

Article

# Paradigm Shift of Healthcare Cost for Patients with Inflammatory Bowel Diseases: A Claims Data-Based Analysis in Japan

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**Abstract:** Anti-tumor necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) agents are used for induction and maintenance of remission in patients with inflammatory bowel diseases (IBD). However, biologic drugs present a large economic burden on health insurance systems. We aimed to estimate the mean annual health care cost per patient with IBD and cost contribution of anti-TNF $\alpha$  agents. We performed an analysis of patients with Crohn's disease (CD) and ulcerative colitis (UC) based on a large-scale administrative claims database constructed by Japan Medical Data Center (JMDC) Co. Ltd., comprising inpatient, outpatient, and pharmacy claims data. We evaluated all claims from 1 April 2013 through 31 March 2016. Descriptive statistics were used to measure median health care costs paid per member per year (PMPY) and the relative cost contribution of anti-TNF $\alpha$  agents. A total 1405 patients with CD and 5771 with UC were included. Median costs PMPY were approximately six times higher for CD than UC (JPY 1,957,320 and JPY 278,760, respectively). Medication cost for anti-TNF $\alpha$  agents was the main cost driver, accounting for 59.9% and 17.8% of the total costs for CD and UC, respectively. In Japan, costs for anti-TNF $\alpha$  agents have resulted in drug costs exceeding inpatient costs for IBD. Optimized use of anti-TNF $\alpha$  agents and introduction of biosimilars for anti-TNF $\alpha$  agents can be expected to substantially reduce the health care costs of IBD.

**Keywords:** biosimilars; claims data; health care costs; inflammatory bowel diseases

## 1. Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic relapsing intestinal inflammation that may lead to severe complications and disability [1]. IBD negatively affect the patient's health-related quality of life and account for substantial costs to the health care system and society [2].

There is no curative therapy for IBD; most patients need continuous drug therapy and some require surgical intervention. Frolkis et al. [3] reported that the cumulative risk of surgery in CD is 47% at 10 years after diagnosis; in addition, approximately 5% of patients with UC will require colectomy within 1 year of diagnosis and 16% within 10 years. Therefore, not only achieving but also maintaining symptom-free remission and endoscopic healing are the primary targets of therapy for IBD.

Over the last decade, the advent of biologic therapy has significantly improved the clinical management of IBD. Anti-tumor necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) agents, such as infliximab and adalimumab, have been widely used for the induction and maintenance of remission in both CD and UC [4]. These agents are monoclonal antibodies that block the pro-inflammatory cytokine TNF involved in the pathogenesis of IBD. Mao et al. [5] suggested that anti-TNF $\alpha$  agents were associated with a statistically significant and meaningful reduction in hospitalization (by 50%) and surgery (by 33–77%) for IBD. The introduction of biologic drugs in clinical practice is expected to improve the natural history of IBD.

