Real-World Data on Topical Therapies and Annual Health Resource Utilization in Hospitalized Swiss Patients with Ulcerative Colitis

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Abstract
Objectives: Topical treatment with aminosalicylates and/or budesonide was shown to be highly effective in patients with ulcerative colitis (UC), while reducing the likelihood of systemic adverse effects. However, previous research has shown that topical treatment is clearly underused. We aimed to evaluate the use of topical therapy in the real-world setting. Methods: This is an observational study based on claims data of 201 Swiss adult patients who were hospitalized for UC between 2012 and 2014 and who were then followed for 1 year. A variety of factors presumably associated with topical treatment were examined. Annual health care utilization (UC-related medications, diagnostic procedures, consultations, and rehospitalizations) of patients with versus without topical therapy was compared. Results: Of the 201 hospitalized UC patients, 82 (40.8%) were treated with topical 5-acytylsalicylic acid (ASA) and/or topical rectal steroids. The main factors significantly and positively associated with receiving topical treatment were the use of topical treatment in the year prior to the hospitalization, receiving oral 5-ASA, and living in an urban area. The mode of administration was further related to the language area. Patients with topical therapy significantly more often received other UC-related medications, such as combinations with systemic steroids. They significantly more often underwent colonoscopies and calprotectin measurements, and more often consulted a gastroenterologist in the follow-up, while there was no significant difference regarding rehospitalizations. Conclusions: Topical treatment is underused in patients with UC, which stands in contrast to the current European Crohn’s and Colitis Organization guidelines. Patients’ preferences and considerations need to be taken into account when prescribing medical therapy.

Introduction
Ulcerative colitis (UC) is a chronic relapsing inflammatory disorder of the colon. The etiology and pathophysiology of UC are not yet entirely understood, but immunological and environmental factors along with genetic susceptibility seem to mainly be responsible for the onset of UC [1, 2]. The prevalence of UC is estimated to be around 260–500/100,000 in Western countries, and
prevalence seems to increase over time [3–5]. UC always involves the rectum and shows variable extension to the left side (left-sided colitis) or the entire colon (pancolitis). More than two thirds of UC patients in population-based studies exhibit only a proctitis/proctosigmoiditis or left-sided colitis whereas about one third of patients have extensive colitis at diagnosis [6–8]. 5-Aminosalicylic acid products (5-ASA; mesalazine or mesalamine) are considered to be first-line treatment in mild to moderate UC, irrespective of the disease localization [9–12]. In patients with proctitis or left-sided colitis, topical applications of 5-ASA as suppository, enema, or foam preparation were shown to be more effective compared with oral treatment [9, 13, 14]. Rectally administered 5-ASA was superior to rectal steroids, while rectal steroids are superior to placebo in this situation [15–19]. In contrast, a meta-analysis by Manguso and Balzano [20] found similar efficacy of rectal steroids (beclomethasone dipropionate) and topical 5-ASA in patients with distal mild to moderate UC. Moreover, a previous study has found a beneficial effect of a combined oral and topical treatment also in patients with pancolitis [21]. Topical treatment (5-ASA and/or steroids) is associated with fewer side effects compared with a systemic administration, because rectally administered medications deliver a high dose of the active drug compound directly to the site of inflammation [22, 23]. In the study by Seibold et al. [22], 334/790 (42.3%) patients had a past topical treatment. Side effects were experienced in 7.5% of these patients, compared to 48.5% in patients with immunomodulators, 24% in patients with tumor necrosis factor (TNF) antagonists, and 13.1% in patients with oral 5-ASA [22]. However, low adherence levels result in ineffective disease control and an increased risk of acute flares [24, 25]. The 5-ASA adherence rate was low in real-world practice, and it was significantly lower in topical therapy compared with oral therapy [26]. Therefore, patients’ preferences and considerations need to be taken into account when prescribing medical therapy. According to previous findings, patients clearly preferred foam preparations, with respect to steroids, as well as with respect to 5-ASA medications [27, 28].

In summary, topical treatment was shown to be highly effective, while reducing the likelihood of systemic adverse effects. Especially patients with proctitis, rectosigmoiditis, or left-sided colitis could benefit from topical therapy. However, previous research has shown that topical treatment is clearly underused in a cohort of Swiss patients who were mainly treated in a university hospital setting and in a US setting, respectively [22, 29]. As of yet, little is known about the frequency of topical treatment and the factors associated with topical therapy in the real-life setting.

