted their outcomes.[6,7] No such assessment of variation in the care of elderly patients with IBD has been undertaken. In this study, we used large, health administrative datasets from the United States of America (US), Canada, the United Kingdom (UK), and Denmark to assess prescription variation among elderly patients with IBD.

2. Materials and methods

This study was approved by the research ethics boards of participating institutions, or has been considered not to be research on human subjects based on analysis of previously collected and de-identified data. Data were shared in aggregate without individual patient data shared across jurisdictions.

2.1. Data sources

We used health administrative or primary care databases to determine medication prescription rates for elderly patients in four jurisdictions. Patients were identified using validated combinations of diagnostic codes derived from both inpatient (except in patients from the UK) and outpatient contacts with their respective health systems. Data from the US were drawn from Thompson Reuters (TR) MarketScan databases (Ann Arbor, Michigan) including the Commercial Claims and Encounters database (January 1, 2000–December 31, 2009), the Medicare Supplemental and Coordination of Benefits database and the Medicaid Multi-State external database (January 1, 2006–December 31, 2009). The TR Commercial data are projectable to the US population covered by employer-sponsored insurance (58% of population) and the TR Medicare data are projectable to the U.S. population with Medicare and supplemental insurance. US Medicare patients required supplemental pharmacy coverage to be included in the TR databases. In 2007, 23% of the 44 million Medicare beneficiaries received their drug benefits through an employer or union-sponsored health plan. The database includes the Medicare-covered portion of payment (represented as Coordination of Benefits Amount), the employer-paid portion, and any out-of-pocket patient expenses. The Medicaid data in the TR database are representative of 12 geographically dispersed US states; these states cannot be identified to ensure anonymity of the population. The number of people >65 years (y) contained within these databases who were eligible for this study ranged from 193,534 to 338,036 from 2004 to 2006 and increased to 2,063,515 to 2,508,534 from 2007 to 2009. Patients with IBD were identified using a previously-described algorithm.[8,9]

Data from Ontario, Canada were derived from provincial health administrative databases (Ontario Health Insurance Plan and Canadian Institute for Health Information Discharge Abstract Database) linked to a database of all prescriptions filled by elderly patients in the province (Ontario Drug Benefits (ODB) database) and the Registered Persons Database. Ontario health administrative data comprise all patients in the province with a valid health card (>99.7% of Ontario's 12.8 million residents, with those >65 y contained within the ODB database increasing from 1,663,774 in 2004 to 1,970,629 in 2009). Since 1991, all health care contacts (inpatient, outpatient, emergency department and surgical procedures) are tracked longitudinally for all qualifying residents of the province. Patients with IBD were identified using an algorithm validated in Manitoba[10] and previously applied across multiple Canadian provinces.[11,12]

Data from the United Kingdom were derived from the General Practitioners Research Database (GPRD), a population-based dataset derived from 629 primary care practices across the UK and comprising approximately 10 million patients, of whom 713,340 to 784,786 were elderly patients.[13] Identification is based on outpatient visits to general practitioners, with coding for IBD cases validated previously using the OXMIS coding dictionary.[14] The newer and more detailed READ coding system is now used.

In Denmark, IBD patients from the central and northern regions (approximately 1/3 of the Danish population corresponding to 1.8 million inhabitants) were derived from the Danish National Patient Register using validated diagnostic codes.[15] Between 241,385 and 279,849 patients were elderly in any given quarter. This registry includes information on all outpatient visits since 1995, non-psychiatric hospitalizations since 1977, and selected in-hospital treatments such as biologic therapies. Prescriptions for Danish IBD patients were identified in Aarhus University Prescription Database, which include all reimbursed medication in the central and northern Denmark regions beginning in 1989 (complete coverage from 1998).[16]

Diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) were derived using algorithms specific to the database and jurisdiction of patient origin.[8,14,17,18] Patients with codes that could not distinguish the diagnosis of CD from UC were excluded from this study. Details on each jurisdiction's identification and classification algorithms are presented in Supplemental Table 1.

To identify prescriptions in each database, Canadian drug identification numbers (DINs) were adapted to the appropriate jurisdictional codes and used to identify IBD-related medications (see Supplemental Table 2 for DIN codes used). Prescriptions for biologic therapies are not available in the GPRD and therefore the UK was excluded from these analyses. Additionally, there was negligible usage of certolizumab, golimumab and natalizumab in all jurisdictions and therefore these medications were not included in the analyses.

2.2. Study design

We conducted a series of rolling cross-sectional comparisons in each quarterly period from January 2004 through December 2009 (total 24 quarters). In each quarter, patients were included in the study if they were prevalent cases of CD or UC (or were newly diagnosed during that quarter), ≥65 y (including those turning 65 years of age within that quarter) and filled ≥1 prescription for any IBD-related medication. Patients were excluded from analysis in a quarter if they had not yet been diagnosed with IBD, had died, did not have an IBD-related prescription, were <65y, or were not contained within the database during that entire quarter (due to emigration or loss of insurance coverage). Therefore a patient could be included in some quarters but excluded from others, and the patients included in each quarterly analysis were different depending on qualifying criteria. We calculated medication prescription rates for each IBD-related medication, defined as the number of patients who filled a prescription for that medication divided by the total number of patients who filled a prescription for any IBD-related medication during that quarter.

2.3. Statistical analysis

IBD-related medication prescription rates were computed quarterly for each jurisdiction and compared between jurisdictions for each quarter between 2004 and 2009. Statistical comparisons between jurisdictions were performed using the Fisher exact test, with P values of <0.05 being considered significant. As different patients were included in the numerator and denominator of each quarterly analysis, each was considered a distinct analysis and no correction for multiple testing was performed. However to provide measures of confidence in statistical comparisons, wherever P values are noted, we provided the number of quarters (out of a possible 24 quarters) with P values of <0.05, <0.01 and <0.001. All statistical analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC).

