Ulcerative Colitis in Northern Portugal and Galicia in Spain

Manuel Barreiro-de Acosta, MD, PhD,[†] Fernando Magro, MD, PhD,[‡,§,¶] Daniel Carpio, MD,[*‖] Paula Lago, MD,[‡,**] Ana Echarri, MD,[*††] José Cotter, MD,[‡,‡‡] Santos Pereira, MD,[*,§§] Raquel Gonçalves, MD,[‡,¶¶] Aurelio Lorenzo, MD,[*†] Laura Carvalho, MD,[‡,†††] Javier Castro, MD,[*††] Luisa Barros, MD,[‡,‡‡‡] Jorge Amil Dias, MD, PhD,[‡,§] Susana Rodrigues, MD,[‡,§] Francisco Portela, MD,[‡,***] Camila Dias, MD,[¶,¶¶¶] and Altamiro da Costa-Pereira, MD, PhD,[¶,¶¶¶] and GEDII and EIGA*

Background: Clinical and therapeutic patterns of ulcerative colitis (UC) are variable in different world regions. The purpose of this study was to examine two close independent southern European UC populations from 2 bordering countries and observe how demographic and clinical characteristics of patients can influence the severity of UC.

Methods: A cross-sectional study was conducted during a 15-month period (September 2005 to December 2006) based on data of 2 Web registries of UC patients. Patients were stratified according to the Montreal Classification and disease severity was defined by the type of treatment taken.

Results: A total of 1549 UC patients were included, 1008 (65%) from northern Portugal and 541 (35%) from Galicia (northwest Spain). A female predominance (57%) was observed in Portuguese patients ($P < 0.001$). The median age at diagnosis was 35 years and median years of disease was 7. The majority of patients (53%) were treated only with mesalamine, while 15% had taken immunosuppressant drugs, and 3% biologic treatment. Most patients in both groups were not at risk for aggressive therapy. Extensive colitis was a predictive risk factor for immunosuppression in northern Portugal and Galicia (odds ratio [OR] 2.737, 95% confidence interval [CI]: 1.846–4.058; OR 5.799, 95% CI: 3.433–9.795, respectively) and biologic treatment in Galicia (OR 6.329, 95% CI: 2.641–15.166). Younger patients presented a severe course at onset with more frequent use of immunosuppressors in both countries.

Conclusions: In a large population of UC patients from two independent southern European countries, most patients did not require aggressive therapy, but extensive colitis was a clear risk factor for more severe disease.

(Inflamm Bowel Dis 2010;16:1227–1238)

Key Words: ulcerative colitis, Portugal, Galicia, southern Europe, predictive factors, clinical activity, Montreal Classification, biologic treatment, immunosuppression

The incidence and prevalence of ulcerative colitis (UC) are very variable in different countries. In Shivananda's et al's classic study,[1] a north–south gradient was detected in European countries, with a lower incidence of inflammatory bowel disease (IBD) in southern countries such as Portugal and Spain. In the last decades this difference has diminished, possibly because of notable advances of health resources in both countries, and currently both Iberian nations are considered as having a mid-level prevalence of UC, with gradual propensity toward the higher level group.[2,3]

There are insufficient data heretofore comparing different geographical populations of patients with UC regarding disease severity; additionally, most of these studies compared either close populations in the same country[4] or populations with very different geographical and genetic characteristics.[5] The allocation of patients into major categories, such as the Montreal Classification,[6] makes this approach possible.

Northern Portugal and Galicia (northwest Spain) are two proximate areas that have been politically separated for the last six centuries. Despite this political separation, the populations have maintained a strong contact due to similar languages, cultures, and traditions.

The aim of this study was to compare two independent geographically and genetically close UC populations from two different countries and analyze how demographic and

Received for publication October 14, 2009; Accepted October 15, 2009.

From the *EIGA (Inflammatory Bowel Disease Group of Galicia), †Gastroenterology, University Hospital of Santiago, Santiago de Compostela, Spain, ‡Portuguese Group of Studies of Inflammatory Bowel Diseases, §Hospital de São João, ¶Faculty of Medicine, Oporto University, Portugal, ‖Complexo Hospitalario of Pontevedra, Spain, **Hospital Geral de Santo António, ††Arquitecto Marcide Hospital, Ferrol, Spain, ‡‡Centro Hospitalar do Alto Ave – Guimarães, §§Xeral Cies Hospital, Vigo, Spain, ¶¶Hospital S Marcos-Braga, †††Hospital de Vila Real, ‡‡‡Centro Hospitalar do Vale do Ave Paredes, ***Hospitais da Universidade de Coimbra, ¶¶¶Department of Biostatistics and Medical Informatics, Faculty of Medicine, Oporto University, Portugal.

The first 2 authors contributed equally.

Reprints: Manuel Barreiro-de Acosta, Gastroenterology, University Hospital, C/Choupana s/n 15706 Santiago de Compostela, Spain (e-mail: manubarreiro@hotmail.com) or Fernando Magro, MD, PhD, Institute of Pharmacology and Therapeutics, Faculdade de Medicina, 4200 Porto, Portugal (e-mail: fm@med.up.pt)

DOI 10.1002/ibd.21170

Published online 18 November 2009 in Wiley InterScience (www.interscience.wiley.com).

clinical characteristics of patients may affect the severity of UC.

MATERIALS AND METHODS

Patient Inclusion

During a 15-month period (September 2005 to December 2006), Portuguese doctors following patients with IBD had the opportunity to collect clinical data and send it to a central database via the Internet (http://www.gedi2005.med.up.pt/). Patient registration was carried out through a Web-based system with password and user name validated by a scientific committee. The database was approved by national authorities and was supported by the Portuguese group of studies of IBD (GEDII: http:/www.gedii.med.up.pt). From these subjects only those from northern Portugal were chosen, thereby including all patients from hospitals situated north of the Douro River (Fig. 1). Twenty-one doctors participated in the study. UC patients were included from 2 third-level hospitals (São João Hospital of Porto and Santo António Hospital of Porto) (55%), from 4 second-level hospitals (Guimarães, Paredes, Vila Real, and Braga Hospitals) (44.5%), and patients from private physicians (0.5%). Many first- and second-level hospitals refer their patients to third-level medical centers.