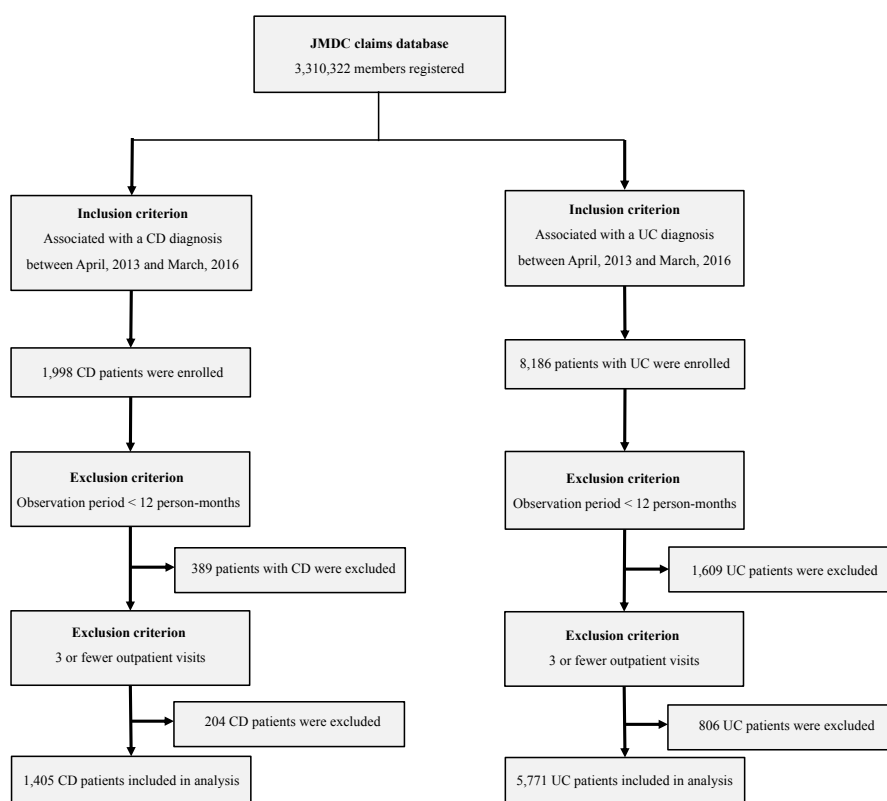
Long-term maintenance of biologic therapy is required for IBD, and biologic drugs are more expensive than conventional drugs, which leads to a significant economic burden for the health insurance system in Japan [6]. Several studies have showed that the health care costs of IBD are mainly driven by the drug cost of anti-TNF $\alpha$  agents. However, the economic impact of biologics in the treatment of IBD in Japan has not been clearly analyzed [7–9]. We hypothesized that most IBD-related costs are allocated to the group of patients with IBD who are receiving biologic therapy in Japan.

The aim of this study was to estimate the mean annual health care cost per patient and the cost contribution of anti-TNF $\alpha$  agents among patients with IBD, using claims data from Japan.

## 2. Results

### 2.1. Patient Summary

Figure 1 shows a flowchart of the selection of patients for inclusion in this study. The JMDC claims database included data of 3,310,322 members during the study period. In the cohort, the number of patients diagnosed with CD or UC at least once were 1998 and 8186, respectively. We excluded 503 patients with CD and 2415 patients with UC from the cohort, according to the exclusion criteria. Therefore, in this study, we analyzed 1405 patients with CD, including 303 women (21.6%) and 1102 men (78.4%), and 5771 patients with UC, including 2134 (37.0%) women and 3637 (63.0%) men.



**Figure 1.** Flowchart for selection of patients with inflammatory bowel disease in this study.

## 2.2. Estimation of Health Care Costs and Use of Anti-TNF $\alpha$ Agents

The median costs PMPY were JPY 1,957,320 (IQR 383,220–2,996,340) and JPY 278,760 (IQR 160,560–456,720) for CD and UC, respectively. These costs were approximately six times higher for CD than for UC. A total 55.2% (95% CI 52.6–57.8%) of patients with CD and 7.5% (95% CI 6.9–8.2%) of those with UC received biologic therapy. The patient subgroup aged 20–29 years for CD had the highest percentage of biologic therapy use (67.0%). In contrast to CD, the highest percentage for UC was only 20.0% in patients aged 10–19 years (Tables 1 and 2).

**Table 1.** Median health care costs and use of biologic therapy for CD.

Item	Subgroup	CD				
		n	%	PMPY (JPY)		Anti-TNF $\alpha$ Agents Used (95% CI)
				Median	Interquartile Range	
N	All	1405		1,957,320	383,220–2,996,340	0.552 (0.526–0.578)
By sex	Woman	303	21.6%	1,446,480	318,120–2,525,520	0.502 (0.446–0.558)
	Man	1102	78.4%	2,053,680	406,620–3,103,830	0.566 (0.537–0.595)
By age group (years)	0–9	6	0.4%	1,129,380	835,800–7,063,740	0.167 (0.030–0.563)
	10–19	82	5.8%	2,292,240	557,250–3,180,630	0.634 (0.526–0.730)
	20–29	285	20.3%	2,173,800	697,860–3,071,940	0.670 (0.614–0.722)
	30–39	389	27.7%	2,056,080	383,100–3,103,500	0.584 (0.534–0.631)
	40–49	377	26.8%	1,930,800	363,840–3,105,480	0.538 (0.488–0.588)
	50–59	207	14.7%	1,341,720	306,840–2,718,000	0.440 (0.374–0.508)
	60–69	52	3.7%	373,560	231,660–1,745,340	0.216 (0.122–0.340)
70+	7	0.5%	161,040	69,240–293,640	0 (NA)	

