Title: **Influence of familial forms of inflammatory bowel disease on the use of immunosuppressants, biological agents and surgery in the era of biological therapies. Results from the ENEIDA project.**

Short title: **Familial vs sporadic IBD**

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ABSTRACT

Background and aims: Familial inflammatory bowel disease (IBD) history is a controversial prognostic factor in IBD. We aimed to evaluate the impact of a familial history of IBD on the use of medical and surgical treatments in the biological era.

Methods: Patients included in the prospectively maintained ENEIDA database and diagnosed with IBD after 2005 were included. Familial forms were defined as those cases with at least one first-degree relative diagnosed with IBD. Disease phenotype, the use of biological agents or surgical treatments were the main outcomes.

Results: A total of 5,263 patients (2,627 Crohn's disease - CD; 2,636 ulcerative colitis - UC) were included, with a median follow-up of 31 months. Of these, 507 (10%) corresponded to familial forms. No clinical differences were observed between familial and sporadic IBD forms except a lower age at IBD diagnosis and a higher rate of males in familial forms of UC. In CD, the proportions of patients treated with thiopurines (54.4% vs 46.7%; p=0.015) and survival time free of thiopurines (p=0.009) were lower in familial forms. No differences were found regarding the use of biological agents . Concerning surgery, a higher rate of intestinal resections was observed in sporadic CD (14.8% vs 9.9%, p=0.027). No differences were observed in UC.

Conclusions: In the era of biological therapies, familial and sporadic forms of IBD show similar phenotypes and are managed medically in a similar way; whether these is due to lack of phenotypical differences or an effect of biological therapies is uncertain.

Keywords: familial history, inflammatory bowel disease, surgery, biologicals

What is already known on this topic:

- Inflammatory bowel diseases's ethiopatogenesis point to an interaction between environmental and genetic factors, being familial history a controversial prognostic factor.
- Biological agents use and need for surgery regarding familial or sporadic forms of inflammatory bowel diseases present conflicting results.

What this study adds:

- Familial and sporadic forms of IBD have similar phenotypes and are managed medically and surgically in a similar way.

How this study might affect research, practice or policy:

- Familial aggregation should not be considered a factor associated with more aggressive disease.

INTRODUCTION

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), have a prevalences of 0.3% and 0.5%, respectively in different countries in Europe, with a progressive increase in incidence in recent decades, particularly in developing countries [1]. Its etiopathogenesis is not yet well established, though multiple studies point to an interaction between environmental and genetic factors [2–8]. In fact, a 7-fold increase in the relative risk of incidence in CD and a 4-fold increase in UC have been reported in relatives of IBD patients [9]. In population-based studies, between 2% and 6% of IBD patients have a familial history of the disease [9,10].

Although environmental factors may be strong contributors to IBD susceptibility and course, it is known that some genetic variants are associated, not only with an increased susceptibility to IBD, but also with age at IBD onset, disease location and behaviour, as well as surgical requirements [11]. Moreover, several genetic polymorphisms have been associated with the response to anti-TNF and anti-IL12/23 therapies. Therefore, it is plausible that IBD familial forms might have different treatment requirements and might also show a different response to medical therapies [12].Haga clic o pulse aquí para escribir texto. Finally, it is also important to consider that familial forms of IBD may share not only a genetic background but also some environmental factors such as diet, geographical location and lifestyle, which may drive disease behaviour.

The disease characteristics and outcomes of familial IBD have been compared with sporadic forms (with no familial history) of the disease and differences in age at diagnosis [13–16], disease location [17], disease pattern [18], extraintestinal manifestations [15], clinical relapse rates [14] and level of dependence in daily life [10] have been observed. Disease phenotype may influence

therapeutic decision-making, and familial forms might therefore be associated with different therapeutic requirements. The availability of selective immunosuppressive drugs (both biological agents and new small molecules) since the beginning of the 21st century changed the paradigm of the therapeutic approach to these conditions. Despite the widespread use of these drugs, there is scarce literature on their effectiveness regarding familial or sporadic forms of the disease. Early studies that compared familial versus sporadic forms of IBD were performed during the pre-biological era [13–15,18]. Later studies mostly assessed non-European populations with heterogeneous access to biological therapies and led to inconclusive results due to low statistical power [9,18–21].