Concurrently, Galician doctors following patients with IBD had the opportunity to collect clinical data and send it to a central database via the Internet (http://www.alceingenieria.net). Patient registration was processed through a Web-based system with password and user name validated by a scientific committee. The database was supported by the Galician group of studies of IBD (EIGA). Patients from Galicia (Spain) (Fig. 1) were included from 4 reference hospitals (University Hospital of Santiago, Complexo Hospitalario of Pontevedra, Arquitecto Marcide Hospital from Ferrol, and Xeral Cíes Hospital from Vigo). No patients from private practices were included. These 4 hospitals have IBD units and are all third-level centers, receiving patients from smaller centers (Comarcal Hospitals, i.e., first- or second-level hospitals).

Spain and Portugal have very similar healthcare systems. Both countries have public universal healthcare systems and all Spanish and Portuguese citizens have free access to healthcare provided by the National Health Services (NHS).[7,8]

The information used to complete the data was obtained from clinical charts during a routine medical examination. Several reunions between members of both countries were organized to standardize and clarify the different parameters used. The diagnostic criteria for UC were based on a suggestive clinical history associated with endoscopic and histological signs of inflammation of the mucosa, after excluding infectious disease by culture and microscopic stool examination.

Data Collection

For each patient several parameters were collected: date and age of diagnosis onset, disease extent, family history of IBD, extraintestinal manifestations, use and response to steroids, immunosuppression, biologic treatment, and need for surgery. Only patients who underwent colectomy or proctocolectomy were considered as being submitted to abdominal surgery. The extent of lesions, that is, the most proximal level achieved at any time since the diagnosis, was measured and patients were classified as proctitis, left-sided, and extensive colitis.[6] Age at diagnosis was divided into 3 groups ($\leq$16 years, 17–40 years, and $>$40 years). In relation to steroids, only oral or intravenous forms were taken into consideration and steroid resistance was presumed when patients maintained active disease despite a prednisolone dose up to 1 mg/kg/day over a 2-week period. Steroid-dependent disease was stipulated as the inability to taper steroids below the equivalent of 10 mg/day of prednisolone without recurrence of active disease, or the need for a second course of steroids in a 6-month period.

Disease Severity

Disease severity was defined by the type of treatment administered (adapted from Loftus et al[9]). Patients were categorized into 3 different severity grades: Group 1 representing mild/moderate disease (patients with no treatment or with salicylates, or episodic pulses of steroids without steroid refraction or dependency), Group 2 for severe disease with drug-dependent or drug-refractory behavior (patients treated with steroids, with steroid resistance or dependency, or immunomodulators/biological) and Group 3 for patients with medically refractory disease, submitted to surgery. In order to confirm and attribute a stronger value to the results, a second analysis was performed excluding all UC patients with less than 5 years of diagnosed disease.

Statistics

Categorical variables were divided in absolute frequencies (n) and relative frequencies (%). Means and standard deviations (SDs) for continuous variables were used if a normal distribution could be assumed, or median and interquartile range (IQR: 25th to 75th percentile) if normality could not be assumed. A Kolmogorov–Smirnov test was used to test for normality.

When testing a hypothesis concerning continuous variables, nonparametric tests (Mann–Whitney and Kruskal–Wallis tests) were used as appropriate, taking into account normality assumptions and the number of groups compared. When testing a hypothesis regarding categorical variables a chi-square test and Fisher's exact test were used, as appropriate. In order to have a more thorough understanding of the factors associated with the use of immunosuppression and biologic treatment, univariate and multivariate logistic regression modeling

FIGURE 1. Map of the two regions where the UC populations were selected: Galica (A) (North West of Spain) and North of Portugal (B). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

was used. In the multivariate logistic regression models the dependent variables were immunosuppression and biologic treatment. The model's goodness-of-fit was assessed using the Hosmer–Lemeshow statistic. The significance level used was 0.05. Statistical analysis was performed using the software Statistical Package for the Social Sciences v. 16.0 for Windows (SPSS, Chicago, IL).

RESULTS

Global Demographic Characteristics

A total of 1549 UC patients were included, 1008 (65%) from northern Portugal and 541 (35%) from Galicia (northwest Spain). Overall, 721 (47%) were male and 828 (53%) female. Median age at diagnosis was 35 years (percentile 25-26 and percentile 75-46) and median years of disease was 7 (percentile 25-3 and percentile 75-11) (Table 1). When patients were classified by age at diagnosis, 72 (5%) were diagnosed at 16 years or below, 899 (59%) were diagnosed between 17 and 40 years, and 558 (36%) were diagnosed over 40 years (Table 1). An analysis of age distribution did not show a second peak at the age of 50–70 years (Fig. 2). Regarding classification of disease extent, the maximum limit and not extent at diagnosis was chosen because previous studies showed that the initial extent did not affect the subsequent disease activity course. Proctitis was found in 449 (29%) patients (E1 in Montreal Classification), 683 (44%) had left-sided colitis (E2 in Montreal Classification), and 415 (27%) had extensive colitis (E3 in Montreal Classification) (Table 2). When the patients were stratified in different categories of disease duration it was possible to see some changes over time. Concerning proctitis there was a decrease in

TABLE 1. Demographic Characteristics Comparing UC Patients from Northern Portugal and Galicia (Global and Adjusted by Age at Diagnosis)

