

• FULL-LENGTH ARTICLES •

Medication Profiles of Patients in the University of Puerto Rico Inflammatory Bowel Disease Registry

Jorge D. Meléndez, MD†; Yaritza Larregui, PharmD*; Jewel M. Vázquez, PharmD*; Víctor L. Carlo, MD†; Esther A. Torres, MD†

Objective: The prevalence of inflammatory bowel disease [IBD, Crohn's disease (CD) and ulcerative colitis (UC)] in Puerto Rico has increased significantly in recent years. Experience with these diseases outside of a referral center is limited. A registry for IBD, created by the University of Puerto Rico (UPR) Center for IBD, has collected data from subjects all over the island for 15 years. We analyzed the medication profiles and IBD-related surgeries of the registrants in order to characterize the therapies used and to identify any trends in disease severity.

Methods: This descriptive study reports on the medication profiles of 507 individuals with IBD (1995 to 2007). Descriptive statistics related to gender, diagnosis, pharmacological therapies (aminosalicylates, steroids, immune modulators, and anti-TNF antibodies), and IBD-related surgical interventions (as indicators of disease severity) are presented.

Results: The study included 256 females and 251 men. There were 241 patients with UC (48%) and 266 patients with CD (52%). The great majority of them had received aminosalicylates and steroids. Biological agents and immune modulators were less commonly used, generally in IBD patients who had undergone surgical procedures. Steroid use was almost equivalent in both IBD populations despite a trend towards greater steroid use both in UC patients with colectomies and in nonsurgical CD patients.

Conclusion: Aminosalicylates and steroids are the mainstays of medical treatment for IBD in Puerto Rico. The use of biological agents and immune modulators appears to be limited to severe disease. A prospective analysis to detect changes in prescribing practices, as a step-down approach becomes more prevalent, is needed. [*PR Health Sci J* 2011;1:3-8]

Key words: Medications, Ulcerative colitis, Crohn's disease

The most appropriate treatment for inflammatory bowel disease (IBD) requires that the health care professional be well informed about the disease and its therapeutic options. Crohn's disease (CD) and ulcerative colitis (UC), collectively known as the inflammatory bowel diseases, are largely diseases of the twentieth century and are associated with the rise of modern, westernized industrial society. The causes of these diseases remain incompletely understood (1). Researchers have proposed various theories offering different etiologies that lead to these conditions, but none have adequately explained the pathogenesis of IBD. The consensus is that the etiology of UC and CD are a response to environmental triggers (infection, drugs, or other agents) in genetically susceptible individuals (2). It is now part of the clinical practice that IBD treatment be directed to its pathogenetic basis. Monitoring the approved modalities of treatment is an important factor in reaching

the goals of inducing and maintaining remission, preventing relapse, improving the quality of life, and preventing or curing complications in patients with IBD (3).

Published clinical trials, guidelines, and the individual experiences of clinicians have supported the safe and effective use of certain groups of medications for the treatment of IBD, including CD and UC. Knowing the exact location of the disease, its severity, and its manifestations or complications influences the choice of therapy. The aminosalicylate group

*School of Pharmacy, †Gastroenterology Research Unit, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

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Author correspondence to: Esther A. Torres, Department of Medicine A-838, PO Box 365067, San Juan, PR 00936-5067. Tel: (787) 751-6034 • Email: etorres@pol.net

of drugs has become the first-line therapy to induce and maintain remission for mild to moderate inflammatory bowel disease (mild to moderate UC and mild CD) (4-5). This group includes mesalamine, or 5-aminosalicylic acid (5-ASA), sulphasalazine, olsalazine, and balsalazide. Corticosteroids are also frequently used for the treatment of IBD. Nevertheless, because of the multiple adverse effects associated with their long term use, corticosteroids are recommended for the induction of remission only. Newer agents such as budesonide delayed-release tablets are less toxic because of an extensive first-pass hepatic metabolism. Nonetheless, they are more expensive and less effective than conventional corticosteroids at inducing remission because only 11% of the drug is systemically available to treat transmural disease. This class of drugs is approved for mild to moderate ileocecal Crohn's disease.