We therefore aimed to examine the proportion of UC patients treated with topical therapies, the mode of administration of topical therapy, as well as the factors associated with topical treatment in a real-world setting. Moreover, we aimed to compare the utilization of various health care resources (UC-related medications, diagnostic procedures, consultations, and rehospitalizations) in the year following UC-related hospitalization in patients with versus without topical therapy.

**Methods**

**Study Design and Study Population**
This is an observational study based on claims data of the Helsana Group, one of the leading insurance companies in Switzerland. Helsana provides insurance coverage for about 1.2 million inhabitants in Switzerland which roughly corresponds to 15% of the entire Swiss population (which currently counts 8 million inhabitants). Patients hospitalized for UC were followed for 1 year, thereby comparing patients with and without topical therapy with 5-ASA and/or rectal steroids. We focused on UC patients who required a hospitalization as only in this population the UC diagnosis is coded as such whereas it would be only approximative in UC outpatients never requiring a hospitalization (see methods below) [30, 31]. The year before the index hospitalization was also included in order to examine the prestationary medical therapies. The study population consists of 256 adult UC patients who were hospitalized with a main diagnosis of UC between January 1st, 2012, and December 31st, 2014. The main diagnosis of UC means that the main reason for the hospitalization was the underlying UC. Fourteen (5.4%) patients aged 17 years and younger, 14 patients who died during the follow-up, as well as 27 (10.5%) patients with missing data (i.e., patients living abroad, lump sums used for reimbursement of nursing home residents, or no full insurance coverage at Helsana Group for the observation time of 2 years) were excluded. As such, a total of 201 UC patients were included for analysis.

The present study falls outside the scope of the Swiss Federal Act on Research involving Human Beings (Human Research Act), as the study is retrospective and based on anonymized routine administrative health care claims data. Therefore, in accordance with the Swiss national ethical and legal regulations, no patient informed consent and no further ethics approval were needed.

**Measures**

The organization of the Swiss health care system has been described in a recent publication [31]. In Switzerland, a “diagnosis-related group” system was introduced in 2012, which refers to ICD-10 codes and applied procedures. As such, UC patients were identified using the directional ICD-10 code K51. Main outcome variables comprise the proportion of patients with topical therapy, as well as the application form of the topical treatment. In addition, the need for further UC-related medications and/or combination therapies, the rate of rehospitalizations and disease-related rehos-
pitalizations, the number of face-to-face consultations by primary care physicians, gastroenterologists and/or other specialists, as well as the number of diagnostic procedures (computed tomography scans, magnetic resonance imaging, X-ray, ultrasound, colonoscopy, and calprotectin measurement) in patients with versus without topical therapy were assessed. Further UC-related medications include: oral 5-ASA (mesalazine and sulfasalazine), immunomodulators (methotrexate, azathioprine, and mercaptopurine), TNF antagonists (infliximab, adalimumab, golimumab), integrin inhibitors (vedolizumab, that got its first marketing approval in Switzerland in January 2015), and/or steroids (prednisone, oral budesonide).

We analyzed the following factors regarding their association with the use of topical therapies: topical 5-ASA and/or rectal steroid therapy in the year prior to the index hospitalization, patient characteristics (age group: 18–40, 41–60, and ≥61 years, sex, and additional chronic conditions), the type of patients’ health insurance plan (managed care, deductible class, supplementary insurance), and regional factors (type of residence and language area).

Additional chronic conditions were identified based on the Anatomical Therapeutic Chemical classification system, using an updated measure of the Pharmacy-Based Cost Group model by Huber et al. [32]. Twenty-one additionally treated chronic conditions were considered: acid-related disorders, bone diseases (osteoarthritis), cancer, cardiovascular diseases (incl. hypertension), dementia, diabetes mellitus, epilepsy, glaucoma, gout/hyperuricemia, HIV, hyperlipidemia, iron deficiency anemia, migraines, pain, Parkinson’s disease, psychological disorders (sleeper disorders, depression), psychoses, respiratory illness (asthma, COPD), rheumatologic conditions, thyroid disorders, and tuberculosis.

### Statistical Analysis

Descriptive statistics were used to evaluate differences between the characteristics of UC patients with and without topical treatment using Fisher’s exact test for dichotomous variables, and the χ² test for categorical variables. ns, not significant. Including rectosigmoiditis, proctitis, and left-sided colitis.