	Age at Diagnosis												Total			
	≤16 years				17–40 years				>40 years							
	Northern Portugal		Galicia		*P*	Northern Portugal		Galicia		*P*	Northern Portugal		Galicia		*P*	Northern Portugal		Galicia	
Gender, *n* (%)																			
Male	18	(39)	12	(46)	0.561[a]	259	(42)	130	(47)	0.139[a]	152	(47)	141	(60)	0.003[a]	437	(43)	284	(52)
Female	28	(61)	14	(54)		363	(58)	147	(53)		170	(53)	95	(40)		571	(57)	257	(48)
F. His.IBD, *n* (%)	3	(7)	5	(19)	0.245[c]	56	(11)	34	(12)	0.675[a]	18	(7)	22	(9)	0.338[a]	79	(10)	61	(11)
Age, median (P25–P75)	13	(10–15)	15	(11–15)	0.551[b]	29	(24–34)	29	(25–35)	0.551[b]	50	(45–58)	52	(46–60)	0.028[b]	34	(25–44)	38	(27–50)
Years of disease, median (P25–75)	8	(4–12)	7	(3–13)	0.129[b]	7	(3–12)	7	(3–12)	0.129[b]	6	(3–10)	5	(2–10)	0.112[b]	7	(3–11)	6	(3–12)

[a]Chi–square test.
[b]Mann–Whitney test.
[c]Fisher's exact test.
F. His.IBD, family history of IBD.

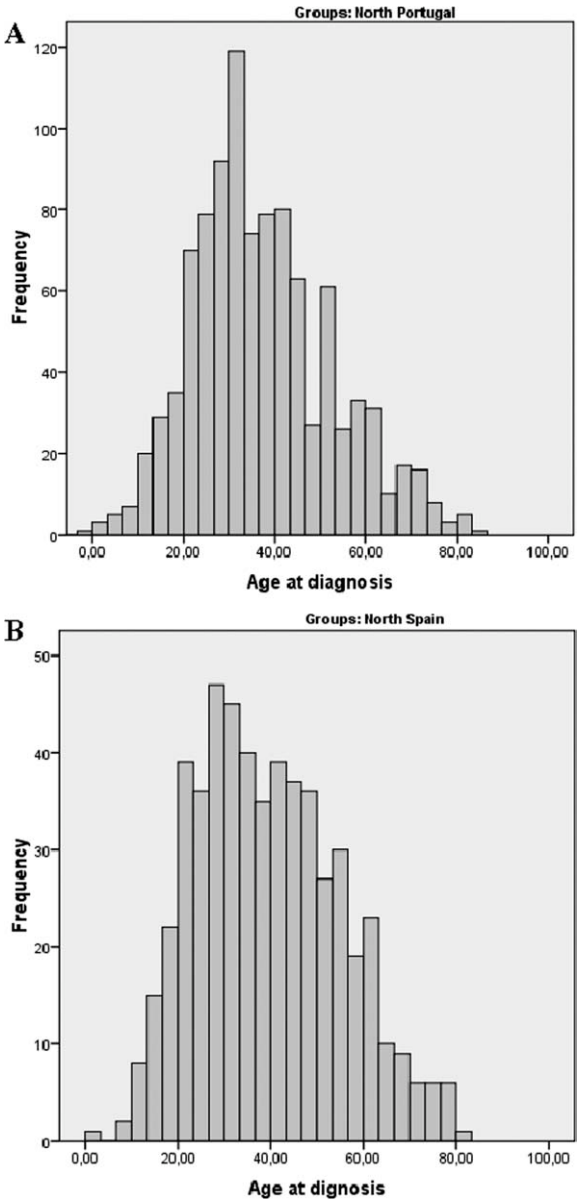

FIGURE 2. Frequency of age at diagnosis in North of Portugal (A) and Galica (B).

frequency after 4 years of diagnosis, achieving a steady state subsequently: 34% in those with less than 4 years of disease and thereafter 30% (5–9 years of disease), 25% (10–14 years), 25% (15–19 years), and 28% (more than 19 years). In both populations there was a rise in the frequency of left-sided colitis in the patients with more than 4 years of diagnosis (44%, 46%, 49%, and 45%, at 5–9, 10–14, 15–19, and more than 19 years after diagnosis, respectively) in comparison to those with a more recent diagnoses (until 4 years, 41%). In extensive colitis there was no change over time (25%, 25%, 28%, 24%, and 24%, at 5–9, 10–14, 15–19, and more than 19 years after diagnosis, respectively). That is, in our population after the fourth year of disease the variation in terms of location was not worth mentioning. A family history of IBD was detected in 140 patients (11%) and 256 patients (17%) had extraintestinal manifestations (Table 2). After analyzing treatment characteristics it was found that 72 (5%) patients had developed steroid-resistance and 195 (14%) steroid-dependency (Table 2). Regarding the use of more advanced drugs, it was observed that 227 (15%) patients had taken immunosuppressant drugs and 48 (3%) biologic treatment (Table 2).

Comparison Between Populations According to Age at Diagnosis

Important differences were shown in demographic characteristics between patients from Portugal and Galicia (Table 1). Considering gender distribution, in Portugal most patients were female (57%), while in Galicia only 48% were of this gender ($P < 0.001$). Nevertheless, when the population was stratified by age, gender differences were found only in patients diagnosed above 40 years, where there was a significant predominance of female patients in the Portuguese group of patients (53%) compared to the Galician group (40%) ($P = 0.003$). Concerning age at presentation, no significant differences in the percentage of patients diagnosed before 16 years of age were observed, contrary to data found in the older population (>40 years), where the Galician population was significantly older (52%) at diagnosis when compared to the Portuguese (50%) ($P = 0.028$).

After applying the Montreal Classification for disease extent (Table 2), the most common type was E2 (left-sided colitis). In the Galician group there was a predominance of proctitis, while extensive colitis was more common among Portuguese patients, the latter being particularly evident in the older group (>40 years). Regarding treatment patterns, more steroid-resistant and steroid-dependant patients were found in the Galician group of patients and subsequently more immunosuppression and biologic treatment were applied in those diagnosed in the intermediate age group (17–40 years) (Table 2).