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are thiopurines that are purine antimetabolites. These medications have a proven efficacy in patients with IBD for both the induction and the maintenance of remission (6). Other unique and important indications for either AZA or 6-MP therapy are in the treatment of fistulizing CD and steroid-dependent CD and UC (7). Methotrexate is known to be efficacious in the treatment of active or relapsing CD in those individuals who are refractory to or intolerant of AZA or MP (8). This medication is used for the induction of remission and its maintenance in CD. Cyclosporine is used as a salvage therapy for patients with refractory ulcerative colitis after corticosteroids have failed, but its use is controversial because of its toxicity and long-term failure rate. Infliximab is approved for the induction and maintenance of the remission of CD that is not responsive to standard therapy, of fistulizing CD, and of UC that is not responsive to standard therapy (9-11). It is remarkably effective in approximately 60% of steroid-resistant patients who have CD (12). Other biologics recently introduced include two other anti-TNF agents (adalimumab and certolizumab pegol, approved for CD) and an anti-integrin antibody, natalizumab, which is also for CD (13-15).

There are conflicting issues on which treatment should be used in a specific patient with IBD. Clinical judgment, as well as applied knowledge of the diseases and their medications, has to be employed in these cases because of the various possibilities in the patients' pharmacotherapies (16-17). Because of the lack of specific data about physicians' prescribing patterns, a description of the medications used by patients with IBD is essential. This information will serve as a necessary tool for other health care professionals so that they can be aware of the different modalities of treatment used in community and clinical practices. The lack of descriptive research regarding medication use in these patients in our community is the main concern and reason for the study described herein.

The IBD Registry of the University of Puerto Rico (UPR) Gastroenterology Research Unit was created in 1995. It is an ongoing database of demographic and medical information

of patients with IBD from all over the island. Patient data are collected through an interview and a medical-record review after recruitment at the UPR clinics (both private and academic gastroenterology clinics). The information includes age, gender, education, income and living area at the time of diagnosis and at the interview, extraintestinal manifestations, extent of disease, and the medications used and surgeries performed after diagnosis. Our objective is to describe the medications used by patients in this registry. The descriptive information compiled by means of this research study will aid in the identification of the different treatment modalities used in a large Puerto Rican population with IBD. This study could be the foundation of other research studies aimed at evaluating trends in therapies used for one or both of the IBD conditions, UC and CD. It could also help in the comparison of the Puerto Rican IBD population with those of other Hispanics with this condition. Finally, it could suggest areas for educational interventions in the healthcare community.

Methods

The study is descriptive and includes a simple data presentation. It contains a compilation of the medications used by patients who are part of the registry of IBD (UC and CD) of the University of Puerto Rico Gastroenterology Research Unit. The study includes 507 individuals from different areas of Puerto Rico, which sample size is considered to be significant. This could be considered a convenience sample because it is limited to the registrants of the study. The Registry of IBD is a database of demographic and medical information obtained by interviews with and medical record reviews of patients with IBD and collected by a questionnaire since 1995. The questionnaire has a specific section related to medications used. The current study retrieved the data on medications for each subject as well as information regarding gender, diagnosis, and history of surgery for IBD (as an indicator of disease severity). Descriptive statistics for age, income, education, and living area are also included. The Registry of IBD has the continuing approval of the Medical Sciences Campus Institutional Review Board.

Results

The entire Registry (with data from 1995 to 2007) was reviewed. Five hundred seven patients were included in this study. For each registrant, a history of all prescription medications for IBD ever used was obtained at the time of recruitment. Medical therapy for inflammatory bowel disease was grouped by class, including aminosalicylates, steroids, immune modulators (azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine), and anti-TNF inhibitors (infliximab and adalimumab). Surgical interventions for IBD were included as indicators of disease severity.

There were 241 patients with UC (105 men and 136 women) and 266 patients with CD (146 men and 120 women). A total of 199 patients (39%) in this study had surgical interventions for IBD, 53 patients with UC (22%) and 146 patients with CD (55%) (Figure 1). Surgical procedures included intestinal resection with and without fistulectomy, abscess drainage, and fistula repair. All UC patients who underwent surgery had total colectomies.