### Results

#### Topical Treatment, Mode of Administration, and Its Associated Factors

The mean age of the study population was 54.3 (±20.4) years, and 44.8% were males. Descriptive statistics of the

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**Table 1. Characteristics of the study population**

| Characteristics                          | Total   | No topical treatment | Topical treatment | p   |
|------------------------------------------|---------|----------------------|-------------------|-----|
| Number                                   | 201     | 119 (59.2%)          | 82 (40.8%)        |     |
| Female sex                               | 111 (55.2%) | 71 (59.7%)          | 40 (48.8%)        | ns  |
| Age                                      | ns      |                      |                   |     |
| 18–40 years                              | 53 (26.4%) | 25 (21.0%)          | 28 (34.1%)        |     |
| 41–60 years                              | 46 (22.9%) | 26 (21.8%)          | 20 (24.4%)        |     |
| >60 years                                | 102 (50.7%) | 68 (57.1%)          | 34 (41.5%)        |     |
| Language area: German                    | 168 (83.6%) | 100 (84.0%)         | 68 (82.9%)        | ns  |
| Language area: French/Italian            | 33 (16.4%) | 19 (16.0%)          | 14 (17.1%)        |     |
| Type of residence (urban area)           | 155 (77.1%) | 84 (70.6%)          | 71 (86.6%)        | 0.010|
| Chronic condition (excl. UC; 0–1)        | 91 (45.3%) | 45 (37.8%)          | 46 (56.1%)        | 0.007|
| 2–4 chronic conditions                   | 65 (32.3%) | 39 (32.8%)          | 26 (31.7%)        |     |
| ≥5 chronic conditions                    | 45 (22.4%) | 35 (29.4%)          | 10 (12.2%)        |     |
| Home care nursing dependency             | 33 (16.4%) | 22 (18.5%)          | 11 (13.4%)        | ns  |
| Health insurance plan                    |         |                      |                   |     |
| Managed care                             | 93 (46.3%) | 51 (42.9%)          | 42 (51.2%)        | ns  |
| Higher deductible                        | 18 (9.0%) | 7 (5.9%)             | 11 (13.4%)        |     |
| Supplementary hospital insurance         | 36 (17.9%) | 25 (21.0%)          | 11 (13.4%)        | ns  |
| Left-sided colitis<sup>a</sup>           | 68 (33.8%) | 40 (33.6%)          | 28 (34.1%)        |     |
| Previous topical therapy                 | 63 (31.3%) | 21 (17.6%)          | 42 (51.2%)        | <0.001|
| Surgery at index hospitalization         | 15 (7.5%) | 10 (8.4%)           | 5 (6.1%)          | ns  |

<sup>a</sup> Including rectosigmoiditis, proctitis, and left-sided colitis.

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*p* values, assigning the differences between UC patients with and without topical therapy, were calculated using Fisher’s exact test for dichotomous variables and the χ² test for categorical variables. ns, not significant.
characteristics of patients with versus without topical treatment in the year after the hospitalization are presented in Table 1. Of the 201 hospitalized adult patients with a main diagnosis of UC, 82 (40.8%) were treated with topical 5-ASA and/or topical rectal steroids (Fig. 1). Ninety percent (74/82) of these patients had a combined oral and topical treatment. Looking solely at the 68 patients with rectosigmoiditis, proctitis or left-sided colitis, the proportion of patients with topical treatment hardly changed (41.2% with topical treatment, Fig. 1). Topical treatment in the year prior to the UC-related hospitalization was found in 63/201 (31.3%) patients, whereby 32 patients received 5-ASA, 12 patients received steroids, and 19 patients were treated with both drugs. Patients with topical therapy more often lived in an urban area and had fewer additional chronic conditions (Table 1). The proportions of patients with topical treatment by disease localization are shown in Table 2. In summary, 68 (33.8%) of UC patients suffered from a proctitis, a rectosigmoiditis or a left-sided colitis.