Finally, surgical requirements in UC and CD may also be related to the aggressiveness of the disease. The available studies comparing the need for surgery between familial and sporadic forms obtained conflicting results. In the pre-biological era, no significant differences were observed [15,21], whereas those performed in the biological era showed a trend towards higher surgical requirements in familial forms [9,18–20].

The aim of the present study is to evaluate the impact of a familial history of IBD on the use of medical and surgical treatments in patients diagnosed with IBD since the availability of biological drugs.

METHODS

Study design

This is an observational, retrospective, multicentre, nationwide study. Patients were identified from the ENEIDA project, which is a hospital-based and prospectively maintained database of patients with IBD containing demographic, clinical and therapeutic data on patients with IBD promoted by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) [22]. The database was approved by the local Ethics Committees of all participating centres and all patients signed the informed consent form.

Study population, data collection and definitions

The inclusion criteria were: 1) patients aged 18 years or older at the time of IBD diagnosis; 2) Caucasian ethnicity and born in Spain; 3) IBD diagnosis made after December 2004 and followed prospectively at the same centre. Patients whose date of entry into the database exceeded six months from the date of IBD diagnosis, patients with indeterminate or unclassified IBD and those with a change in the diagnosis were excluded. The ENEIDA database includes, among the risk factors for IBD, the existence of familial cases and their degree of kinship. Familial forms of IBD were defined as those cases with at least one first-degree relative diagnosed with IBD. Sporadic forms were defined as those with no family members (of any degree) with IBD. For this reason, patients with a family history of IBD other than first-degree were also excluded from the study.

Follow-up time was defined as the interval between IBD diagnosis and the last visit, loss to follow-up or death, whichever occurred first.

Data recorded included demographic features, age at diagnosis, smoking habit at diagnosis, IBD phenotype according to the Montreal classification [23](extent, location, disease pattern, perianal disease and extraintestinal manifestations), use and date of initiation of the first biological agent, use and date of thiopurines during follow-up and date of the first IBD-related abdominal surgery.

Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR) and Student's t test was used for comparison. Categorical variables are expressed as absolute values and frequencies and the Chi-square or Fisher's exact test was used for comparison. Patients with UC and CD were analysed separately in order to assess whether there was a different impact on the evolution of the two diseases. Kaplan-Meier curves were used to evaluate survival time free of thiopurines, biological agents and surgery. The log-rank test was used to compare survival curves between familial and sporadic forms.

RESULTS

Among the 68,000 patients included in the ENEIDA project at the time of data extraction (December 2020), 5,263 (2,627 CD and 2,636 UC) met the selection criteria and were included in the analysis. Of these, 507 (10%) corresponded to familial forms (274 [10.4%] CD and 233 [8.8%] UC; p=0.05).

Overall, a higher proportion of patients with CD were active smokers (41%) at the time of diagnosis compared to those with UC (12%) (p<0.0001). Extraintestinal manifestations developed in 12.3% of patients during follow-up. Among UC patients, 32.5% presented extensive forms. In CD, the most frequent location was ileal (45.8%), the predominant disease pattern was inflammatory (74.4%) and 18.3% of patients developed perianal disease. No differences were observed in all these parameters between familial and sporadic forms; however, familial forms were diagnosed at a significantly younger age and a lower proportion of males in UC was observed (**Table 1**).

The median follow-up was similar in both study groups, being 31 months (IQR, 7-57) in sporadic forms and 28 months (IQR, 6-51) in familial forms (p=0.086). A total of 1,409 patients with CD (53.6%) received treatment with thiopurines, compared to 469 (17.9%) of those with UC. **Figure 1** shows the cumulative incidence of thiopurine exposure. The cumulative probability of starting thiopurines at one, three and five years was 52.5%, 61.5% and 65.6% for CD and 14.1%, 21.8% and 25.7% for UC, respectively. In CD, the proportion of patients treated with thiopurines at the end of follow-up (54.4% vs 46.7%; p=0.015) was significantly lower and the survival time free of thiopurines (p=0.009) significantly longer among the familial forms, but these differences were not observed in UC.