3. Results

The proportion of patients with ≥1 prescription for an IBD-related medication is described in Table 1. Quarterly, approximately 54.7–73.0% of US patients, 43.2–47.7% of Canadian patients, 34.1–38.0% of Denmark patients, and 47.2–57.7% of UK patients had at least one prescription. In general, the proportion of patients treated with any IBD medication remained stable for each jurisdiction between 2004 and 2009, except in the UK where approximately 10% more patients had at least one prescription in later years. Prescription rates of commonly used medications are presented in Fig. 1 (for CD patients) and Fig. 2 (for UC patients).

3.1. 5-Aminosalicylates (ASA) and sulfasalazine (SASP)

Of patients with ≥1 prescription for any IBD-related medication, Canadian patients were most likely to receive an oral 5-ASA medication in any given quarter, with lowest rates in UK patients (see Fig. 1b for CD patients and Fig. 2c for UC patients). This was true for both CD and UC patients ($P<0.0001$ in all quarters between 2004 and 2009) until 2007 when Denmark patients with CD began having lower usage of 5-ASAs. Conversely, Canadian patients were less likely to

Table 1 The number of elderly patients with IBD identified in each jurisdiction by quarter 2004–2009, and the proportion of patients with at least one prescription in each quarter 2004–2009. Quarterly comparison of medication prescription rates was conducted on those with at least one prescription in that quarter.

	Ontario, Canada		Denmark		UK		USA	
	IBD patients ≥65 y	Patients with any IBD prescription (%)	IBD patients ≥65 y	Patients with any IBD prescription (%)	IBD patients ≥65 y	Patients with any IBD prescription (%)	IBD patients ≥65 y	Patients with any IBD prescription (%)
2004–Q1	9742	4596 (47.2%)	1481	527 (35.6%)	8067	3808 (47.2%)	304	201 (66.1%)
2004–Q2	9921	4653 (46.9%)	1508	561 (37.2%)	8119	3853 (47.5%)	278	167 (60.1%)
2004–Q3	10,046	4796 (47.7%)	1535	554 (36.1%)	8088	3931 (48.6%)	225	123 (54.7%)
2004–Q4	10,189	4583 (45.0%)	1553	581 (37.4%)	8053	3971 (49.3%)	171	96 (56.1%)
2005–Q1	10,339	4852 (46.9%)	1573	586 (37.3%)	8499	4158 (48.9%)	426	262 (61.5%)
2005–Q2	10,497	4831 (46.0%)	1602	608 (38.0%)	8431	4172 (49.5%)	373	243 (65.1%)
2005–Q3	10,631	4977 (46.8%)	1611	604 (37.5%)	8356	4152 (49.7%)	281	174 (61.9%)
2005–Q4	10,796	4849 (44.9%)	1632	603 (36.9%)	8294	4197 (50.6%)	200	126 (63.0%)
2006–Q1	10,994	5153 (46.9%)	1660	608 (36.6%)	8674	4391 (50.6%)	618	419 (67.8%)
2006–Q2	11,170	5237 (46.9%)	1683	625 (37.1%)	8579	4404 (51.3%)	902	648 (71.8%)
2006–Q3	11,334	5373 (47.4%)	1710	606 (35.4%)	8490	4306 (50.7%)	1314	943 (71.8%)
2006–Q4	11,469	5264 (45.9%)	1729	647 (37.4%)	8479	4438 (52.3%)	1614	1179 (73.0%)
2007–Q1	11,674	5485 (47.0%)	1808	657 (36.3%)	8903	4715 (53.0%)	2410	1671 (69.3%)
2007–Q2	11,873	5438 (45.8%)	1832	676 (36.9%)	8733	4583 (52.5%)	2631	1827 (69.4%)
2007–Q3	12,019	5673 (47.2%)	1852	685 (37.0%)	8644	4657 (53.9%)	2812	1967 (70.0%)
2007–Q4	12,172	5498 (45.2%)	1900	696 (36.6%)	8562	4679 (54.6%)	2927	2081 (71.1%)
2008–Q1	12,344	5732 (46.4%)	1917	712 (37.1%)	9092	4905 (53.9%)	3592	2468 (68.7%)
2008–Q2	12,525	5776 (46.1%)	1947	705 (36.2%)	8965	4925 (54.9%)	3657	2518 (68.9%)
2008–Q3	12,661	5894 (46.6%)	2007	708 (35.3%)	8838	4827 (54.6%)	3674	2513 (68.4%)
2008–Q4	12,766	5652 (44.3%)	2044	744 (36.4%)	8728	4884 (56.0%)	3671	2511 (68.4%)
2009–Q1	12,942	5972 (46.1%)	2061	743 (36.1%)	9311	5096 (54.7%)	3946	2633 (66.7%)
2009–Q2	13,107	6009 (45.8%)	2084	743 (35.7%)	9181	5167 (56.3%)	4033	2713 (67.3%)
2009–Q3	13,242	6065 (45.8%)	2114	743 (35.1%)	8963	5105 (57.0%)	4026	2670 (66.3%)
2009–Q4	13,361	5777 (43.2%)	2150	734 (34.1%)	8860	5110 (57.7%)	3922	2604 (66.4%)

receive SASP or salazopyrin, with highest rates in UK patients ($P<0.0001$ in all quarters for both CD and UC). Over time, patients from Canada and Denmark with CD were less likely to be prescribed a 5-ASA, while prescription rates in the UK and US were stable. Prescriptions of SASP remained relatively stable over time.

Prescriptions for rectal 5-ASA therapy were negligible in patients with CD (data not shown). In UC, prescriptions for rectal 5-ASA therapy were markedly higher in Denmark and Canada than in the US and the UK, with very low rates in the UK (see Fig. 2d, P<0.0001 in all quarters between 2004 and 2009). Rectal therapy rates decreased over time in the US, from 6.1–10.6% in 2004 to 5.1–6.6% in 2009. Rates remained relatively stable over time in the other jurisdictions.