Severity

Regarding severity, notably 53% of patients did not need steroids, 16% had taken steroids without more drugs supplied, and 75% were not submitted to immunosuppression, biologicals, or surgery (Table 3). Nonetheless, there was a trend toward steroid-dependency and the use of immunosuppression or biologicals in the Galician group compared to northern Portugal in all age groups (Fig. 3B). Contrariwise, in Portugal an inclination toward surgery was observed at all ages in comparison with the Galician group (Fig. 3B).

Although differences in severity in the proctitis (E1) group were not observed among the different populations, in left-sided colitis (E2) there was a trend toward

TABLE 2. Clinical Characteristics Comparing UC Patients from Northern Portugal and Galicia (Global and Adjusted by Age at Diagnosis)

	Age at Diagnosis													
	≤16 years			17–40 years			>40 years			Total				
	Northern Portugal		Galicia	*P*	Northern Portugal		Galicia	*P*	Northern Portugal		Galicia	*P*	Northern Portugal		Galicia	
Extent of disease, *n* (%)																
Proctitis	8	(17)	5 (19)	0.976[a]	173	(28)	101 (36)	0.056[a]	77	(24)	79 (33)	<0.001[a]	263	(26)	186	(34)
Left-sided colitis	15	(33)	8 (31)		262	(42)	117 (42)		151	(47)	120 (51)		438	(44)	245	(45)
Extensive colitis	23	(50)	13 (50)		186	(30)	59 (21)		94	(29)	37 (16)		305	(30)	110	(20)
E.I.M., *n* (%)	12	(26)	3 (12)	0.144	110	(18)	52 (19)	0.743[a]	39	(12)	37 (16)	0.225[a]	164	(16)	92	(17)
Steroid resistance, *n* (%)	1	(2)	1 (4)	0.745[c]	23	(5)	23 (8)	0.030[a]	8	(3)	15 (6)	0.106[a]	32	(4)	40	(7)
Steroid dependency, *n* (%)	8	(20)	6 (23)	0.727	59	(11)	52 (19)	0.002[a]	32	(12)	36 (15)	0.285[a]	100	(12)	95	(18)
Immunosupression, *n* (%)	12	(26)	9 (35)	0.444	81	(13)	53 (19)	0.019[a]	38	(12)	32 (14)	0.536[a]	132	(13)	95	(18)
Biologic treatment, *n* (%)	2	(4)	2 (8)	0.620[c]	15	(2)	17 (6)	0.006[a]	1	(0)	10 (4)	0.001[b]	18	(2)	30	(6)

E.I.M., extraintestinal manifestations.
[a]Chi-square test.
[b]Mann-Whitney test.
[c]Fisher's exact test.

immunosuppression in Galician patients, while a propensity toward surgery was detected in Portuguese patients (Fig. 3A). This trend was more noteworthy in patients of the E3 group (Fig. 3A). Remarkably, an overwhelmingly large percentage of patients in the proctitis group did not require treatment with immunomodulators or biologicals (98%), contrary to the extensive colitis population, where 25% were solely treated with mesalamine.

Concerning age of onset, those diagnosed before 16 years had a more aggressive initial course in Portugal and in Galicia requiring more steroids (51% and 40%, respectively, in northern Portugal and Galicia) and immunomodulators (26 and 35%, respectively in northern Portugal and Galicia). In order to highlight age onset, patients were stratified in more categories than those found in the Montreal Classification: 41–50 years, 51–60 years, and more than 60 years. In northern Portugal the severity curve drops until 40 years at disease onset, flattening thereafter. In Galicia the same behavior was detected until 40 years of disease onset; however, the curve continues to drop (Fig. 4A,B).

Furthermore, considering the 3 grades of disease severity, a tendency for increasing severity was found among patients with disease duration of 0–10 years, primarily in Galicia, followed by a slow descending gradient (Fig. 4C,D). However, emphasizing the low mean disease score found is fundamental because it suggests that the majority of the patients had mild disease.

Comparing Populations with Less Than and More Than 5 Years of Diagnosed Disease

In order to emphasize the results, as previously done in CD in the Montreal Classification, patients with 5 or less years of diagnosed UC were excluded to detect if the results observed were maintained. By excluding these patients, the cohort was reduced to 960 UC patients, 645 (67%) from northern Portugal and 315 (33%) from Galicia (Table 4). When comparing patients with less than 5 years or 5 or more years of disease no differences were found in Portugal or in Spain in relation to age distribution. Regarding disease location, in Portugal there was a larger percentage of patients with proctitis in the less than 5 years group, in contrast to the extensive colitis group, which remained constant in time. Concerning disease severity, many patients in Portugal and in Spain did not require aggressive therapy, regardless of the disease duration (Fig. 5). Nevertheless, there was a clear trend toward immunosuppression in extensive colitis patients in those with 5 or more years of disease (Fig. 5A). The same trend was observed in Galician patients diagnosed before age 16 years (Fig. 5B).

TABLE 3. Classification of UC According to Severity Score

	Disease Severity						
	1		2		3		
	n	(%)	*n*	(%)	*n*	(%)	*P*[a]
Age at diagnosis, *n* (%)							
≤16 years	44	(76)	11	(19)	3	(5)	0.263
17-40 years	673	(85)	90	(11)	32	(4)	
>40 years	442	(87)	50	(10)	18	(4)	
Extent of disease, *n* (%)							
Proctitis	408	(99)	4	(1)	2	(0)	<0.001
Left-sided colitis	538	(87)	64	(10)	17	(3)	
Extensive colitis	223	(65)	85	(25)	35	(10)	

[a]Chi-square test.
Disease severity was defined by the type of treatment administered (adapted from Loftus et al[10]). Patients were categorized into 4 different severity grades: group 1 representing mild/moderate disease (patients with no treatment or with salicylates, or episodic pulses of steroids without steroid refraction or dependency), group 2 for severe disease with drug-dependent or drug-refractory behavior (patients treated with steroids, with steroid resistance or dependency, or immunomodulators/biological), and group 3 for patients with medical refractory disease, submitted to surgery.