Regarding the use of biological agents, a total of 1,598 patients (30.4%) received at least one biological drug during follow-up, with no differences between familial (30.4%) and sporadic forms (29.8%). The cumulative probability of starting biological agents at one, three and five years was 32%, 47.5% and 57.4% for CD and 10.2%, 18.7% and 24.8% for UC, respectively, with no differences between familial and sporadic forms in either CD and UC (**Figure 2**); in fact, the median time for thiopurine introduction and biologic introduction was similar in both study groups (sporadic UC thiopurine/biologic introduction: 17 months (3-42)/10 months (2-30); familial UC thiopurine/biologic introduction: 15 months (3-42)/19 months (6-35); sporadic CD thiopurine/biologic introduction: 4 months (1-19)/7 months(2-22); familial CD thiopurine/biologic introduction: 5 months (2-22)/7 months (2-19).

A total of 444 individuals (8.4%), 69 with UC (2.6%) and 375 with CD (14.3%), underwent surgery during follow-up. The cumulative probability of abdominal surgery at one, three and five years was 10%, 15.8% and 20% for CD and 1.6%, 3.3% and 4.3% for UC, respectively. In UC, 65 patients with sporadic forms (2.7%) and four with familial forms (1.7%) underwent surgery. No differences in the rate of colectomy nor in the time to colectomy were observed between both study groups: sporadic/familial UC: 10 months (1-27)/32 months (8-74) (p=0.254). In an exploratory analysis, no differences in the rate and time to colectomy were observed when only patients with extensive UC were included (data not shown). In CD, a total of 348 patients with sporadic forms (14.8%) and 27 with familial forms (9.9%) underwent intestinal resection (p=0.027), with a marked trend towards a shorter time to first surgery in the sporadic forms (10.4%, 16.2%, 20.7% at one, three and five years) than in familial forms (6.9%, 12%, 13.5%), although this trend did not reach statistical significance (p=0.051) (**Figure 3**).

DISCUSSION

The impact of familial forms of IBD on disease phenotype and therapeutic requirements has been evaluated in a small number of studies with marked methodological differences among them. The definition of familial forms has been particularly heterogeneous among the published studies, having been defined as at least one first-degree relative [14,17,21], two relatives of at least second degree [13], one of second degree [10,19] and even one of third degree [15,18,20]. In addition, certain geographical areas and ethnic groups have a particularly high incidence of IBD. All these factors may explain why the prevalence rates of familial forms of IBD range from 2.6% [10] to 16% [21]. The potential relevance of familial forms relies on the weight that genetics has in both the phenotypic presentation of the disease (which will determine the therapeutic approach in most cases) and the response to drugs. In this sense, the present study was designed to include a population as genetically homogeneous as possible. To this end, we only included patients of Caucasian ethnicity who had been born in Spain. On the other hand, to enhance the potential effect of genetics, we limited the definition of familial forms to those with any first-degree relative diagnosed with IBD and we excluded those patients with second or third-degree relatives diagnosed with IBD. This selection criteria might explain the slightly lower prevalence of familial forms found in our cohort (10%) when compared to those reported in previous studies [13–15,17,18,21].

In line with previous studies, we found a significantly lower age at IBD diagnosis among familial forms. This observation may have different explanations; firstly, the phenomenon of genetic anticipation [10,13–15,18,20], which was claimed some decades ago when the genetic implication in IBD pathogenesis was only suspected. Moreover, the clinical threshold for

suspicion of IBD is lower when there is a family history of IBD and leads to a prompt and targeted diagnostic approach in many cases.