3.2. Systemic and topical corticosteroids

In patients with CD, prescriptions for oral systemic steroids were higher in Denmark than other countries (see Fig. 1a, P<0.05 in 18/24 quarters, P<0.01 in 12/24 quarters). Rates were relatively stable over time. The quarterly prescription rate for CD ranged in 2004 to 2009 from 25.3–33.5% in Denmark, 18.6–23.3% in Canada, 20.3–33.3% in the US and 17.9–22.1% in the UK. In patients with UC, oral systemic corticosteroid prescriptions were highest in the US (21.4–35.9%), followed by Denmark (16.6–22.5%), with Canada (14.6–17.1%) and the UK (14.3–16.3%) having similarly low rates (see Fig. 2a, P<0.05 in 22/24 quarters, P<0.01 19/24 quarters, P<0.001 in 18/24 quarters). Rates in UC were stable over time. The use of budesonide in CD was highest in the US (4.4–15.1%), followed by Denmark (3.4–8.8%), with Canadian (0.7–1.6%) and UK (1.0–2.4%) rates being similarly low (P<0.01 in 24/24 quarters, P<0.001 in 22/24 quarters). Budesonide use in UC patients was negligible (data not shown).

Rectal corticosteroid use mirrored that of rectal 5-ASA therapy and remained stable over time. CD patients rarely used rectal steroids (data not shown), but rates in UC patients were significantly lower in the US compared with other jurisdictions (see Fig. 2b, P<0.05 in 21/24 quarters, P<0.01 in 19/24 quarters, P<0.001 in 13/24 quarters). Quarterly prescription rates ranged from 4.8–7.7% in the UK, 3.2–8.2% in Denmark, 4.0–6.4% in Canada and 0–2.6% in the US.

3.3. Immunosuppressive medications

For patients with CD, use of azathioprine or mercaptopurine (MP) was consistently higher in the US than other jurisdictions (see Fig. 1c, P<0.05 in 23/24 quarters, P<0.01 in 19/24 quarters and P<0.001 in 18/24 quarters). Rates ranged from 15.8–34.8% in the US, 12.9–18.5% in Canada (with increasing rates over time), 11.6–20.0% in Denmark (with increasing rates over time), and 10.4–13.9% in the UK (with a slight increase over time). In UC patients, rates were again highest in the US (see Fig. 2e, P<0.05 in 22/24 quarters, P<0.01 in 21/24 quarters, P<0.001 in 19/24 quarters). Rates ranged from 10.2–26.2% in the US, 6.4–10.6% in Canada (with increasing rates over time), 7.3–10.9% in Denmark, and 5.6–7.4% in the UK.

For methotrexate, prescription rates among CD patients were consistently higher in Canada with an increased difference compared to other jurisdictions in later years (see Fig. 1d, P<0.05 in 21/24 quarters, P<0.01 in 18/24 quarters, P<0.001 in 12/24 quarters, and P<0.001 in all quarters after 2007). Canadian methotrexate prescription rates were 3.0–3.3% in 2004, and increased to 6.0–6.5% in 2009. Danish prescription rates increased from 0.7–2.1% in 2004 to 4–5.5% in 2009. American prescription rates remained stable and ranged from 1.4–5.9% and UK rates ranged from 1.3–3.1%. Methotrexate prescriptions were lower in UC patients and not significantly different between jurisdictions (P<0.05 in only 2/24 quarters). Rates were 1.5–2.0% in Canada, 1.6–3.6% in Denmark, 1.4–2.0% in the UK and 1.2–6.1% in the US.

Prescription rates for tacrolimus or cyclosporine in patients with CD were <0.5% in every quarter for all jurisdictions except the US (range 0–2.3%). Similarly, usage of tacrolimus and cyclosporine in UC patients was consistently <0.5% except in the US where rates ranged from 0.8–3.0% (P<0.05 in 16/24 quarters, P<0.01 in 8/24 quarters, P<0.001 in 5/24 quarters).

3.4. Biologic therapies

Records of biologic prescriptions (infliximab or adalimumab) were not available for UK patients. Prescriptions of biologics were consistently higher in the US than in Canada or Denmark (P<0.05 in 22/24 quarters, P<0.01 in 21/24 quarters, P<0.001 20/24 quarters) and have increased over time. For CD patients, rates increased from 1.8–7.9% in 2004 to 12.7–15.2% in 2009 in the US (see Fig. 1e). Similarly in Canada, rates increased from 1.2–1.8% in 2004 to 5.4–5.9% in 2009. In Denmark, rates increased from 0% in 2004 to 1.7–2.9% in 2009. For UC patients, infliximab prescription rates were <1% per quarter until 2006 when increased utilization was noted in the US and Canada (see Fig. 2f). For the US, prescription rates were stable, and were 3.5–5.7% in 2006 and 4.2–5.3% 2009. Rates increased in Canada from 0.2–0.4% in 2006 to 1.2–1.7% in 2009. Rates in Denmark remained relatively stable (0.2–0.4% in 2006 and 0.2–0.5% in 2009). There were significant differences between jurisdictions from 2006 onward (P<0.0001 in 16/24 quarters, and all quarters after Q1-2006; P>0.05 in all quarters before Q1-2006).

Adalimumab prescriptions were insignificant before 2007 and then increased most rapidly in the US followed by Denmark and Canada. In patients with CD, prescription rates in the US were 2.0–3.1% in 2007 and 4.9–6.0% in 2009. Rates in Denmark were 0.6–1.6% in 2007, and 1.2–2.3% in 2009. Rates in Canada were 0.1–0.2% in 2007, and 1.4–1.8% in 2009. In CD patients, rates were significantly different between jurisdictions (P<0.05 in 14/24 quarters, and P<0.001 in 12/12 quarters after Q1-2007). Similarly, adalimumab prescriptions in UC patients were highest in the US (P<0.05 in 12/24 quarters, and P<0.001 in 9/12 quarters after Q1-2007). Rates of adalimumab prescriptions were much lower in UC with all jurisdictions reporting rates of <1% in all quarters except in 2009 in the US where rates ranged from 1.2–1.6%.