Univariate and Multivariate Analysis of Factors Associated with Immunosuppression, Biological Treatment, and Abdominal Surgery

Table 5 shows the variables associated with the use of immunosuppressants and biologic therapy on uni- and multivariate analysis. Extensive colitis was clearly a predictive risk factor for immunosuppression in northern Portugal and in Galicia (Table 5) and biologic therapy in Galicia (odds ratio [OR] 6.329; 95% confidence interval [CI]: 2.641–15.166). In relation to age, the older Portuguese group (>40 years) was at a significantly lower risk for biologic treatment (OR 0.067; 95% CI: 0.007–0.893) when compared to younger groups, as opposed to the Galician population, where no evident differences were found concerning age.

DISCUSSION

Northern Portugal and Galicia (northwest Spain) are two contiguous areas with similar extents separated by the river Miño. Although politically separated, these areas share some characteristics besides genetics, culture, and language, such as climate, geographic distribution of the population in rural areas, and similar food habits (high fish and shellfish consumption).

A comparative cross-sectional study of two populations was performed; the intention was not to perform an epidemiological study. Some previous series had compared different populations from different countries like the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD),[1,10,11] and others that compared different areas from the same country[4,12,13] or different ethnic groups in the same area.[14] Notwithstanding, few have directly compared populations from different countries and those that exist were restricted to nonbordering nation populations[15] or new data with others previously published.[16] To our knowledge, this is the first study comparing two genetically close populations from bordering countries.

Regarding family history rate or the presence of extraintestinal manifestations, no differences were observed between the two groups. The family history rate observed was 10%, similar to that found in similar publications,[17] as well as the occurrence of extraintestinal manifestations.[18,19] Concerning gender, in Portugal a female predominance was detected (57%). In the majority of UC studies no gender differences were reported,[20–22] although similar results as found in the northern Portuguese group of patients have been previously mentioned.[23,24] Furthermore, in the Galician group diagnosed over 40 years there was a predominance of males, a fact found in a previous Canadian[25] and EC-IBD studies,[1] where gender divergence at older ages was seen, consistent with a dramatic decline of new diagnoses in women after the third decade. In relation to age of onset of UC a second peak was not detected. This is in conformity with recent studies in which a second peak was not apparent. Whether this reflects a real change in the pattern or is due to recent larger and more scientifically sound studies remains uncertain.[26]

In the Galician group there were more patients with proctitis (34% versus 26%) and less extensive colitis (20% versus 30%), a fact logically related with a higher number of older diagnosis patients in Galicia. In concordance, a higher rate of proctitis in elderly UC has also been reported.[27]

In the IBSEN study[28] the majority (78%) of patients did not use systemic steroids during the second 5-year

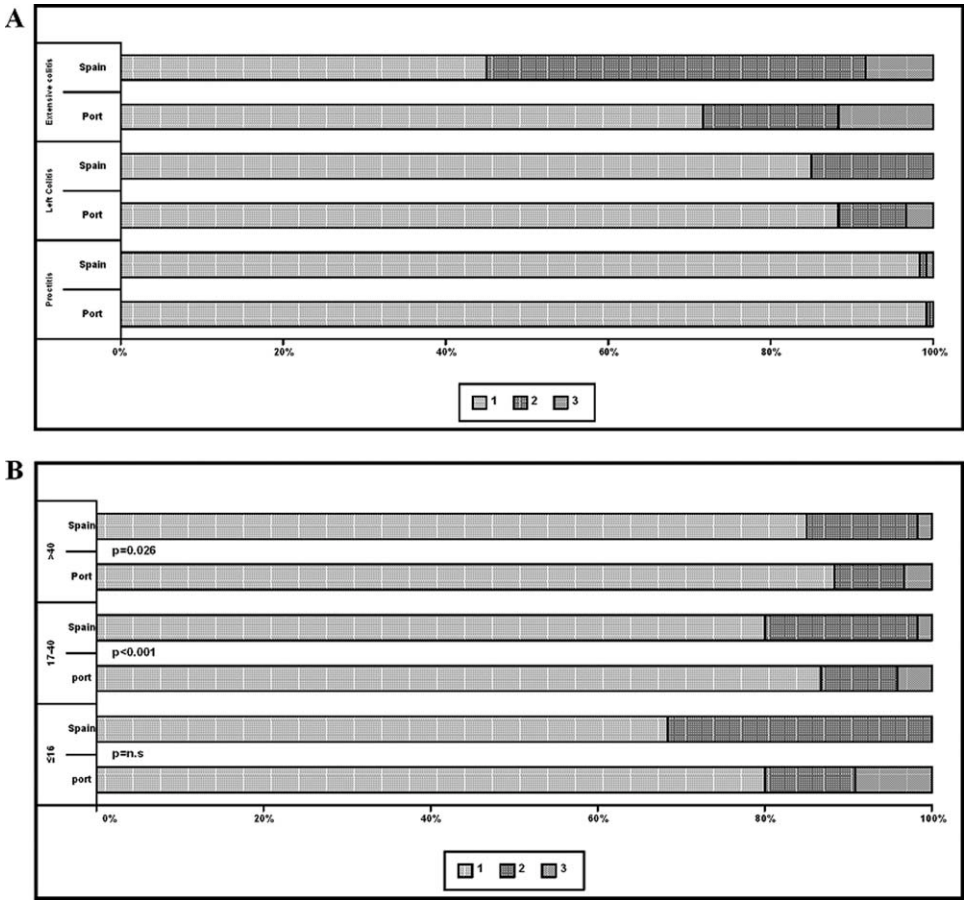

FIGURE 3. Distribution of severity of UC defined by type of treatment administered (adapted from Loftus et al) (10) according to extension of colitis (A) and age at diagnosis onset (B). Patients were categorized into three different severity grades: group 1 representing mild/moderate disease (patients with no treatment or with salicylates, or episodic pulses of steroids without steroid refraction or dependency), group 2 for severe diesase with drug-dependent or drug-refractory behaviour (patients treated with steroids, with steroid resistance or dependency, or immunomodulators/biological) and group 3 for patients with medical refractory disease, submitted to surgery.