In agreement with similar studies, we did not find differences in UC extent nor in any phenotypic feature of CD between familial and sporadic forms [18,20]. Conversely, a number of previous studies reported a higher prevalence of ileocolic location [13,15], penetrating pattern [15], perianal disease, extraintestinal manifestations [15] and complex disease behaviour (stenosing or penetrating) [18]. Many factors related to the design of the available studies may have biased the obtained results, as the definition of familial IBD or the fact that some of these studies were performed in cohorts from referral centres to which more complex cases are referred. Of course, the use of biological agents and the early introduction of thiopurines may also play a role in preventing disease-related complications, particularly in CD. This is the reason why we decided to identify only incident cases diagnosed as of 2005, when anti-TNF agents were widely and uniformly used in Spain for both CD and UC. In fact, we observed that the cumulative probability of being exposed to biological agents within the first three years from diagnosis was almost 50% in our CD cohort, confirming that the early introduction of biologicals is becoming more and more common, particularly for CD.

Although the main driver of the therapeutic approach in IBD is disease phenotype, other factors may play a role. In this sense, the fact that a familial history of IBD is the main risk factor for developing the disease may also prompt a more intensive approach by the physician, particularly if the index case followed a complicated course. Although this has been previously assessed in some studies, few of them were performed when biological agents were widely used. Globally, we only found a more frequent use of thiopurines (in contrast to previous reports [18,20,21]) and a higher rate of intestinal resection in sporadic forms of CD. We do not have a clear explanation for the higher use of thiopurines in sporadic forms. In fact, given that we observed

a higher rate of first intestinal resections in sporadic forms, we assessed whether this could have resulted from the indication of thiopurines for the prevention of post-operative CD recurrence, but this was not the case (data not shown). Therefore, our hypothesis that the familial history of IBD could influence our therapeutic decision must be rejected. Moreover, the fact that familial forms did not show worse clinical outcomes (disease-related complications and surgery) in spite of a similar (or even less intense) therapeutic approach also supports the idea that familial forms are not phenotypically more aggressive. Nevertheless, it cannot be ruled out that the high rate of early introduction of biologicals may change the natural history of the disease.

Regarding the use of biological agents, our findings are in line with a number of previous studies [9,21], although others found a higher rate of use of anti-TNF agents in familial forms of both CD [19,20] and UC [19]. However, these were single-centre studies from geographical areas with a restricted use of biological drugs. In addition, although familial forms are associated with a younger disease onset and a more intense therapeutic approach is common in paediatric IBD, we excluded those patients with paediatric onset of the disease.

In relation to the need for abdominal surgery, we found a clear trend towards a higher rate of intestinal resections in sporadic forms of CD. The lack of differences in disease phenotype do not support a greater need for surgery except in those patients in whom the diagnosis was not clear, a scenario that is less likely when there is a first-degree relative diagnosed with CD. Older studies did not find differences between familial and sporadic forms [10,13–15,17], but more recent studies reported a higher surgery rate in familial forms of CD [9,20].

Our study has several strengths, such as the strict criteria for defining familial and sporadic forms, the homogeneity in the genetic background of our cohort, being an incident cohort while biologicals agents were widely and uniformly used, and its prospective follow-up. We are also

aware of certain limitations of our study, particularly the follow-up time, which may be too short to evaluate surgical requirements in CD. While most colectomies for refractory disease in UC are performed within the first two years after diagnosis [24], the risk of surgery in CD remains almost constant up to 10 years after diagnosis [25]. In fact, a study by Moller et al [9] observed an increase in surgical requirements in familial forms of CD only when patients with more than two years of disease duration were selected. Moreover, the use of biologicals in almost half of our CD cohort may also change or delay the need for surgery. In addition, the absence of monitoring the IBD family history status of sporadic cases may have underestimated the familial total number of cases in the cohort. Finally, the exclusion of patients with paediatric onset of IBD, in whom the weight of genetics is likely to be greater, might hamper our findings, though the uneven inclusion of paediatric patients among the participating centres in the database led us to their exclusion.