4. Discussion

In 2009, the UK Department of Health convened the "Extent and Causes of International Variation in Drug Usage" Steering Group. The resulting RAND Europe report reviewed the literature on this topic and found literature in six chronic diseases.[19] IBD was not included in the report due to lack of evidence. To our knowledge, this is the first study to compare medication prescription rates in large international IBD populations. We found a high degree of variability in IBD medication prescription rates across four countries, with an overall trend of rising rates of immunosuppressive and

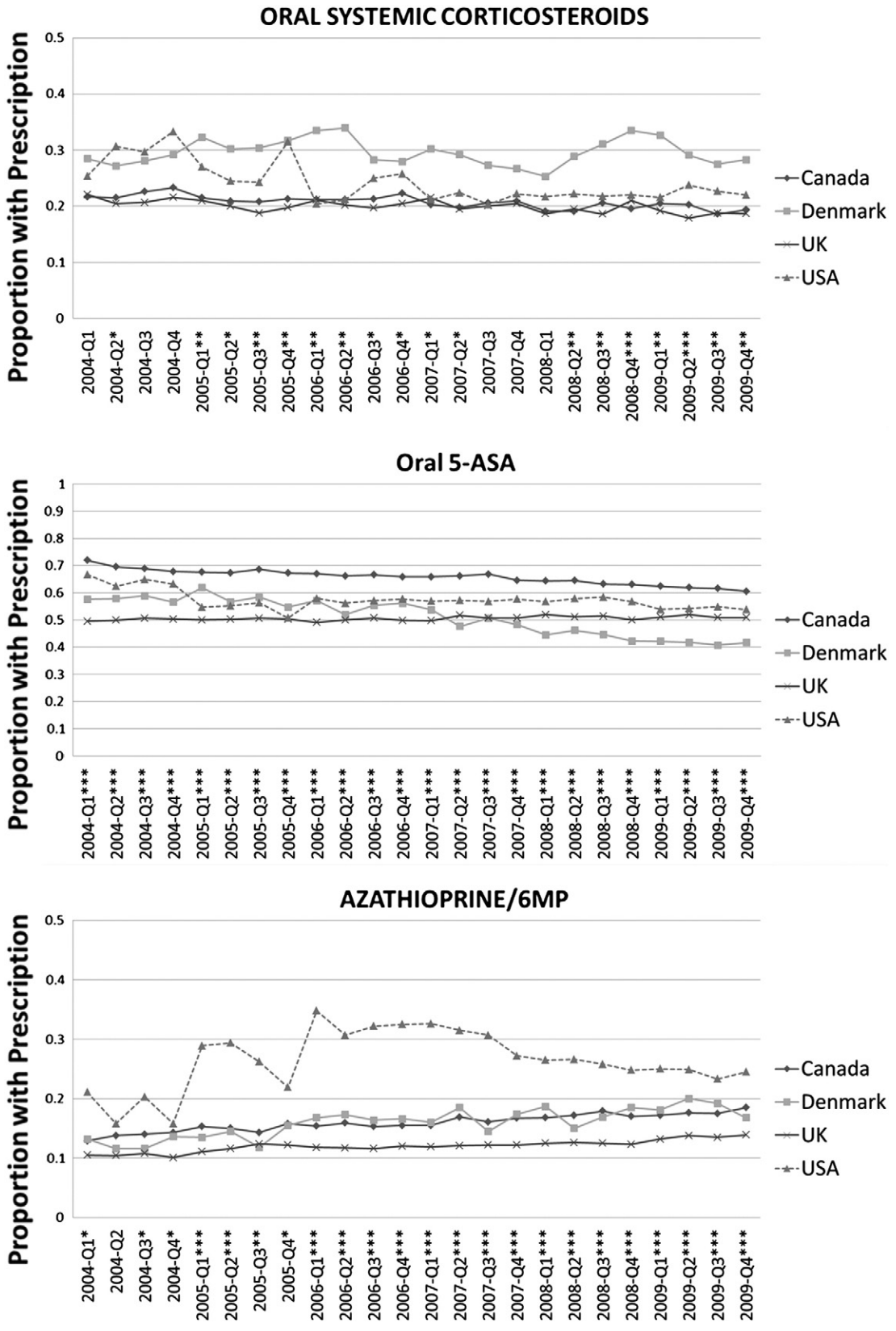

Figure 1 International medication prescription rates per quarter for patients with Crohn's disease. *P<0.05, **P<0.01, ***P<0.001.