period and, according to patient perceptions, remission or mild symptoms after initial activity represented the most common course, while chronic continuous symptoms were rare. Our data support this observation because after 10 years of disease there is a progressive decline in disease severity and overall the mean score is low. Likewise, 53% of patients did not need steroids, and 75% were not submitted to immunosuppression, biologicals, or surgery, revealing a mild clinical behavior. This observation is crucial because an overwhelmingly large percentage of patients in the proctitis group did not require treatment with immunomodulators or biologicals (90%), reinforcing the importance of salicylates in UC. Moreover, and in contrast to recent series from countries traditionally reported as regions of low incidence and milder disease,[29] 15% of the patients needed immunosuppressors and 3% were submitted to surgery. In the Galician population there was a higher rate of steroid-dependency and steroid-resistance. No clear explanation was found to justify this disparity, particularly considering that both the Galician and northern Portuguese rates are lower than those described in classic studies.[30] One could speculate that this could be due to the relatively low median of years after diagnosis; however, after excluding patients with 5 or less years since diagnosis, the percentages were only slightly changed. In relation to surgical needs, the colectomy rate was lower than most previously reported,[31] but comparable to figures from the European multicenter study,[32] especially for the southern European centers included (3.9% at 10 years).

The most substantial difference in this study is the higher use of immunosuppressants and biological therapies among Galician patients. Once confirmed that patients from both countries resembled each other regarding healthcare access (Portugal and Spain NHS have free access) and did not have substantial differences concerning medication prices,[8] this difference could be attributed to the higher

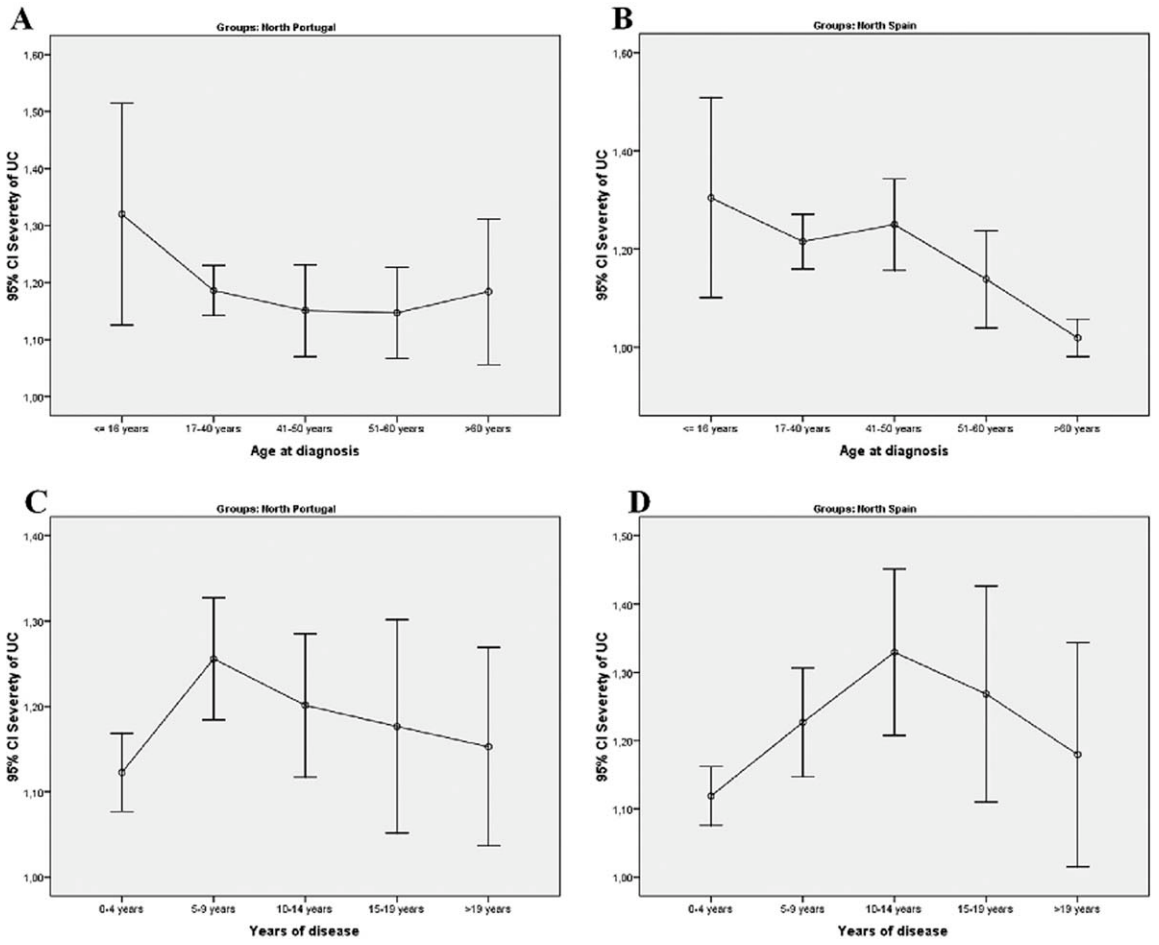

FIGURE 4. Disease severity (median and 25th and 75th percentiles) in different intervals of age of onset and intervals of disease duration. The disease severity index was classified in 3 caterories defined by the type of treatment administered (adapted from Loftus et al[9]).

rate of steroid-dependency and resistance in these patients or could plausibly be explained by the fact that the Galician patients are treated in IBD units, where physicians and nurses are more experienced with the use of more aggressive drugs,[33,34] leading to an earlier introduction in a "top-down"[35] or accelerated strategy. In this context, in northern Portugal the proportion of patients taking immunosuppressants and biologics was lower, especially in those with extensive colitis, than that found in Galicia, but colectomy rates were higher. At the present, the dearth of prospective studies in UC does not support the tendency of early introduction of immunosuppressors and biologics[36] as shown in the SONIC study in CD.[37]