In the logistic regression model, the main factors significantly associated with receiving topical treatment were the use of topical treatment in the year prior to the disease-related hospitalization, receiving oral 5-ASA, and living in an urban area (Table 3). In contrast, sociodemographic factors such as age and sex, as well as additional chronic conditions did not seem to play an important role in the multivariate model.
Overall, foam was the most prevalent application form in topical therapy (Table 4; Fig. 2). In logistic regression models, looking at factors associated with the mode of administration of topical treatment, pretreatment with topical 5-ASA and/or steroids was significantly and positively associated with receiving foam (OR = 2.67 [1.18–6.22], p = 0.020) or suppositories (OR = 5.16 [1.97–14.50], p = 0.001), but not enema in the follow-up period. Receiving oral 5-ASA was also positively associated with taking foam (OR = 2.75 [1.17–6.87], p = 0.024) and/or enema (OR = 6.99 [2.29–25.56], p = 0.001) in the 1-year follow-up. Living in the French or Italian region was significantly and positively associated with receiving 5-ASA foam (OR = 3.29 [1.06–10.19], p = 0.037), and significantly and negatively associated with 5-ASA enema use (OR = 0.10 [0.01–0.52], p = 0.017). Regarding disease location, left-sided colitis was only significantly related to foam use (OR = 2.52 [1.13–5.73], p = 0.025).

In the population with topical treatment, 23 (28.0%) patients used more than one mode to administer medications. In the multinomial logistic regression model, controlling for age group, sex, further chronic conditions, disease location, language area, and further UC-related medications, patients with prior topical treatment had 4.6 times higher odds of receiving topical treatment (CI = 1.99–10.55), and 6 times higher odds of using more than one mode of administration (CI = 1.97–18.20). Treatment with oral 5-ASA was also associated with higher

### Table 5. Medications and drug combinations in patients treated with and without topical therapy during the 12-month follow-up (n = 201)

| Medications                        | Total | No topical treatment | Topical treatment | p     |
|-----------------------------------|-------|----------------------|-------------------|-------|
| Number                            | 201   | 119 (59.2%)          | 82 (40.8%)        | <0.001|
| 5-ASA orally                      | 109   | 48 (40.3%)           | 61 (74.4%)        | <0.001|
| Thiopurines                        | 69    | 31 (26.1%)           | 38 (46.3%)        | 0.004 |
| TNF antagonists                    | 42    | 18 (15.1%)           | 24 (29.3%)        | 0.021 |
| Systemic steroids                  | 128   | 66 (55.5%)           | 62 (75.6%)        | 0.004 |
| 5-ASA + thiopurines                | 54    | 19 (16.0%)           | 35 (42.7%)        | <0.001|
| 5-ASA + biologics                  | 32    | 11 (9.2%)            | 21 (25.6%)        | 0.003 |
| Thiopurines + biologics            | 24    | 5 (4.2%)             | 19 (23.2%)        | <0.001|
| Thiopurines + biologics + 5-ASA    | 20    | 4 (3.4%)             | 16 (19.5%)        | <0.001|
| Systemic steroids + 5-ASA          | 149   | 75 (63.0%)           | 74 (90.2%)        | <0.001|
| Systemic steroids + thiopurines    | 133   | 69 (58.0%)           | 64 (78.0%)        | 0.003 |
| Systemic steroids + biologics      | 132   | 68 (57.1%)           | 64 (78.0%)        | 0.002 |

p values, assigning the differences between UC patients with and without topical therapy, were calculated using Fisher’s exact test.

**Fig. 2.** Proportion of patients with topical therapy and respective application form in the year after index hospitalization.
odds of receiving topical treatment (OR = 3.20, CI = 1.42–7.23). However, due to the wide confidence interval, results need to be interpreted with caution.

**Health Care Utilization during the 1-Year Follow-Up**

Patients with topical therapy significantly more often received all other UC-related medications, such as combinations with systemic steroids (Table 5). Integrin inhibitors were only found in 1 patient who additionally received TNF antagonists and topical treatment. Patients with topical treatment were also more likely to receive a higher number of further UC-related drug prescriptions, notably for systemic steroids and oral 5-ASA (results not shown).

Patients with topical therapy significantly more often underwent diagnostic procedures, especially colonoscopies and measurements of fecal calprotectin (Table 6). Patients treated with topical therapy had a significantly higher median number of face-to-face consultations, whereby the biggest difference was found for consultations with gastroenterologists (Table 7).