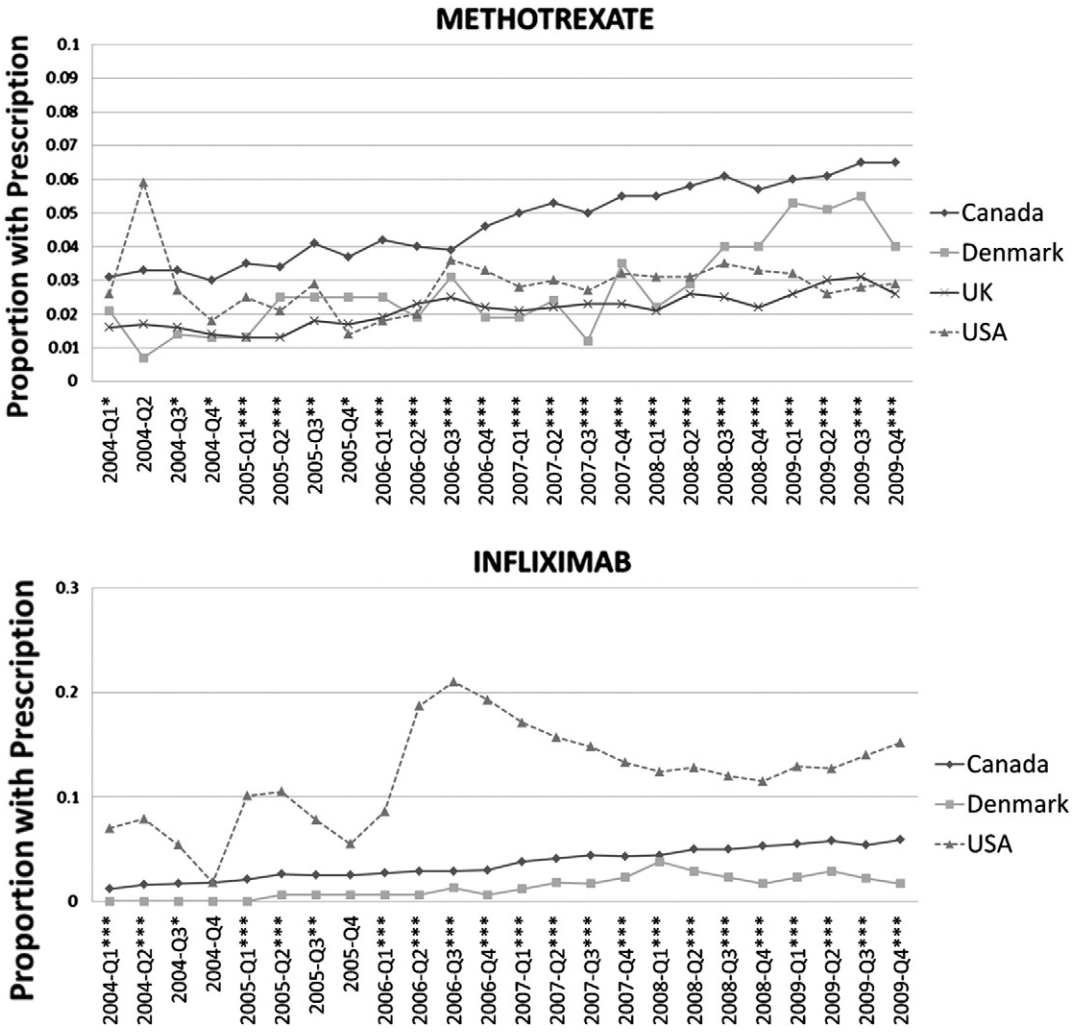

Figure 1 (*continued*).

biologic medication prescription rates. The RAND report concluded that international variation in medication usage is likely multifactorial, encompassing system-level factors, service organization and delivery, and clinical practice variation.[19] Similarly, in elderly patients with IBD, many factors may have contributed to the variability among prescription rates. Firstly, patient and provider preference may determine therapeutic decisions. Tolerance for potential adverse effects, interpretation of efficacy studies and cultural differences may have all played roles. Additionally, variability in medication usage may arise from differences in systems of healthcare delivery and financing, with each country having different policies for medication coverage and health insurance. For example, low rates of budesonide usage in Canada may be secondary to its restricted access by public drug programs in Ontario (and other provinces).[20] Moreover, variation in published treatment guidelines, local expertise and pharmaceutical industry marketing techniques may all have impacted on differences in rates. Finally, variation in prescription rates may be associated with differences in quality of care[5,21] and may represent an area of focus for future quality improvement initiatives.

There was marked variation in 5-ASA and SASP prescription rates across the four countries. Interestingly, there continues to be a high rate of usage of these medications among patients with CD, despite limited evidence for their efficacy.[22–24] The rate of usage decreased gradually over time in most jurisdictions, however 60–70% of CD patients had prescriptions for 5-ASA or SASP in any given quarter. As expected, usage of 5-ASA and SASP was higher in UC patients, with 75–85% (of those receiving any medication) filling a prescription in any given quarter, with no evidence of decreasing prescription rates in UC. Interestingly, there was a high degree of variability of rectal therapy (either 5-ASA or topical corticosteroids) in UC patients, with greater uptake in Denmark and Canada (15–20% of patients), and very low utilization in the US (7–10%). This may represent cultural differences in the acceptance of rectal therapy, physician preference, and/or a difference in disease extent.

Immunosuppressive and biologic utilization also varied significantly among jurisdictions, with a temporal trend toward increased usage in all regions. Patients in the US had markedly increased rates of azathioprine/6-MP and biologic use compared with other jurisdictions, although use of biologics in Canada and Denmark increased in recent years. When use of azathioprine, 6-MP and methotrexate are taken together for CD patients, Canada appeared to have similar utilization of immunosuppressives compared with the US.

This was due to greater use of methotrexate in Canada compared with other countries, perhaps because early efficacy studies of methotrexate originated in Canada.[25]

Unfortunately, the increased use of these medications in recent years was not associated with decreased use of systemic corticosteroids over time. While Denmark (the