In conclusion, in the era of biological therapies, familial and sporadic forms of IBD have similar phenotypes and are managed medically and surgically in a similar way; whether these is due to lack of phenotypical differences or an effect of biological therapies is uncertain. Therefore, familial aggregation should not be considered a factor associated with more aggressive disease in the era of biological therapies.

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Conflicts of interest

The authors declare the following conflicts of interest: Carlos González-Muñoza has received educational funding from Abbvie, Janssen, Kern Pharma, MSD, Tillots Pharma; Javier P. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma; Beatriz Sicilia has served as consultant or has received research or educational funding or advisory fees from Abbvie, FAES, Chiesi, Dr. Falk, MSD, Tillots Pharma, Khern Pharma, Janssen, Pfizer and Takeda; Fernando Gomollón has served as speaker, consultant or has received research or educational funding or advisory fees from AbbVie, Galapagos, Janssen, MSD, Pfizer, Takeda, Tillots and Faes Farma; Elena Ricart has provided scientific advice / participated in medical meetings / received research funding from / received payment for presentations and advice from: MSD, Schering-Plough, Ferring, Abbvie, Takeda, Janssen, Fresenius Kabi, Pfizer, Kern Pharma; Luisa Castro have been speaker and / or has received research or education funds from MSD, Abbvie, Kern, Gebro, Pfizer, Takeda, Jansen, Ferring, Shire Pharmaceuticals, Faes Farma, Tillotts Pharma, Pfizer; Montserrat Rivero has served as speaker, consultant and advisory member for Pfizer, Takeda and Janssen; Francisco Mesonero has served as speaker for and has received consulting fees from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring, Kern-Pharma, Dr. Falk Pharma, Galapagos, Chiesi and Faes Farma; Lucía Márquez has served as speaker and / or has received research or educational funds

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Author contributions

CGM, EGP and ED designed the study, performed statistical analyses, interpreted the results and drafted the manuscript. MC and JGA participated in the statistical analysis. The remaining authors included patients in the database and critically reviewed the manuscript. All authors are aware and agree to the contents of the manuscript and accept their authorship.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Table 1. Characteristics of patients with sporadic and familial forms. Data are expressed in absolute value (frequency) and median (interquartile range).

	Sporadic (n=4,756)	**Familial** (n=507)	**p-value**
Males			
Crohn's disease	1245 (52.9)	131 (47.8)	0.110
Ulcerative Colitis	1287 (53.6)	109 (46.8)	0.048
Age at diagnosis (*years*)	42.7 (30-56)	40.1 (28-53)	0.022
Follow-up time (*months*)	31 (7-57)	28 (6-51)	0.086
Active smoking habit at diagnosis			
Crohn's disease	942 (41.5)	105 (40.1)	0.650
Ulcerative Colitis	266 (11.7)	29 (12.9)	0.574
CD phenotype			
ileal/colonic/ileo-colonic	1072/351/841 (47/16/37)	132/42/88 (50/16/34)	0.521
inflammatory/stricturing/penetrating	1742/369/242 (74/16/10)	213/34/23 (79/13/8)	0.221
Extensive UC	784 (32.6)	74 (31.8)	0.788
Perianal disease during follow-up (fissure, fistulae, abscess)	434 (9.2)	49 (9.8)	0.681
Extraintestinal manifestations during follow-up	582 (12.3)	64 (12.6)	0.801

Figure legends

Figure 1. A) Cumulative incidence of thiopurine exposure in ulcerative colitis (dotted line) and Crohn's disease (continuous line). B) Cumulative incidence of thiopurine exposure in ulcerative colitis regarding familial forms (dotted line) and sporadic forms (continuous line). C) Cumulative incidence of thiopurine exposure in Crohn's disease regarding familial forms (dotted line) and sporadic forms (continuous line).

Figure 2. Cumulative incidence of biological agent exposure for familial forms (dotted line) and sporadic forms (continuous line) in ulcerative colitis (A) and in Crohn's disease (B)

Figure 3. Cumulative incidence of surgery for familial forms (dotted line) and sporadic forms (continuous line) in ulcerative colitis (A) and in Crohn's disease (B)

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Appendix

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