We found no significant difference between patients treated with and without topical therapy regarding rehospitalizations (ever had a rehospitalization or the number of rehospitalizations) in the year following the index hospitalization (Table 8). More than one third of all UC patients had at least one rehospitalization within 12 months after the index hospitalization. In the multivariate logistic regression model, there was again no significant difference regarding rehospitalization between patients with and without topical therapy, when controlling for age group, sex, further chronic conditions, disease location, language area, urbanity, patients’ health insurance plan, and further UC-related medications (results not shown).
Discussion

In this study we present population-based real-life data on the use of topical therapies and health care consumption in Swiss UC patients who were followed for 1 year after an index hospitalization. Our analysis contains several clinically relevant messages. First, only 41% of UC patients (all disease locations) were treated with topical 5-ASA and/or topical rectal steroids. Second, topical treatment in the year prior to the UC-related hospitalization was found in only 31% of patients. Third, the main factors significantly and positively associated with receiving topical treatment were the use of topical treatment in the year prior to the UC-related hospitalization, receiving oral 5-ASA, and living in an urban area. Fourth, patients with topical therapy significantly more often received other UC-related medications, which points towards a severer disease pattern when compared to UC patients without topical therapies. And fifth, patients with topical therapies significantly more often consumed health care compared to patients without topical therapies.

Based on the solid literature evidence, the current European Crohn’s and Colitis Organization guidelines state that mild to moderately active UC (proctitis, left-sided colitis, and extensive colitis) should be treated with local 5-ASA therapy (suppositories or enema, respectively) plus a combination of oral 5-ASA products [34]. The guidelines further state that patients with severe UC should be admitted to hospital for intensive treatment [35]. Topical treatment was shown to be highly effective, while reducing the likelihood of systemic adverse effects. In a follow-up study of a median of 6 years, combined oral and rectal treatment was clearly superior to oral treatment alone in 84 UC patients, with no dropouts or side effects in either group [35]. Patients with a combined therapy had a significant reduction in the incidence of relapses [36]. Moreover, patients with a combined oral and rectal therapy had lower overall costs, because the higher drug costs were offset by 48% lower costs due to the reduction in relapses and due to no accruing costs for hospitalizations in the follow-up [36]. Our real-life data document an important underuse of local therapy that stands in clear contrast to the therapeutic guidelines [35]. Patients under topical treatment more often received other UC-related medications, had more endoscopies, and had more frequently consultations by gastroenterologists. Based on these observations we hypothesize that topical therapy was applied in patients with severer disease in combination with systemic steroids and biologics to more rapidly achieve a clinical response or remission, respectively. Of note, a recent paper by Singh et al. [36] showed that continuation of 5-ASA in moderate-to-severe UC patients who were escalated to TNF antagonists did not improve clinical outcomes. Our data on the frequency of topical treatments are in accordance with data from Seibold et al. [22], who showed that 334/790 (42.3%) of UC patients had a past topical treatment. The main difference between the two studies is that in the Seibold study UC patients were recruited in 80% of cases by gastroenterologists working in hospital while in our study the results can be regarded as a population-based selection of hospitalized patients [12]. There might exist several reasons from the side of the prescribing physicians and from the patients’ side as well to explain the underuse of local therapies in UC patients. First of all, it is possible that prescribing physicians are not sufficiently aware of the data demonstrating the efficacy and safety of the different forms of local therapy in UC. It is also possible that physicians, despite their knowledge of the data, fail to transport the important information onto the patient and empower them to use local therapies. On the patient’s side it is well possible that there exist psychosocial barri-

### Table 8. Rehospitalizations in patients treated with and without topical therapy during the 12-month follow-up

| Rehospitalization                  | Total          | No topical treatment | Topical treatment | p    |
|-----------------------------------|----------------|----------------------|-------------------|-----|
| Rehospitalization                 | 74 (36.8%)     | 44 (37.0%)           | 30 (36.6%)        | ns  |
| Number of rehospitalizations (median/IQR) | 0 (0–1.0)     | 0 (0–1.0)            | 0 (0–1.0)         | ns  |
| Surgery¹                          | 28 (37.8%)     | 24 (54.5%)           | 4 (13.3%)         | na  |
| Disease-related surgery¹          | 13 (18.3%)     | 10 (23.8%)           | 3 (10.3%)         | na  |