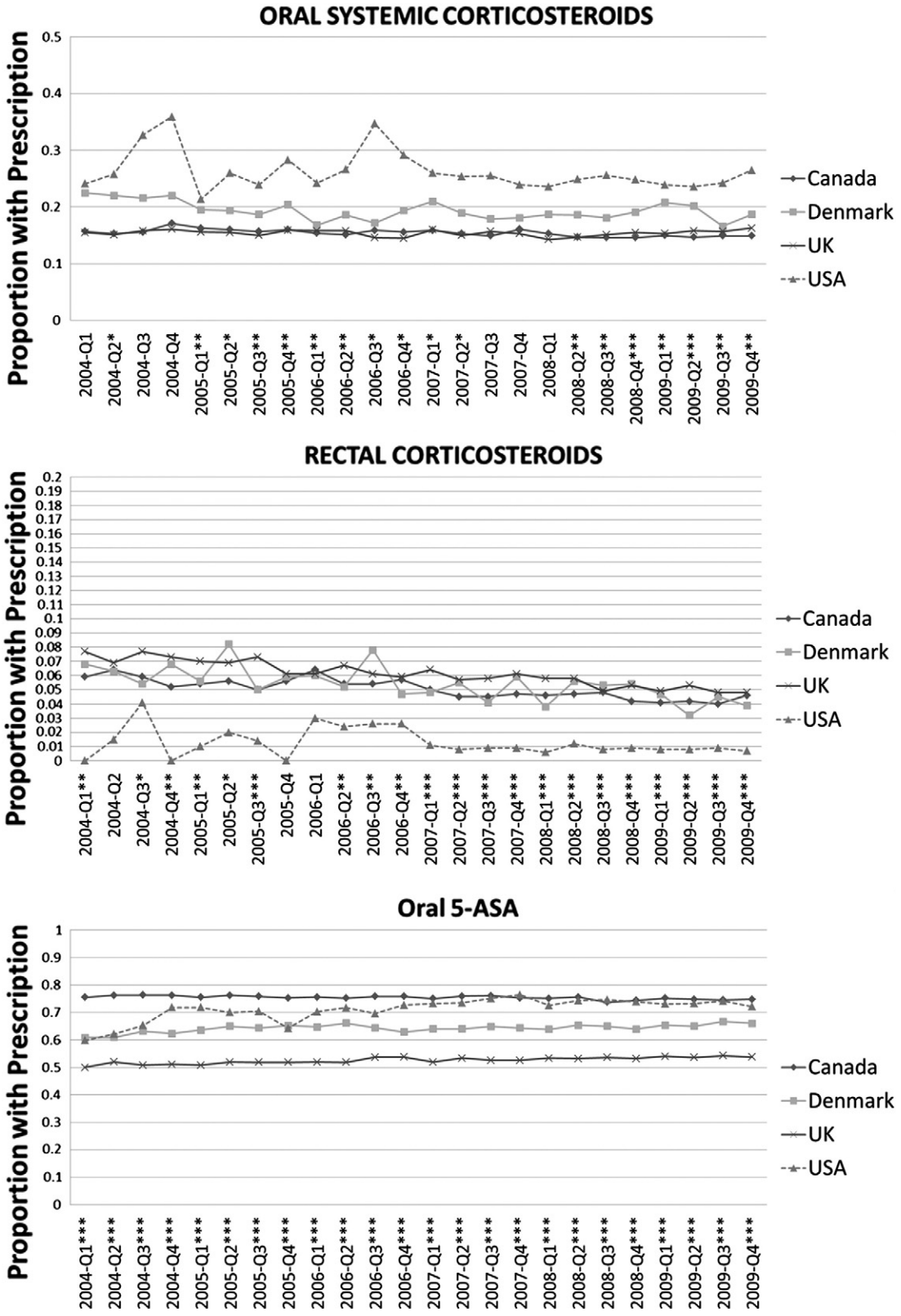

Figure 2 International medication prescription rates per quarter for patients with ulcerative colitis. *P<0.05, **P<0.01, ***P<0.001.

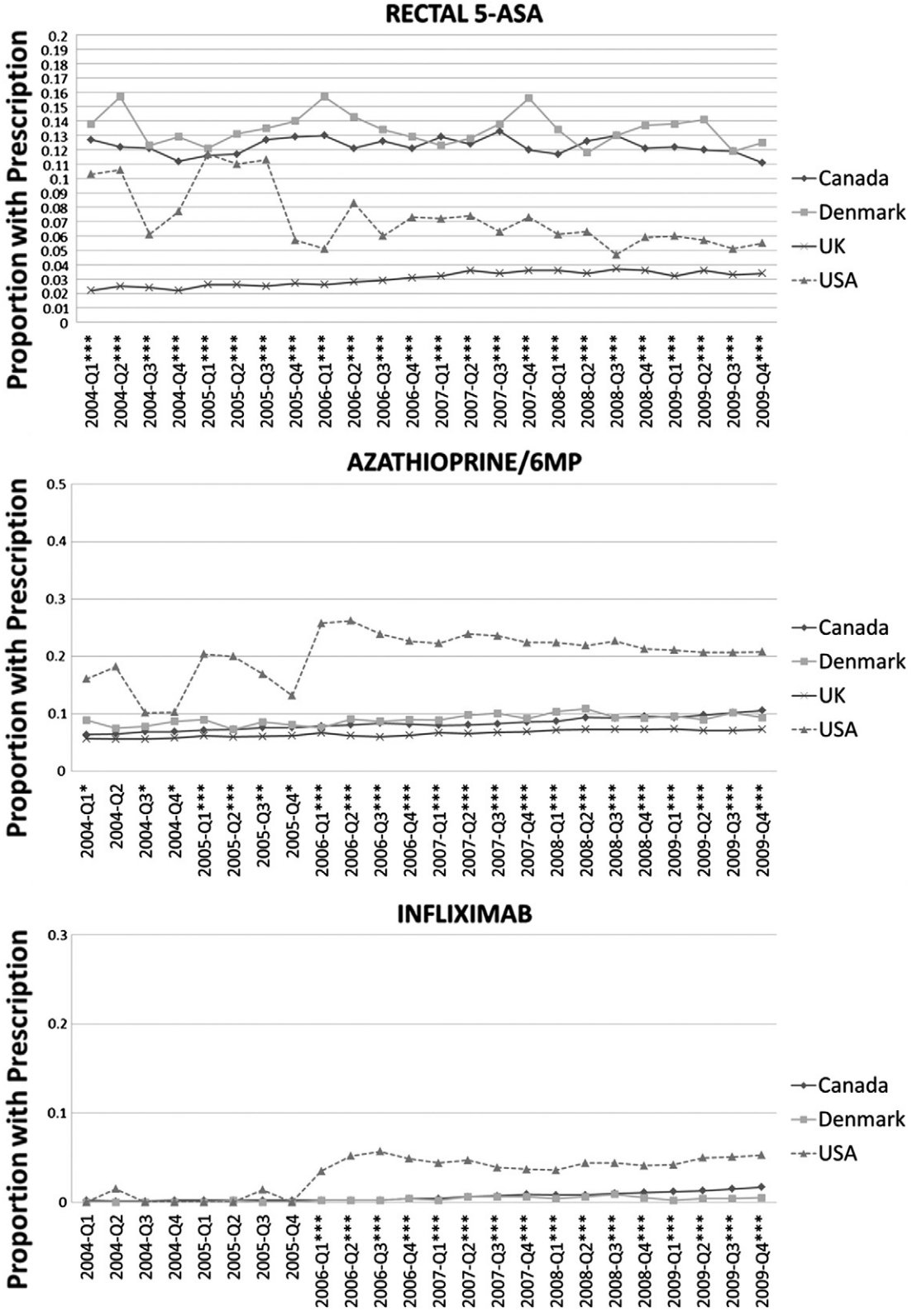

Figure 2 (*continued*).

country with the lowest use of immunosuppressives and biologics) had the highest rate of corticosteroid utilization in CD patients, patients with UC in the US had the highest rates of steroid use despite higher rates of azathioprine and infliximab. Therefore, the higher use of biologic therapy in the US warrants further investigation, particularly to assess whether this more aggressive approach is associated with improved outcomes.