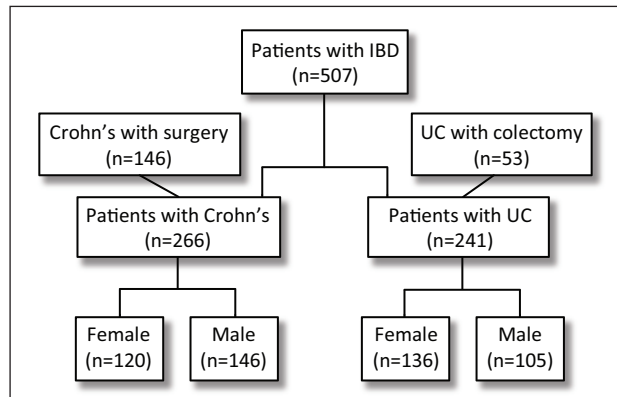


Figure 1. Patients included in the study

Patients with UC had the following medication profiles: 180 patients (75%) used aminosalicylates, 173 patients (72%) used steroids, 35 patients (15%) were on immune modulators, and 2 patients (0.8%) used anti-Tumor Necrosis Factor (TNF) (Figure 2). The medication profiles for patients with CD included the following: 218 patients (82%) used aminosalicylates, 197 patients (74%) used steroids, 118 patients (44%) received immune modulators, and 26 patients (10%) used anti-TNF (Figure 3).

The medication profiles of patients with ulcerative colitis with colectomy were as follows: 37 patients (70%) used aminosalicylates, 47 patients (89%) used steroids, 11 (21%) received immune modulators, and 1 patient (2%) used anti-TNF inhibitors. There were 188 UC patients without surgical interventions. A total of 143 patients (76%) used aminosalicylates, 126 patients (67%) used steroids, 24 (13%) received immune modulators, and 1 patient (0.5%) used anti-TNF inhibitors (Figure 4).

When patients with UC were analyzed by gender, it was found that 25 of the 105 males (24%) and 28 of 136 females (21%) had required colectomies. Their medication profiles show that 18 (72%) versus 19 patients (68%) used aminosalicylates, 21 (84%) versus 26 patients (93%) received steroids, and 5 (20%) versus 6 patients (21%) used immune modulators, for males and females, respectively. No male patient and only 1 female patient (4%) used TNF inhibitors.

There were also 80 of 105 males (76%) and 108 of 136 females (79%) with UC who had no surgical interventions. Their

respective medication profiles by gender show that 52 (65%) versus 91 (84%) of them used aminosalicylates, and 54 males (68%) versus 72 females (67%) received steroids. Twelve (15%) males and 12 (11%) females received immune modulators. One male (1%) and no females used anti-TNF inhibitors.

Of the 146 (55%) patients with CD who required surgery, 119 (82%) used aminosalicylates, 105 (72%) used steroids, 70 (48%) were on immune modulators, and 17 (12%) used anti-TNF inhibitors. On the other hand, there were 120 patients (45%) with CD who had no surgical intervention. Of those, 99 (83%) used aminosalicylates, 92 (77%) used steroids, 48 (40%) were on immune modulators, and 9 (8%) used anti-TNF inhibitors (Figure 5).

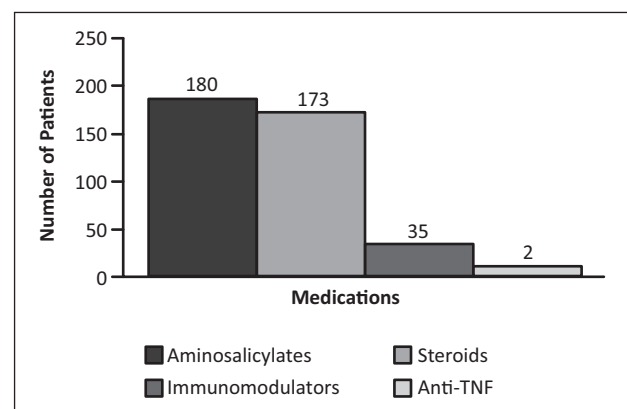


Figure 2. Medications Profile in Patients with Ulcerative Colitis

When CD patients were studied by gender, 87 of 146 males (60%) and 59 of 120 females (49%) required surgical interventions. Their medication profiles show that 72 (83%) versus 47 patients (80%) used aminosalicylates, 57 (66%) versus 48 patients (81%) were on steroids, 46 (53%) versus 24 patients (41%) used immune modulators, and 9 (10%) versus 8 (14%) used anti-TNF inhibitors, in terms of male and female patients, respectively.