p values, assigning the differences between UC patients with and without topical therapy, were calculated using Fisher’s exact test for dichotomous variables and Wilcoxon’s rank-sum test for continuous variables. ns, not significant; na, not applicable; IQR, interquartile range. ¹In those 74 patients with at least 1 rehospitalization.
ers that limit the use of local treatment. We claim that physicians prescribing local therapy should be proactive in informing patients regarding the efficacy and safety, but also take into account the patients’ preferences and considerations as low adherence levels result in ineffective disease control [24]. Several studies have evaluated the patient’s view regarding local therapy in UC. Even though steroid enemas and steroid foam were both shown to be effective in the treatment of distal UC, patients clearly preferred foam preparations [27]. Due to their higher volume, enemas are often less well tolerated than foam during acute flares and may cause pain and discomfort. In 233 patients with UC, 5-ASA foam was better accepted than 5-ASA enema, because it was more comfortable, interfered less with daily living and was well tolerated [28]. Treatment with 5-ASA suppositories was more effective and found to be more practical in patients with distal UC in comparison to treatment with hydrocortisone foam [37]. The superiority of 5-ASA enemas and suppositories over topical steroids or oral therapies was confirmed by the results of a meta-analysis by Cohen and colleagues [17]. We conclude that every prescribing physician should be aware about the data regarding topical therapies and communicate them in a proactive way to the concerned patients. Treatment decisions should be made on a joint basis between prescribing physician and patient in order to achieve a patient empowerment with consecutively better adherence rates to the prescribed treatment which ultimately results in better clinical outcomes [38, 39].

According to our analysis, 50.2% of all patients had a colonoscopy within 1 year after the disease-related hospitalization, whereby the proportion was significantly higher in patients with topical treatment. Other disease-monitoring tools such as measurement of fecal calprotectin were also significantly more frequently found in UC patients with topical treatment. We assume that UC patients with topical disease represented a cohort characterized by a severer disease activity compared to patients without local treatment and therefore indeed were in need of more frequently applied monitoring of endoscopic activity. More than one third of the patients of our cohort were rehospitalized within 1 year after the index hospitalization without detecting a difference between patients with and without topical treatment. A total of 18% of rehospitalized patients underwent UC-related surgery; again no difference was found between patients with and without topical treatment. In a Canadian study, 18.5–20.3% of UC patients were rehospitalized at least once per year, whereby, 55% had to undergo a major surgery [40].

Our population-based study has several strengths and also some limitations. The analyses are based on health insurance claims data that cover a broad range of highly reliable and comprehensive information on in- and outpatient care. These data were not collected by means of self-reports, and results were therefore not distorted due to recall bias. As a first limitation, we were not able to consider medications applied during hospitalizations. Additionally, variables such as disease activity, disease duration, disease evolution, as well as patients’ preferences were not assessed [41]. The study looks at health care utilization in the year following UC-related hospitalization, independently of the reason for use. As such, the entire health care utilization may not be necessarily related to UC treatment. Secondly, as a limitation that is inherent to our study methodology, we had to focus on the population of UC patients in need of a hospitalization. Our target population might be characterized by a disease course that is severer when compared to UC patients not in need of a hospitalization. As such, all results are valid only for inpatients with UC and can therefore not be generalized to the entire population of UC patients in Switzerland. Third, the data we present in this paper are specific for Switzerland and cannot be generalized to other countries.

In conclusion, our real-life data show that topical therapies are clearly underused in UC patients which stands in sharp contrast with the current European Crohn’s and Colitis Organization guidelines on the management of UC. A good adherence to local therapies in UC patients has shown to save health care costs by reducing the risk of flares and hospitalizations. Factors on the physicians’ and patients’ side hampering the use of local therapies need to be further evaluated.

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Statement of Ethics

According to the Swiss Federal Law on data protection, this study was exempted from ethics committee approval as all data were anonymized, retrospective, pre-existing, and de-identified in order to protect the privacy of patients, physicians, and hospitals.
Availability of Data and Material

Individual data cannot be made fully available because the study is based on claims data of the Helsana Group, the owner of the data. Thus, data underlie data protection and privacy restrictions. These restrictions prohibit us from sharing the collected data.

Disclosure Statement

A.M.S. consulted and received speaker’s honoraria from Abbvie, UCB, Falk, MSD, Tillotts, Vifor, Pfizer, Ferringer, Receptos, and Takeda. S.R.V. consulted and received speaker’s honoraria from Abbvie, UCB, Falk, MSD, Tillotts, Vifor, Pfizer, Takeda, and Ferringer. The other authors have no competing interests to declare.

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Author Contributions

A.M.S., S.R.V., B.B., O.R., E.B., and C.B. conceptualized and designed the study. C.B. and B.B. performed the statistical analysis. All authors contributed to data interpretation and manuscript writing and had full access to all data in the study. All authors read and approved the final manuscript.

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