Overall in 2009, 15.8–28.2% of CD patients were on an immunosuppressive (either azathioprine or methotrexate),

while 1.7–15.2% were on a biologic (either infliximab or adalimumab). Of UC patients, 9.1–22.8% were on an immunosuppressive, while 0.7–6.9% were on a biologic. These rates of biologic and immunosuppressive use in the elderly are considerably lower than the rates we described recently for children using similar methodologies and databases.[26] In children with CD, 42.9–82.2% were on an immunosuppressive in 2009, while 17.8–30.9% were on a biologic. In children with UC, 22.2–61.5% were on an immunosuppressive, while 3.3–19.2% were on a biologic.[26] The lower rates among elderly IBD patients may be related to a number of factors. It may be that the elderly have milder disease warranting less therapy. It is also possible that providers question efficacy due to limited data in elderly patients, or are concerned about side effects of these medications in older individuals. There are little safety data specifically in this population. In the rheumatoid arthritis (RA) population, 72 patients over the age of 65 were treated with infliximab in one trial without increased complications.[27] However, randomized controlled trials are likely too short in duration, too specific in inclusion criteria, and too small to detect all complications in elderly patients. A systematic review of the risk of dying from sepsis with infliximab found the risk to be 4/1000 patient years, with increased risk associated with older age, comorbidities, corticosteroids or narcotics, and long-standing disease.[28–30] With increasing age, there is also an increased risk of non-Hodgkin's lymphoma and non-melanoma skin cancer associated with immunomodulators and anti-TNF biologics.[31,32] It is possible that these factors limited the choice for immunosuppressives and biologics by older individuals or their physicians. Poly-pharmacy may also be a concern in elderly patients. Indeed while 43.2–47.7% of Ontario IBD patients in our study had at least one prescription for an IBD-related medication, 88.8–92.5% of patients had a prescription for any medication (data not shown), indicating that most elderly IBD patients are on medication for other conditions. A recent study from the US found that the mean number of drugs regularly used by the elderly population with IBD was 7.0 ± 3.5.[33]

Use of claims data allowed for assessment of large numbers of patients over a prolonged period of time in geographically diverse regions, which may be subject to variations in care provision by many different types of care providers (e.g. primary care physicians, gastroenterologists, surgeons, etc.). Unfortunately, the data do not allow assessment of medication adherence. In the case of Canada, the US and Denmark, rates of prescription filling were measured, rather than rates of written prescriptions. Conversely, the GPRD collects prescriptions in the UK written by general practitioners, or those patients are noted to be taking (prescribed by a specialist) upon contact with their general practitioner, but not dispensation by pharmacies. This difference may have led to different usage rates. However, the overall proportion of patients with a prescription written in the UK was not significantly different from prescription fill-rates in Canada, and rates in the UK and Canada were between prescription-fill rates of Denmark and the US (Table 1). Additionally, rates of complete medication non-compliance for prescribed immunomodulators and biologics have been found to be low (3–4%), demonstrating that medications are at least filled in the vast majority of cases.[34,35] The indications for medication prescriptions could not be determined from the data. This may have led to an overestimation of some medications such as cyclosporine (used in transplant recipients) or methotrexate and biologics (used in arthritis patients).

This study is limited in a number of other ways. The administrative databases in Denmark and Ontario, Canada include all individuals within a given population and the GPRD in the UK collects a representative population from general practices. Notably, the GPRD does not include inpatient prescriptions or those written by discharging physicians, and therefore rates may underestimate acute therapies. However, a medication would be recorded if the patient continued it until their first visit to the general practice. The US database used in this study, although large, does not represent a random sample of the US elderly population. Medicare patients were included in the database only if they had supplemental pharmacy coverage. In 2007, this represented approximately 23% of the US Medicare population, and therefore the US data is not considered population-based. This study could not include IBD patients who did not have contact with the health system or who were uninsured, however this would make up a very small proportion of seniors in three of four jurisdictions as Denmark, the UK and Canada have universal coverage for legal residents. Patients provided with medication supply of more than 6 months would have registered as not having been given that medication in the quarter following their initial prescription. However, we were able to provide a snapshot of the IBD population on a cross-sectional basis for each quarter between 2004 and 2009. Therefore, these biases should balance over time and patients receiving a medication missing from the prescription databases in a given quarter would reappear in a subsequent quarter.

Misclassification bias is always a concern when using health administrative data to assess patients with a chronic disease.[36] Any study using administrative data to examine elderly patients with IBD may risk misclassification of ischemic or infectious colitis as chronic IBD. These are typically self-limited, may not require any specific therapy and therefore may have resulted in lower than expected prescription rates. We identified patients with IBD using validated algorithms and included patients only if they had a prescription for an IBD-related medication during each quarter examined. This minimized the amount of misclassification of non-IBD patients as having IBD, however may have resulted in a cohort comprising patients with more severe disease, since many mild IBD patients may not receive medications for long periods of time. This may explain our high rates of medication utilization compared with a recent study of a 20-hospital setting in Pittsburgh.[33] However, that study only included medications if they were taken continuously for six or more months, examining maintenance or chronic therapies and not short-term or induction prescriptions. Nevertheless the trends described were similar to our study: high use of 5-ASA in both CD and UC (44% of their cohort), high use of chronic systemic corticosteroids (31.6%), low use of rectal corticosteroids (4.8%), and low use of immunosuppressives (5.6% azathioprine, 1.3% methotrexate) and biologics (1.3% infliximab, 1.3% adalimumab).[33] Additionally, the relatively lower usage of biologics and immunomodulators (particularly in Denmark) may have been due to lower sensitivity of codes used to identify prescriptions of those medications. While these have not been validated, a recent assessment of the codes for

bisphosphonates using the same Danish database revealed a high positive predictive value but lower sensitivity.[37] If lower sensitivities are found for the codes of other infusion medications (such as infliximab), we may have underestimated biologic prescription rates in Denmark.