Abbreviations: CI, Confidence interval; NA, not applicable; CD, Crohn disease; PMPY, per member per year; TNF $\alpha$ , tumor necrosis factor alpha; JPY, Japanese yen. Anti-TNF $\alpha$  agents include infliximab and adalimumab. “N” means the all patients in CD cohort.

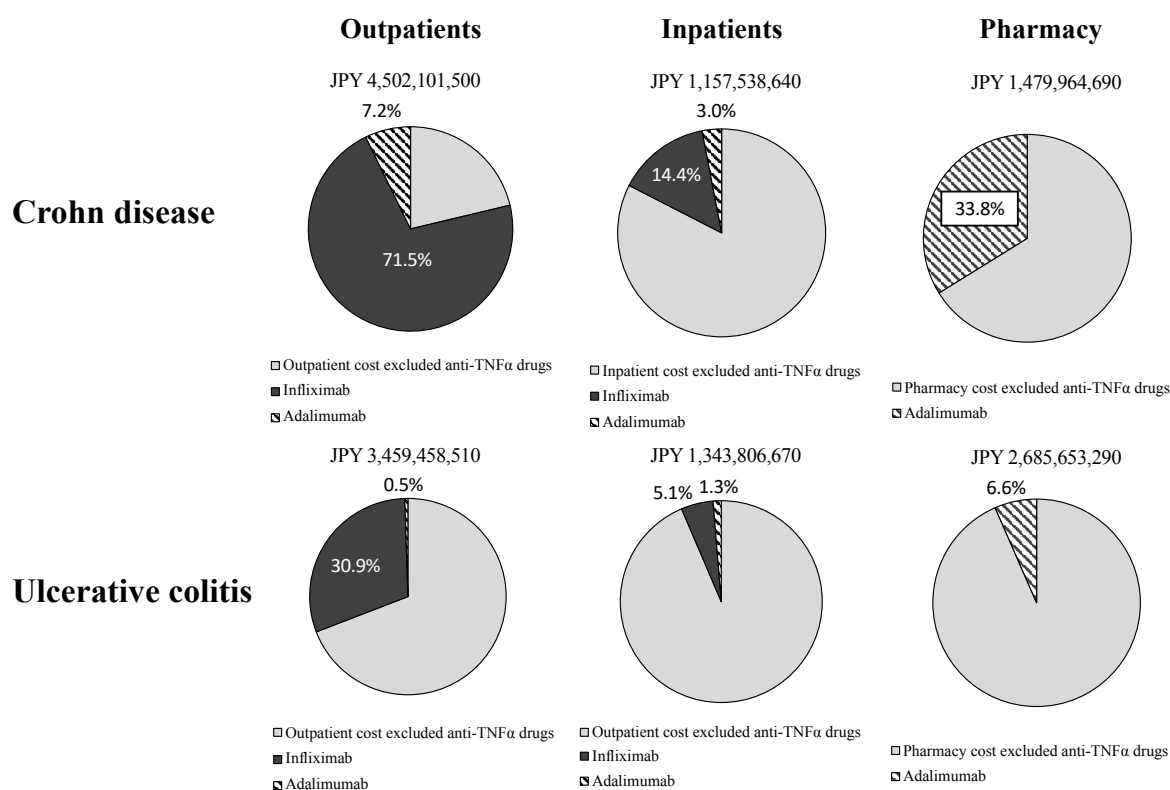
**Table 2.** Median health care costs and use of biologic therapy for UC.

