Phenotypic concordance in familial inflammatory bowel disease (IBD). Results of a nationwide IBD Spanish database

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Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Familial aggregation;

Abstract

Background & aims: Disease outcome has been found to be poorer in familial inflammatory bowel disease (IBD) than in sporadic forms, but assessment of phenotypic concordance in familial IBD provided controversial results. We assessed the concordance for disease type and phenotypic features in IBD families.

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1. Introduction

The most widely accepted pathogenic hypothesis for inflammatory bowel diseases (IBD) considers both ulcerative colitis (UC) and Crohn’s disease (CD) as conditions characterized by exaggerated and sustained immune response against intestinal luminal antigens (e.g. the intestinal microbiota), which develops in genetically susceptible individuals under the influence of some environmental factors unfortunately not fully understood.3-5

Sharing susceptibility genes and/or environmental factors by members of the same family must result in familial aggregation for IBD.6-9 Indeed, several studies have shown that relatives of IBD patients have a much higher likelihood to develop IBD, as compared to the general population,10-15 so that familial history is considered to be the strongest risk factor for IBD. Concordance for disease type has been reported by most16-20 but not all21 studies of familial aggregation in IBD. However, data on concordance in phenotypic characteristics and severity among disease-concordant family members are more controversial.13,17-20,22,23 Moreover, data on IBD familial aggregation and concordance in the Mediterranean area are scarce.16,19,24 Reliable estimates of concordance for phenotypic features and disease severity might be of help in planning therapeutic strategies in the latest affected members of IBD families.

The aim of the present study was to assess the prevalence of familial IBD, as well as the concordance for disease type and phenotypic features in IBD families, using data from a nationwide IBD Spanish hospital database.

2. Methods

The ENEIDA Project is a nationwide, hospital-based, prospectively maintained, Spanish database of incident and prevalent IBD cases followed in Spanish hospitals since January 2006, promoted by the Spanish Working Group in Crohn’s Disease and Ulcerative Colitis (GETECCU). Clinical and epidemiological data such as the type of IBD, the extent/localization and behaviour (for CD) of the disease, the use of different therapies, the need for surgical treatment, and risk factors for IBD, including familial history, are recorded in ENEIDA, and prospectively updated since the date of inclusion of the patient in the database. Events occurring before the patient’s inclusion in ENEIDA were retrospectively acquired from local databases or case records. The ENEIDA database is kept under continuous external monitoring for completeness and consistency of the data entered, but these can only be modified by each local investigator.

The study was approved by the ENEIDA Steering Committee. The ENEIDA Project was approved by the Ethics Committee of each participant hospital. Informed consent to participate in the ENEIDA Project was obtained from all patients.

Patients with familial history of IBD in the ENEIDA database were identified. Among these, those families with at least two members included in the database – and hence with complete epidemiological and clinical data – were selected for concordance assessments.

2.1. Data collection and definitions

Data collected included gender, age at diagnosis, type of IBD (CD, UC, or unclassified IBD), smoking status (active smoker, never smoker, or former smoker) at diagnosis, extent (for UC), localization (for CD), and behaviour (for CD) of the disease, perianal involvement, ever use of immunosuppressors or biological agents, need for intestinal surgical resection, and extraintestinal manifestations. Familial history of IBD was recorded as the presence or absence of any relative with IBD. In patients with positive familial history, the type of the IBD and the familial relationship of the affected relatives were also recorded. In incident cases, all these data were obtained from the anamnesis of the patient at the time of inclusion in the database. In prevalent cases, they were searched for in the patient’s case record. In the case that they were not explicitly recorded in the case record, the patient was asked for that at the first routine follow-up visit. No further confirmation of the IBD diagnosis was required for those affected relatives not included in the ENEIDA database.

Diagnosis of CD and UC was based on standard clinical, endoscopic, radiological, and histological grounds.25 Disease extent/localization and CD behaviour were defined according to the Montreal classification.26 The extent of UC was
endoscopically classified as proctitis (E1), left-sided colitis (up to the splenic flexure) (E2), and extensive colitis (proximal to the splenic flexure) (E3). The location of CD was based on identifying macroscopic evidence of CD in any part of the gastrointestinal tract. Possible locations included the ileum (L1), colon (L2), ileum and colon (L3), and the upper gastrointestinal tract (L4), with or without perianal involvement (p). CD behaviour included inflammatory (B1) disease (without fistulizing or stricturing complications), stricturing (B2) disease, defined as the presence of clinical symptoms of partial or complete obstruction with fixed narrowing and/or narrowing with proximal dilatation, and fistulizing (B3) disease, which included the presence of enteric fistulas, intraabdominal abscesses, or bowel perforation. Disease extent/location and disease behaviour were determined according to at least one imaging technique (endoscopy, barium meal and follow through, or a cross sectional imaging technique). The maximal extent of involvement and the most severe form of disease behaviour at any time since diagnosis were recorded.