In this study, stratifying for the variable age of disease onset as the Montreal Classification for CD, younger patients seem to have a more aggressive initial course with a greater need for steroids and immunosuppressants. In addition, among the elderly a notably lower severity index was found, suggesting a decline in severity in this population as interpreted from the decrease in number of exacerbations, regression in extension of the inflammatory lesions, colectomy requirements, and risk of colorectal cancer as previously reported.[38–40] This evidence could be helpful for future classification of UC, indicating that a more meaningful age division may be set at 60 years, stratifying patients above this age as elderly colitis. This observation was previously found in the IBSEN study,[28] suggesting that the course of UC becomes milder with increasing age, and that the initial age should be detached from the clinical classification of patients. Moreover, in both populations extensive colitis was a risk factor for immunosuppression, in concordance with two recent series.[41,42] In relation to biologics, there is a paucity of information in UC, although in this study extensive colitis was related to biologic treatment in Galicia. This fact is supported by indirect data which associated more extensive disease with an increased risk for colectomy,[32] emphasizing disease extent as a biological marker.[43]

TABLE 4. Comparison of Northern Portugal and Galicia Populations with Less Than 5 or More Than 5 Years at Diagnosis According to Gender, Age, and Disease Extent

	Northern Portugal					Galicia				
	<5 years		≥5 years		P^a	<5 years		≥5 years		P^a
Gender, *n* (%)										
Male	175	(50)	259	(40)	0.004	118	(52)	166	(53)	0.954
Female	177	(50)	386	(60)		107	(48)	149	(47)	
Age at diagnosis, *n* (%)										
≤16 years	16	(5)	30	(5)	0.105	8	(4)	18	(6)	0.255
17-40 years	204	(59)	418	(65)		110	(49)	167	(53)	
>40 years	128	(37)	194	(30)		106	(47)	130	(41)	
Age, median (P25-P75)	36	(27–45)	33	(25–43)	0.004[b]	36	(27–45)	33	(25–43)	0.072[b]
Extent of disease, *n* (%)										
Proctitis	108	(31)	151	(23)	0.010	83	(37)	102	(32)	0.359
Left-sided colitis	132	(38)	301	(47)		102	(45)	143	(45)	
Extensive colitis	111	(32)	192	(30)		40	(18)	70	(22)	

[a]Chi-square test.
[b]Mann-Whitney test.

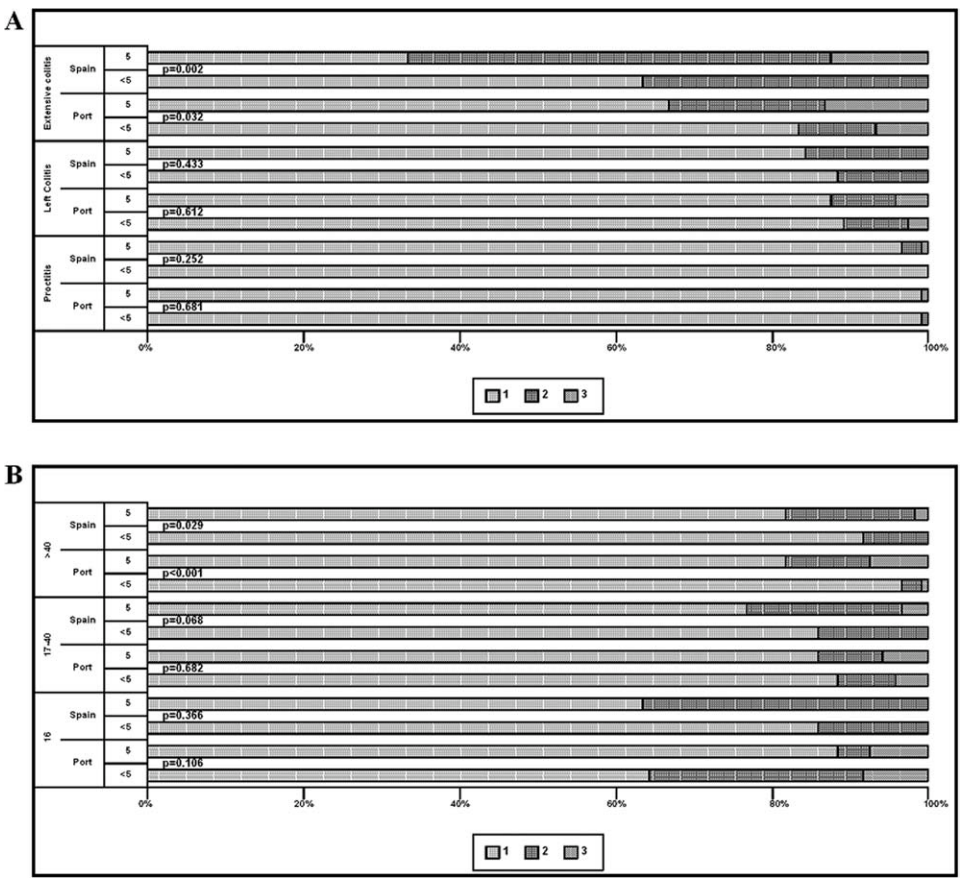

FIGURE 5. Distribution of severity of UC defined by type of treatment administered (adapted from Loftus et al[9]) according to extension of colitis (A) and age at diagnosis onset (B) adjusted by length of disease diagnosed (cut off of five years). Patients were categorized into three different severity grades: group 1 representing mild/moderate disease (patients with no treatment or with salicylates, or episodic pulses of steroids without steroid refraction or dependency), group 2 for severe disease with drug-dependent or drug-refractory behaviour (patients treated with steroids, with steroid resistance or dependency, or immunomodulators/biological) and group 3 for patients with medical refractory disease, submitted to surgery.