Item	Subgroup	UC				
		n	%	PMPY (JPY)		Anti-TNF $\alpha$ Agents Used (95% CI)
				Median	Interquartile Range	
N	All	5771		278,760	160,560–456,720	0.075 (0.069–0.082)
By sex	Woman	2134	37.0%	279,240	158,820–460,620	0.075 (0.065–0.087)
	Man	3637	63.0%	278,280	161,760–453,540	0.075 (0.067–0.084)
By age group (years)	0–9	12	0.2%	903,240	293,040–4,186,050	0.083 (0.015–0.354)
	10–19	170	2.9%	464,100	239,730–1,303,200	0.200 (0.147–0.266)
	20–29	704	12.2%	301,800	172,530–553,470	0.117 (0.095–0.142)
	30–39	1324	22.9%	271,560	158,220–443,670	0.085 (0.071–0.101)
	40–49	1825	31.6%	258,960	148,740–417,960	0.066 (0.055–0.078)
	50–59	1237	21.4%	276,120	163,920–434,220	0.051 (0.040–0.065)
	60–69	440	7.6%	291,900	162,630–504,990	0.048 (0.031–0.072)
70+	59	1.0%	332,880	213,240–623,280	0 (NA)	

Abbreviations: CI, Confidence interval; NA, not applicable; UC, ulcerative colitis; PMPY, per member per year; TNF $\alpha$ , tumor necrosis factor alpha; JPY, Japanese yen. Anti-TNF $\alpha$  agents include infliximab and adalimumab. “N” means the all patients in UC cohort.

## 2.3. Share of Drug Costs Associated with Anti-TNF $\alpha$ Agents in Healthcare Costs

Figure 2 depicts the share of drug costs associated with infliximab and adalimumab, out of the overall health care costs for CD and UC over 3 years. The total cost related to CD and UC was estimated to be JPY 7,139,604,830 and JPY 7,488,918,470, respectively. The medication cost of anti-TNF $\alpha$  agents was the main cost driver, accounting for 59.5% and 17.8% of the entire cost for CD and UC, respectively. Notably, the drug cost of anti-TNF $\alpha$  agents alone comprised nearly four-fifths (78.7%) of outpatient costs. The cumulative cost for inpatients was estimated to be approximately one-quarter and one-third that of outpatients for CD and UC, respectively.



**Figure 2.** Proportion of drug costs associated with infliximab and adalimumab, out of overall healthcare costs.

2.4. Number of Patients with IBD Who Received Biologics among PMPY Subgroups

Table 3 shows the number of patients with CD and UC who received biologics and those who did not, for each subgroup of costs PMPY. Cochran–Armitage analysis showed that the proportion of anti-TNFα agent use was significantly increased among groups with higher costs PMPY, for both CD and UC ( $p < 0.001$ ).

**Table 3.** Biologic therapy in patients with CD and UC, in subgroups by costs PMPY.

	PMPY Subgroup (JPY)				p-Value *
	Minimal Subgroup <1 Million	Low Subgroup 1 Million to 2 Million	Moderate Subgroup 2 Million to 3 Million	High Subgroup >3 Million	
CD					
Biologics	23	85	326	342	<0.001
No biologics	533	68	19	9	
Total (n = 1405)	556	153	345	351	
UC					
Biologics	46	115	165	107	<0.001
No biologics	5060	190	60	28	
Total (n = 5771)	5106	305	225	135	

Abbreviations: CD, Crohn disease; UC, ulcerative colitis; PMPY, per member per year; JPY, Japanese yen. \* p-values were calculated using Cochran–Armitage trend test.

### 3. Discussion

Economic evaluation is used for decision-making processes such as drug pricing and promotion of generic drugs. The number of patients with IBD has been increasing during the previous decade in Japan. It is expected that the use of biologic drugs in these patients may result in a shift from higher costs for hospitalization and surgery to higher outpatient chemotherapy costs in this population. Therefore, accurate estimation of the economic burden of IBD is an important issue for Japanese health policy makers.