2.2. Concordance assessments

As mentioned, concordance assessments were done in those families with at least two affected members included in the ENEIDA database. For concordance analyses, the members of each family were grouped in as many consanguineous pairs as possible.

Primary concordance analysis was made for the type of IBD. Separate analyses were performed according to the concordance for smoking habit at diagnosis. Secondary concordance analyses – which were separately done in pairs concordant for UC and CD – included phenotypic features (UC extent, CD location and behaviour, perianal involvement, extraintestinal manifestations) and therapeutic requirements (immunosuppressors, biological agents, resective surgery) as indicators of severity of the disease.

Subgroup analyses, according to the degree of familial relationship, and generation, were also done.

2.3. Statistical methods

Quantitative and qualitative variables are expressed as median plus interquartile range (IQR) and frequencies, respectively. Comparisons of quantitative variables in pairs were made with the Wilcoxon signed rank test.

Concordance within pairs was assessed by computing the linear Cohen's Kappa (κ) index from contingency tables, given by $\kappa = \frac{(p_o - p_e)}{(1 - p_o)}$, where $p_o$ is the proportion of observed agreement, and $p_e$ is the proportion of agreement expected by chance. As the $\kappa$ index takes into account the probability of agreement by chance, it is a more conservative estimation of concordance than the concordance index (i.e. the proportion of agreements against the total number of pairs).

For those features with more than two categories, the bi-quadratic weighted $\kappa$ was obtained by giving weights to the frequencies in each cell of the table according to their distance from the diagonal that indicates agreement. Ninety-five percent confidence interval (CI) for every $\kappa$ value is provided. If the 95%CI contains the zero value, the concordance is considered not significant. Also, a “strength of concordance” was attributed to the $\kappa$ value, according to the classification by Landis & Koch, who characterized values $<0$ as indicating no concordance, and 0–0.20 as poor, 0.21–0.40 as mild, 0.41–0.60 as moderate, 0.61–0.80 as good/substantial, and 0.81–1.00 as very good/almost perfect concordance.

3. Results

At the time the present study was undertaken, the ENEIDA database included 11,905 patients (40% incident cases), with a year of diagnosis ranging from 1954 to 2009, and a median follow-up of 125.5 months (IQR: 69.9–208.6) from diagnosis of IBD. Seven hundred ninety-eight of these patients had familial history of IBD (418 CD, 364 UC, 16 unclassified IBD) for a 7% global prevalence of familial IBD (8.8% in prevalent vs. 3.5% in incident cases; p < 0.0005). Among these, 107 familial groups had two or more affected members included in the database (95 with 2 members, 8 with 3 members, 3 with 4 members and 1 with 5 members) for a total of 231 patients (135 CD, 92 UC, 4 unclassified IBD), and 144 consanguineous pairs available for concordance analyses. Of these, 49 pairs (34.0%) were parent/child, 57 (39.6%) siblings, 15 (10.4%) uncle/aunt/nephew/niece, 20 (13.9%) first cousins, and 3 (2.1%) grandparent/grandchild. No instance of twins was found among the 108 families studied. One hundred and six pairs (73.6%) were first-degree relatives, and 77 pairs (53.5%) were composed of members of the same generation. By the time of diagnosis, 87 out of 231 patients (38%) were active smokers, 124 (54%) never smokers, and 20 (8%) former smokers. For purposes of concordance analysis, both never smokers and former smokers were considered as non-smokers. Sixty-eight and 30 out of 144 pairs agreed for non-smoking, and active smoking, respectively, for a concordance rate of 68% for smoking status (κ = 0.31 (95%CI: 0.15–0.47); mild concordance).

The youngest members in the pairs were followed up for a significantly shorter time (median: 100.5 months, IQR: 65.4–144.2) than the older ones (median: 151.9 months, IQR: 92.2–221.4; p = 0.0005). The youngest members in the pairs were diagnosed with IBD at a significantly younger age than the oldest ones, both for pairs of the same and different generations (Table 1).