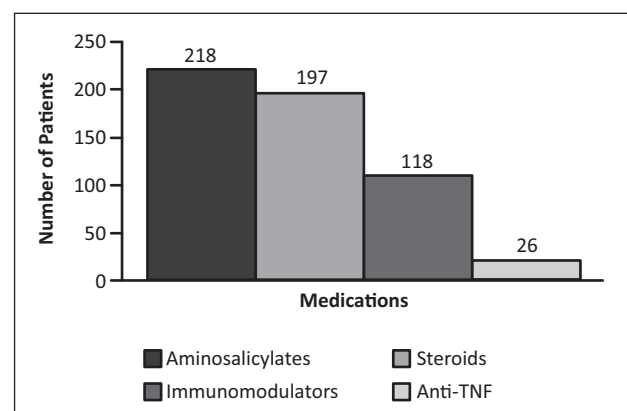


Figure 3. Medications Profile in Patients with Crohn's Disease

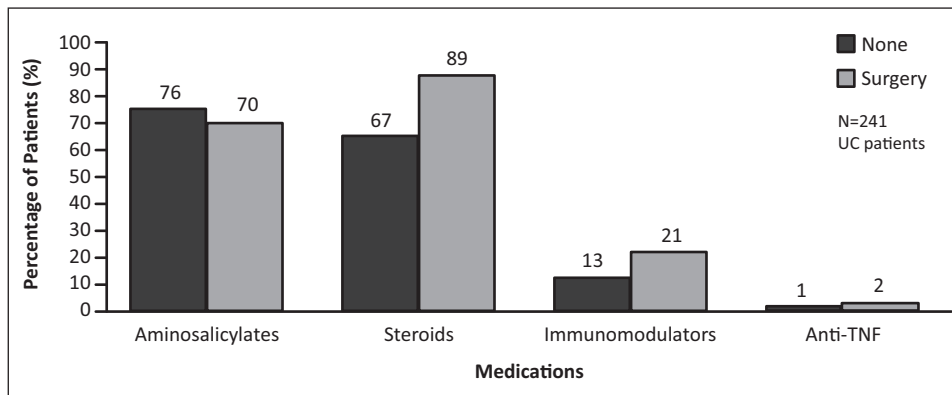


Figure 4. Comparison of pharmacologic therapy in surgical and nonsurgical ulcerative colitis patients

There were also 59 of 146 males (40%) and 61 of 120 females (51%) with CD who had no surgical interventions. Their respective medication profiles by gender show that 55 (93%) versus 44 (72%) used aminosalicylates, 44 (75%) versus 48 (79%) were on steroids, 26 (44%) versus 22 (36%) used immune modulators, and 6 males (10%) versus 3 females (5%) used anti-TNF inhibitors.

Mean age at the time of diagnosis for 484 of 507 patients was 30.5 years (range: 3 to 75 years). The mean age at the time of recruitment (referral to our clinics or inclusion in the Registry) for 488 of 507 patients was 36 years (range: 6 to 85 years). The education level of 485 (95%) of 507 patients is ranked as follows: none with no schooling, 4.5% were educated to the elementary level, 7.4% to the intermediate level, 29.1% finished high school, 6% attended vocational or technical courses after leaving high school, 45.8% attended college, and 7.2% studied through the postgraduate level. Four hundred eighty-two patients out of 507 (95%) included their current living area. Sixty-one percent lived in an urban area and 39% had a rural address. Four hundred fifty-three patients of 507 (89%) filled in their childhood living area in the questionnaire. Results were similar. During their childhoods, 60.5% had lived in an urban area and 39.5% had a rural address. The distribution of the weekly income of 426 of 507 patients (84%) at the time of diagnosis is as follows: less than \$100, 12.2%; \$100 to \$200, 26.3%; \$200 to \$300, 19%; \$300 to \$400, 11.5%; \$400-\$500, 8.7%; and more than \$500, 22.3%. The distribution of the weekly family income of 400 of 507 patients (79%) during their childhoods is as follows: less than \$100, 32.2%; \$100 to \$200, 21.2%;

\$200 to \$300, 18%; \$300 to \$400, 7.8%; \$400-\$500, 6.8%; and more than \$500, 14%.