Health technology assessment is a form of economic evaluation that assesses the health outcome and costs of interventions designed to improve patient's health. It has been used to evaluate the cost-effectiveness of treatment strategies for IBD. A systematic review of cost-effectiveness studies for IBD concluded that whereas biologic agents improved patient outcomes, they incurred high costs and were therefore generally not cost-effective [10]. There have been no economic studies regarding the health care costs in Japan for the use of biologics in IBD.

Recently, economic studies from the United States (US) and the Netherlands identified drug costs related to anti-TNF $\alpha$  agents as one of the primary cost drivers in IBD, accounting for 64% and 31% of the total costs in CD and UC, respectively [7,8]. Those studies concluded that there is an apparent shift in cost profiles from surgery and hospitalization towards biologic therapy in IBD.

A health economic study in the US reported that the proportion of biologics used for CD and UC in 2015 was 44.8% and 16.7%, respectively [11]. Our results showed that the rate for UC in Japan is equivalent to the US data, but the rate for CD in Japan is much higher than that reported in the US. Moreover, Park et al. [6] reported that the mean cost PMPY of CD in the US was USD 18,637 (JPY 1,971,795: USD 1 = JPY 105.8).

Anti-TNF $\alpha$  agents are one of the available clinical options for moderately to severely active CD and UC, according to the diagnosis and treatment guidelines for these diseases [12]. However, the early introduction of biologics as a first-line drug in a "top-down" approach has been accepted as a treatment strategy in patients with CD, to avoid disease progression and bowel damage. Our results might reflect the treatment strategy shift toward aggressive use of biologics for CD in Japan [13,14]. Therefore, our findings suggest that IBD-related costs in Japan have been increasing, as in Western countries, and there is a likelihood that the use of biologics will continue to increase for IBD in Japan.

Recently, biosimilars have shown promise in reducing costs, with initial research suggesting that these biologics enter the market at a cost up to 30% lower than the original biologics [15]. Biosimilars of infliximab have been available for IBD since 2013 in Europe and since 2016 in the US. In Japan, biosimilars of infliximab have been approved for IBD therapy since 2014. However, there were only eight patients with IBD who received biosimilars in our claims data. Using this dataset, we estimate that approximately JPY 100 million in annual drug costs can be saved if more than half of currently used infliximab is replaced with biosimilars for IBD.

Several studies have estimated the budgetary impact of the introduction of biosimilars for infliximab in rheumatoid arthritis treatment. These studies have found that introduction of biosimilar infliximab lead to considerable drug cost savings for rheumatoid arthritis across European countries [16,17]. Our results suggest that replacing original biologic drugs with biosimilars can be expected to reduce the health care costs related to IBD in Japan. Moreover, alternative therapies such as corticosteroid and azathioprine therapy are needed to optimize the use of biologics in Japanese patients with IBD.

Future economic research into IBD management is needed, focusing on the indirect costs, i.e., nonmedical costs incurred by the patient owing to their disease, such as absence from work). IBD is often diagnosed around the age of 20 years; therefore, it affects patients during their peak productive years. Mahlich et al. [18] demonstrated that unemployment was four times higher among patients with IBD than in the general population of Japan. Long-term maintenance of remission with biologic therapy contributes to reducing the indirect costs owing to unemployment. However, there are no

studies demonstrating the relationship between the introduction of biologics and a reduction of indirect costs in Japan.

The current study has several limitations. First, the JMDC database did not include any information about clinical status, such as the results of clinical examination or a physician's assessment of severity. Moreover, the inclusion criterion of the claims data used in this study did not consider the clinical history of each patient prior to April 2013. Therefore, we could not identify the reason for the use of biologics and the length of time from diagnosis to commencement of biologic therapy. Additionally, we did not analyze specific cost profiles because of the complexity of the data in the JMDC database; we only estimated the burden of biologics using the price and amount used according to the records. Finally, the exclusion criteria led to a substantial number of patients being excluded in our analyses. The JMDC database included a considerable number of patients with IBD with no treatment history in their records. We considered that a substantial number of suspected cases were included in the dataset.