3.1. Primary concordance analysis: type of IBD

One hundred and ten out of the 144 pairs (76%) agreed for the type IBD: 41 with UC and 69 with CD, which means a moderate degree of concordance, with a $\kappa = 0.58$ (95%CI: 0.42–0.73) (Table 2). When the analysis was performed in the 137 pairs without members with unclassified IBD, the results were similar with a $\kappa = 0.59$ (95%CI: 0.42–0.75). Also, the strength of concordance was similar in different subgroups of pairs, as shown in Table 3.

Fifty (73%) out of 68 pairs with both members non-smoking at diagnosis agreed for disease type (30 for UC, 20 for CD), with a $\kappa = 0.49$ (95%CI: 0.29–0.69). Twenty-six (87%) of the 30 pairs in which both members were active smokers at diagnosis were concordant for disease type, most of them for CD (n = 22), with $\kappa = 0.60$ (95%CI: 0.23–0.96). Finally, 35 (76%) of the 46 pairs discordant for smoking habit at diagnosis were concordant for disease type (8 for UC, 27 for CD) with a $\kappa = 0.43$ (95%CI: 0.15–0.70). In 8 of the 11 pairs discordant for both smoking habit and disease type, the smoker member developed CD and the non-smoker one developed UC.
3.2. Concordance analyses for phenotypic characteristics

3.2.1. Pairs concordant for UC (Table 4)
Seventeen out of the 41 pairs with both members suffering from UC (41%) were also concordant for localization of the disease, with a \( \kappa \) index of 0.1 (poor concordance). Immunosuppressors were used in 28 of the 82 patients in UC pairs, with a poor degree of concordance (\( \kappa = 0.02 \)). Biological agents and colectomy were required in only seven and six of these patients, respectively. There was no concordance at all for any of these two events, with \( \kappa \) indices of \(-0.07\) and \(-0.04\), respectively. Concordance was also absent for extraintestinal manifestations (\( \kappa = -0.06 \)), which only occurred in 10 out of the 82 patients in UC pairs. These results were similar in different subgroup analyses (see Supplemental Table 1).

3.2.2. Pairs concordant for CD (Table 5)
Thirty-one out of the 69 pairs with both members suffering from CD (45%) were also concordant for localization of the disease, with a \( \kappa \) index of 0.1 (poor concordance). Stricture and fistulizing behaviour occurred in 34 and 29 of the 138 members of the CD pairs, respectively, with a mild degree of concordance for both features (\( \kappa = 0.26 \) in both). There was a poor concordance (\( \kappa = 0.07 \)) for perianal disease, which occurred in 47 of the 138 patients of the CD pairs. Immunosuppressors and biological agents were used in 105 and 46 patients of the CD pairs, with poor (\( \kappa = 0.01 \)) and no concordance at all (\( \kappa = 0.04 \)), which was needed in 61 patients, showed a mild degree of concordance in CD pairs (\( \kappa = 0.23 \)). Concordance was absent for extraintestinal manifestations (\( \kappa = -0.04 \)), which occurred in 25 out of the 138 patients in CD pairs. Similar results were found in subgroup analyses (See Supplemental Table 2).

4. Discussion
In the present study, we assessed the prevalence of familial IBD in a very large cohort of patients, and the phenotypic concordance in 144 family pairs (belonging to 107 families with two or more members with IBD). For this purpose, we used data from the Spanish database ENEIDA. In this database, phenotypic characteristics are recorded in a standardized way according to the Montreal classification, which improves the accuracy of the information obtained. Also, events occurring since January 2006 are prospectively collected, and the information of patients enrolled is updated after each outpatient visit or hospital event, so that follow-up data are mostly prospective. Furthermore, data collection is externally monitored for completeness and consistency. All these facts make our results particularly robust and reliable, with a large number of subjects included, allowing for subgroup analyses as well.

A limitation of the present study is that it is not truly population-based. Being hospital-based, the ENEIDA database might a priori overrepresent IBD patients with positive family history or with a more severe disease course, as compared to population-based cohorts. Nevertheless, due to the open access of patients to referral centres, the growing number of IBD units in hospitals, and the advice of patients associations, care of IBD patients in Spain (both as an in-patient and out-patient basis) is nowadays highly concentrated in the hospital setting, regardless of severity. Indeed, our 7% prevalence of familial IBD fits well within the range of prevalence reported in population-based studies in Western countries, which varies from 4.5% to 11.5%, and is quite similar to that reported in the Mediterranean area (Italy). Anyway, describing the prevalence of familial disease was not the primary aim of this study since, for those relatives with IBD not included in the database, no further confirmation of the diagnosis was looked for beyond the information obtained from the index patient included in ENEIDA.