In summary, we described variability in medication prescription rates in elderly patients with IBD in Canada, Denmark, the UK and the US. This variability may be due to differences in quality of care, adherence to clinical guidelines, patient or physician preference, concern about adverse events and poly-pharmacy, or pharmaceutical industry marketing trends. There were high rates of 5-ASAs and corticosteroids, with relatively low (but increasing) rates of immunosuppressives and biologics. Future pharmaco-epidemiologic research should focus on the reasons behind this variability, assessing for adherence, appropriateness and quality, in order to develop quality improvement programs for the growing population of elderly patients with IBD. Additionally, future research could assess whether this variation in medication prescriptions rates is associated with differences in clinical outcomes.

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Conflicts of interest (past 3 years)

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Statement of authorship

EIB: study conception, contribution of data, data analysis and interpretation, drafted and edited manuscript.

SFC: refinement of study methods, contribution of data, interpretation of results, edited manuscript.

RE: refinement of study methods, contribution of data, interpretation of results, edited manuscript.

MDL: refinement of study methods, edited manuscript.

CNB: study conception, interpretation of results, edited manuscript.

JW: refinement of study methods, data and statistical analysis, interpretation of results, edited manuscript.

CFC: data analysis, interpretation of results, edited manuscript.

TF: data analysis, interpretation of results, edited manuscript.

TS: data analysis, interpretation of results, edited manuscript.

MDK: study conception, contribution of data, data analysis and interpretation, edited manuscript.

References

1. McDevitt TM, Rowe PM. The United States population in international context: 2000 [Webpage]: NationalAtlas.gov. Accessed 2012 March 8 at, http://nationalatlas.gov/articles/people/a_international.html 2000.
2. Sinha SK. Why the elderly could bankrupt Canada and how demographic imperatives will force the redesign of acute care service delivery. *Healthc Pap* 2011;**11**:46–51.
3. Katz S, Pardi DS. Inflammatory bowel disease of the elderly: frequently asked questions (FAQs). *Am J Gastroenterol* 2011;**106**:1889–97.
4. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. *Inflamm Bowel Dis* 2009;**15**:182–9.
5. Chassin MR, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. *JAMA* 1998;**280**:1000–5.
6. Kappelman MD, Bousvaros A, Hyams J, Markowitz J, Pfefferkorn M, Kugathasan S, et al. Intercenter variation in initial management of children with Crohn's disease. *Inflamm Bowel Dis* 2007;**13**:890–5.
7. Crandall W, Kappelman MD, Colletti RB, Leibowitz I, Grunow JE, Ali S, et al. ImproveCareNow: the development of a pediatric inflammatory bowel disease improvement network. *Inflamm Bowel Dis* 2011;**17**:450–7.
8. Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 2007;**5**:1424–9.
9. Kappelman MD, Rifas-Shiman SL, Porter CQ, Ollendorf DA, Sandler RS, Galanko JA, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;**135**:1907–13.
10. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol* 1999;**149**:916–24.
11. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol* 2006;**101**:1559–68.
12. Lowe AM, Roy PO, B-Poulin M, Michel P, Bitton A, St-Onge L, et al. Epidemiology of Crohn's disease in Quebec, Canada. *Inflamm Bowel Dis* 2009;**15**:429–35.
13. GPRD — database [webpage]. GPRD; 2012 (Accessed 2012 Mar 1 at, http://www.gprd.com.).
14. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf* 2002;**11**:211–8.
15. Fonager K, Sorensen HT, Rasmussen SN, Moller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol* 1996;**31**:154–9.
16. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;**2**:273–9.
17. Benchimol EI, Guttmann A, Griffiths AM, Rabeneck L, Mack DR, Brill H, et al. Increasing incidence of paediatric inflammatory

bowel disease in Ontario, Canada: evidence from health administrative data. *Gut* 2009;**58**:1490–7.
18. Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011;**60**:937–43.
19. Nolte E, Newbould J, Conklin A. International variation in the usage of medicines: a review of the literature. London: RAND Corporation; 2010. Document TR-830-DH, http://www.rand.org/pubs/technical_reports/TR830.html.
20. ODBF — Ontario Public Drug Programs — Exceptional Access Program (EAP) [Webpage]: Government of Ontario, Canada. Accessed 2012 Apr 23 at, http://www.health.gov.on.ca/english/providers/program/drugs/eap_mn.html 2011.
21. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: Institute of Medicine (U.S.). Committee on Quality of Health Care in America; 2001. Document.
22. Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:617–29.
23. Lim WC, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010:CD008870.
24. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005:CD003715.
25. Patel V, Macdonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009:CD006884.
26. Benchimol EI, Erichsen R, Cook SF, Bernstein CN, Wong J, Froslev T, et al. International variation in medication prescription rates in children with inflammatory bowel disease (abstract). *Gastroenterology* 2012;**142**:S208.
27. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;**354**:1932–9.
28. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**:621–30.
29. Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol* 2006;**4**:1017–24 [quiz 976].
30. Toruner M, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929–36.
31. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.
32. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology* 2012;**143**:390–9 [e1].
33. Juneja M, Baidoo L, Schwartz MB, Barrie III A, Regueiro M, Dunn M, et al. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. *Dig Dis Sci* 2012;**57**:2408–15.
34. Bloomfeld RS, Onken JE. Mercaptopurine metabolite results in clinical gastroenterology practice. *Aliment Pharmacol Ther* 2003;**17**:69–73.
35. Kane S, Dixon L. Adherence rates with infliximab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2006;**24**:1099–103.
36. Manuel DG, Rosella LC, Stukel TA. Importance of accurately identifying disease in studies using electronic health records. *BMJ* 2010;**341**:c4226.
37. Nielsson MS, Erichsen R, Froslev T, Taylor A, Acquavella J, Ehrenstein V. Positive predictive values of the coding for bisphosphonate therapy among cancer patients in the Danish National Patient Registry. *Clin Epidemiol* 2012;**4**:233–6.