Discussion

The prevalence of IBD in Puerto Rico has been estimated to be in the middle-range of international studies (18). The management of these patients requires medical knowledge of the pharmacological alternatives

available for this condition. Optimal clinical care is needed to decrease complications, maintain remission, avoid exacerbations, and decrease adverse effects commonly associated to IBD medications.

A study done at the University Hospitals Case Medical Center in Cleveland, Ohio, mentioned that “therapy for IBD is a rapidly evolving field with many new biologic agents under investigation, and it is likely that therapeutic strategy will alter significantly in the next decade.” (19). The evaluation of IBD medication profiles should be observed in future research because in terms of the use of biological agents, our study found that of all available drugs employed in the treatment of IBD, biological agents were utilized the least. The patient’s intolerance to the use of other medications, the increasing number of IBD patients presenting severe disease at the moment of diagnosis, and the increasing number of studies on biological therapies could change the tendency of treatment from a step-up to a top-down algorithm.

The data assessed in this research show that the medications used most by patients were aminosalicylates and steroids. Aminosalicylates were the main agents used in both UC and CD patients; the least utilized was anti-TNF. Anti-TNF and immune modulator use was observed mostly in the CD

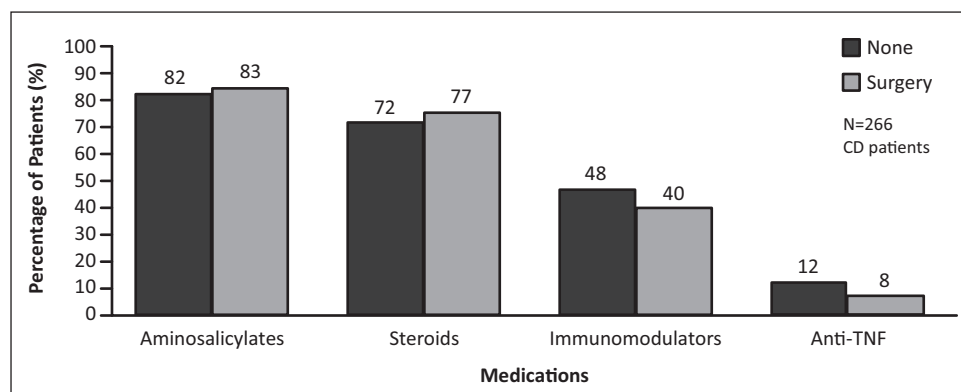


Figure 5. Comparison of pharmacologic therapy in surgical and nonsurgical Crohn's disease patients

population, especially those requiring surgery for severe disease. These results compare to a recent practical guideline published by Kuhbacher, in Germany, that demonstrates that the “classic” treatment used in IBD patients starts with aminosalicylates and ends up with an immunosuppressive and/or biological (20). Steroid use was found to be almost equivalent in both IBD populations, despite a trend towards greater steroid use in UC patients with colectomies and nonsurgical CD patients. This finding probably reflects the fact that the majority of UC patients have colectomies for intractable disease (21). On the other hand, as steroids have no role in the treatment of fistulizing CD, we postulate that most of those nonsurgical CD patients have a non-penetrating inflammatory phenotype. Further studies are needed to validate this hypothesis.

The results acquired through this research confirm a similar treatment regimen of IBD in Puerto Rico as in other countries. Most of the patients started treatment with aminosalicylates, followed by steroids and immune modulators; the least used were the biological agents. To our knowledge, no previous description of the IBD medication profile in a Hispanic population has been published by any online literature database.