TABLE 5. Univariate and Multivariate Analysis of Factors Associated with Immunosuppression and Biological Treatment

	Immunosuppression				Biologic Therapy			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Northern Portugal	Galicia	Northern Portugal	Galicia	Northern Portugal	Galicia	Northern Portugal	Galicia
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Age at diagnosis								
≤16 years	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
17–40 years	0.427 (0.213–0.859)	0.447 (0.189–1.058)	0.557 (0.265–1.171)	0.878 (0.321–2.401)	0.533 (0.118–2.407)	0.785 (0.171–3.601)	0.533 (0.131–2.807)	1.415 (0.288–6.940)
>40 years	0.379 (0.181–0.795)	0.296 (0.122–0.721)	0.479 (0.218–1.052)	0.590 (0.209–1.662)	0.067 (0.006–0.759)	0.531 (0.110–2.566)	0.067 (0.007–0.893)	1.266 (0.244–6.555)
Extent of disease								
Left–side	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Extensive	2.804 (1.900–4.138)	6.244 (3.732–10.447)	2.737 (1.846–4.058)	5.799 (3.433–9.795)	1.625 (0.620–4.259)	6.583 (2.800–15.481)	1.625 (0.559–3.922)	6.329 (2.641–15.166)

Hosmer-Lemeshow test: univariate analysis and multivariate analysis for immunosuppression in northern Portugal, $P = 0.551$; univariate analysis and multivariate analysis for immunosuppression in Galicia, $P = 0.671$; univariate analysis and multivariate analysis for biologic treatment in northern Portugal, $P = 0.781$; univariate analysis and multivariate analysis for biologic treatment in Galicia, $P = 0.440$.

In CD the applicability of the Montreal Classification is only considered accurate in patients with 5 or more years of disease onset, because there is a minimum time of evolution before classifying behavior.[44] In relation to UC patients some qualms persist. In order to elucidate this issue, regarding major clinical characteristics and disease severity, the patients of each country were compared in terms of disease duration in both groups, namely, patients with less or more than 5 years. In this respect, in Portugal there were a larger percentage of patients with proctitis in patients with less than 5 years, while in the extensive colitis group the proportion of patients was constant over time. Longitudinal fluctuation of disease extent has been described[45] and in Portugal a proximal spread from proctitis is perceived to exist. Concerning disease severity, there was a trend toward immunosuppression and surgery in those patients with 5 or more years of disease in extensive colitis; on the other hand, in proctitis and left-sided colitis the severity was immutable over time. Regarding age of disease onset, those diagnosed before 16 years have a more severe initial course in Portugal and Galicia; however, in Portugal this tendency was lost in patients with more than 5 years of disease. A more timely immunosuppression intervention made by pediatricians in the past years in Portugal in light of the latest knowledge suggesting early introduction of immunosuppression in pediatric patients,[46] or by disease severity lessening over time could explain this.

This study presents some limitations. First, it was a cross-sectional study. Second, two different databases were used and crossed, and consequently some differences in data collection could not have been avoided. Notwithstanding, one must stress that several meetings took place in order to unify criteria and explain the aims of the work. In addition, most of gastroenterologists involved were senior gastroenterologists with IBD differentiation, and in Galicia all of them worked in IBD units.

In conclusion, despite some clinical differences, in a large population of UC patients of two independent southern European countries most patients did not need aggressive therapy, and extensive colitis was a clear risk factor for more severe disease. Furthermore, patients diagnosed before 16 years seem to have a more severe initial course, with a greater need for steroids and immunosuppressants.

ACKNOWLEDGMENTS

EIGA: María Victoria Alvaréz, Manuel Barreiro-de Acosta, Pedro Carpintero, Daniel Carpio, Javier Castro, Lucía Dancausa, María Luisa de Castro, Ana Echarri, Alberto Fernández Villaverde, Vicent Hernández, Aurelio Lorenzo, David Martínez Ares, Jesús Martínez Cadilla, Virginia Ollero, Santos Pereira, José Ignacio Rodríguez Prada, Eva Santos, Ramón Vázquez Dourado, Pablo Vega.

GEDII: Amadeu Corte Real Nunes; Ana Isabel Valente; Ana Isabel Vieira; Antónia Duarte; António Marques; Antonio Queiroz; Bernardino Ribeiro; Carolina Duesca; Celeste Fátima Viveiros; Cidalina Caetano; Claudia Sequeira; David Horta; Edgar Gencsi; Estela Monteiro; Fernando Magro; Filipe Gomes Silva; Francisco Portela; Glória Marinho; Helder Cardoso; Helena Vasconcelos; Helena Sousa; Henrique Morna; Horácio Lopes; Isabel Bastos; Isabel Medeiros; Isabel Seves; Isadora Rosa; João Baranda; João Ramos de Deus; Jorge Amil Dias; J Godinho Lopes;; João Freitas; J. Pinto de Matos; Jorge Reis; Jorge Vieira; Jose Cotter; José Estevens; J M Ribeiro; Laura Carvalho; Leopoldo Matos; Luís Correia; Luís Jasmins; Luis Lebre; Luísa Barros; Luísa Gloria; Lurdes Tavares; Marília Cravo; Margarida Marques; Marie Isabelle Cremers; Maria do Rosário Maldonado; Manuel Correia; Maria de Lurdes Gonçalves; Mário César; Miguel Areia; Manuela Ferreira; Mário Júlio Campos; Marta Salgado; Nuno Almeida; Paulo Andrade; Paula Lago; Paula Ministro; Paula Moura Santos; Paula Peixe; Paulo Caldeira; Paulo Freire; Pedro Martins; Raquel Gonçalves; Ricardo Ferreira; Ricardo Freire; Rui Loureiro; Rui Sousa; Rute Cerqueira; Salazar Sousa; Salomé Costa Lima; Sara Folgado Alberto; Silvia Leite; Sofia Mendes; Sónia Barroso; Sandra Lopes; Sónia Nobre; Susana Rodrigues; Tiago Bana e Costa; Vítor Fernandes.

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