Recent studies based on claims data have showed a dramatic increase in IBD-related health care costs worldwide [11,19,20]. In Japan, most of the costs of biologics for IBD are paid by the government, without the need for prior approval and with no time limitation [21]. In the current environment, biologics face few barriers to use by physicians. The use of biologics should be tailored to patients with IBD who are likely to benefit, to reduce overuse of biologic drugs.

## 4. Materials and Methods

### 4.1. Overview of Claims Data

We performed a longitudinal retrospective cohort analysis of patients with IBD based on demographic data and a large-scale claims database constructed by the Japan Medical Data Center (JMDC) Co. Ltd., Tokyo, Japan [10]. This database is completely anonymized and includes approximately 3.2 million cumulative insured persons, mainly company employees and their family members. The JMDC database is an administrative database comprising inpatient, outpatient, and pharmacy claims data. In this study, we evaluated all claims data from 1 April 2013 through 31 March 2016.

### 4.2. Patient Identification

We extracted patients who had at least one health insurance claim associated with a CD or UC diagnosis, with clinical diagnoses coded using International Classification of Diseases 10th Revision (ICD-10) classification (K50 or K51) during the period of analysis. Patient age was determined by considering the age at the midpoint of the claims analysis (30 September 2014). Age groups were further stratified into deciles for the analysis. We excluded patients with IBD who had insurance records for less than 12 months, or fewer than 3 outpatient records, during the study period.

### 4.3. Estimation of Reimbursement of Health Care Costs

The total annual reimbursement cost for all health services rendered for each included patient's health care was equal to the sum of the paid amounts for that patient. All individual paid amounts were summed and divided by the number of person-months. This monthly estimate was then multiplied by 12, to obtain paid costs per member per year (PMPY). The median costs PMPY for patients with CD and UC were calculated by sex and by age group.

We calculated the proportion of the drug cost for infliximab and adalimumab, out of the total cost related to CD and UC, and for outpatients, inpatients, and pharmacy, separately. To examine trends of the treatment rate for biologics, patients were stratified by costs PMPY, as follows: <JPY 1 million, JPY 1–2 million, JPY 2–3 million, >JPY 3 million.

#### 4.4. Statistical Analysis

All statistical analyses were performed using JMP version 13 (SAS Institute, Cary, NC, USA). We calculated the median with interquartile range (IQR) for health care costs (JPY, PMPY) paid for IBD, and the proportion for use of anti-TNF $\alpha$  agents, with 95% confidence intervals (CIs), stratified by age and sex. In addition, we reported the share of costs for anti-TNF $\alpha$  agents out of the cumulative cost for inpatients, outpatients, and pharmacy. The Cochran–Armitage trend test was used to test for linearity in the use of anti-TNF $\alpha$  agents, by subgroups of costs PMPY. For hypothesis testing, a  $p$ -value of <0.05 was selected to represent statistical significance.

#### 4.5. Ethical Considerations

This study was approved by the Ethics Review Committee of Niigata University of Health and Welfare for Research Involving Human Participants (No. 17812; 8 June 2017).

### 5. Conclusions

In conclusion, our investigation suggested that the economic burden of IBD in Japan is significantly owing to the use of biologics, and that the treatment paradigm for CD is rapidly shifting to a top-down approach using anti-TNF $\alpha$  agents in the country. Optimization of the use of anti-TNF $\alpha$  agents and the introduction of biosimilars for anti-TNF $\alpha$  agents can be expected to substantially reduce health care costs related to IBD. Future research into IBD is needed, to optimize the use of value-based anti-TNF $\alpha$  agents and for accurate price revision based on cost-effectiveness analyses, in the era of biologics in Japan.

**Author Contributions:** Conceptualization, S.S., K.A.; Project Administration, K.A.; Data Curation, S.S., K.N.; Methodology and Formal Analysis, S.S., K.S., T.I.; Writing—Original Draft Preparation, S.S.; Writing—Review & Editing, all authors.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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