A limitation of this study is that most of the participants were recruited during their first visits to the UPR IBD Clinic. This may introduce a selection bias and may exclude patients from the community with less severe disease. Nonetheless, since the study sample consists of more than 500 individuals from different areas of Puerto Rico, it is considered to be one that is significant and representative of the Puerto Rican population. Another limitation is that the information is restricted to that gathered on the date of the interview, without data regarding the chronological order of the different therapies received or correlation with the time of surgical interventions. Despite these limitations, we believe that the large sample includes patients with different durations and severities of disease that represent the spectrum of IBD. Regarding the information relating to anti-TNF therapy, it is important to highlight that it applies only in the cohort recruited after 1998, when the first drug of this class was approved for treating CD.

This study is significant to the Puerto Rican healthcare professional. The data acquired match up to those of international publications that describe a possible guide of the medication treatment used by patients with IBD and have been found to be similar.

Table 1. Summary of patients' characteristics and medication profile

Characteristics	Crohn's with surgery (n=146)		Crohn's without surgery (n=120)		UC with colectomy (n=53)		UC without surgery (n=188)	
Number of female patients (%)	59 (40)		61 (51)		28 (53)		108 (57)	
Number of male patients (%)	87 (60%)		59 (49)		25 (47)		80 (43)	
	♂ (%)	♀ (%)	♂ (%)	♀ (%)	♂ (%)	♀ (%)	♂ (%)	♀ (%)
Used aminosalicylates	72 (83)	47 (80)	55 (93)	44 (72)	18 (72)	19 (68)	52 (65)	91 (84)
Used steroids	57 (66)	48 (81)	44 (75)	48 (79)	21 (84)	26 (93)	54 (68)	72 (67)
Used immunomodulators	46 (53)	24 (41)	26 (44)	22 (36)	5 (20)	6 (21)	12 (15)	12 (11)
Used anti-TNF	9 (10)	8 (14)	6 (10)	3 (5)	0 (0)	1 (4)	1 (1)	0 (0)

Resumen

Objetivo: La prevalencia de la enfermedad inflamatoria intestinal (EII, enfermedad de Crohn y la colitis ulcerosa) en Puerto Rico ha aumentado significativamente en los últimos años. La experiencia con estas enfermedades fuera de un centro de referencia es limitada. Un registro de la EII, creado por el Centro de la Universidad de Puerto Rico (UPR) para EII, ha recopilado datos de sujetos en toda la isla durante 15 años. Analizamos sus perfiles de medicación y cirugías relacionadas con la EII con el fin de caracterizar las terapias utilizadas e identificar cualquier tendencia según la gravedad de la enfermedad. **Métodos:** Este estudio descriptivo presenta los perfiles de medicamentos de 507 personas con EII desde 1995 hasta 2007. Presentamos estadísticas descriptivas por sexo, diagnóstico, tratamientos farmacológicos (aminosalicilatos, corticoides, inmunomoduladores y los anticuerpos contra el factor de necrosis tumoral) e intervenciones quirúrgicas relacionadas con la EII (como indicadores de severidad de la enfermedad). **Resultados:** El estudio incluyó 256 mujeres y 251 hombres. Fueron 241 pacientes con colitis ulcerosa (48%) y 266 pacientes con enfermedad de Crohn (52%). La gran mayoría de ellos habían recibido aminosalicilatos y esteroides. Los agentes biológicos y los inmunomoduladores se utilizaron con menor frecuencia, generalmente en pacientes con procedimientos quirúrgicos relacionados con EII. El uso de esteroides fue casi equivalente en ambas poblaciones de EII a pesar de una tendencia hacia un mayor uso de esteroides en pacientes de colitis ulcerosa con colectomía y en pacientes con enfermedad de Crohn sin cirugías. **Conclusión:** Los aminosalicilatos y esteroides son los pilares del tratamiento médico de la EII en Puerto Rico. El uso de agentes biológicos y los inmunomoduladores parece estar limitado a enfermedad severa. Un análisis prospectivo para detectar cambios en la prescripción de medicamentos es necesario, según un abordaje de terapia más agresivo se haga más común.

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