Diagnostic anticipation in familial IBD – i.e. disease diagnosis at an earlier age in the youngest pair member – has been repeatedly reported both in parent–child pairs, and other second generation relationships. The reasons for this phenomenon are intriguing and may include true genetic anticipation, a cohort effect (i.e. a greater impact of an environmental factor in recent years), or several biases inherent to the parent–child study design (e.g., ascertainment bias, selection bias). Our data confirm diagnostic anticipation in affected individuals in the second generation but, in contrast to previous reports, also in the youngest subject in sib-sib and other family pairs within the same generation, thus arguing for a role of a higher suspicion rate in the youngest members of IBD families, rather than genetic or cohort effects.

Some studies, including a recent one from the ENEIDA database, reported an earlier disease onset, increased risk for extraintestinal manifestations, as well as a more severe disease in familial IBD as compared to sporadic cases. However, data on concordance in phenotypic characteristics and severity among disease-concordant family members are more controversial.
habit as well. In agreement with previous reports, in the smoking at diagnosis, and in those discordant for the smoking assessed in pairs concordant for active smoking or non-smoking for disease type remained unchanged when it was separately described16 of 76% for disease type compares well with those previously concordant for that item by chance. Our concordance index frequency of an item, the greater the probability to be very frequent in the sample studied since the greater the degree of concordance either in the disease type, or in the phenotypic features and indicators of disease severity in pairs of relatives concordant for both EC and UC. Most studies dealing with these issues have assessed concordance using the simple concordance index (i.e. the proportion of agreements against the total number of pairs) with reported rates of concordance for disease type ranging from 67% to 86%, which are usually qualified as "high". Instead, we chose to compute the $\kappa$ index, which provides a more conservative estimate of concordance, as it takes into account the probability of agreement by chance. This is particularly relevant for items (or their absence) that are very frequent in the sample studied since the greater the frequency of an item, the greater the probability to be concordant for that item by chance. Our concordance index of 76% for disease type compares well with those previously described but, when interpreted in terms of $\kappa$ index (0.58) it can just be qualified as "moderate". Concordance for disease type remained unchanged when it was separately assessed in pairs concordant for active smoking or non-smoking at diagnosis, and in those discordant for the smoking habit as well. In agreement with previous reports, in the majority of pairs discordant for both disease type and smoking habit, the smoker developed CD and the non-smoker was diagnosed with UC.

Phenotypic concordance in familial IBD has been reported to be higher in CD than UC families. Several studies have reported a high degree of agreement for both location and clinical disease behaviour in pairs of relatives with CD, with concordance indices ranging from 46% to 83%, and 49% to 73%, respectively. In agreement with other studies, however, we were unable to find relevant concordance for these phenotypic features as well as for the presence of perianal disease and extraintestinal manifestations in CD pairs. Also, in our series concordance was poor or absent for the extension of the disease and the presence of extraintestinal manifestations in pairs of UC relatives, in accordance with previous reports. These results are in contrast with the high degree of phenotypic concordance in studies on monzygotic twins, even in those assessing concordance by means of the $\kappa$ index. Of note, no instance of twin pairs was found in our series. As a whole, these findings support the idea that genetic factors predominantly account for concordance in familial IBD. In line with this concept, Bengtson et al. reported the highest disease concordance in monozygotic twins, and the lowest in ordinary siblings, while dizygotic twins showed intermediate values. However, the increased risk for concordant disease among dizygotic twins, as compared to ordinary siblings, might underscore the importance of shared environment already in utero or during childhood in familial IBD.

As for disease phenotype, we were unable to demonstrate any relevant concordance for indicators of disease severity – namely, the need for immunosuppressors, biological agents or resective surgery – both in UC and CD pairs of relatives. As far as we know, these aspects had not previously been assessed, except for bowel resection in familial CD, with poor concordance rates reported. One can argue that period or cohort

### Table 2
Concordance for type of inflammatory bowel disease in the 144 pairs studied.

<table>
<thead>
<tr>
<th>Youngest member</th>
<th>k (95%CI)</th>
<th>p-Value</th>
<th>Strength of concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UC</td>
<td>CD</td>
<td>uIBD</td>
</tr>
<tr>
<td>Oldest member</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>41</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>CD</td>
<td>9</td>
<td>69</td>
<td>5</td>
</tr>
<tr>
<td>uIBD</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>89</td>
<td>5</td>
</tr>
</tbody>
</table>

UC = ulcerative colitis; CD = Crohn’s disease; uIBD = unclassified inflammatory bowel disease.

### Table 3
Subgroup analyses of concordance for type of inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Kind of pair (n)</th>
<th>k (95%CI)</th>
<th>p-Value</th>
<th>Strength of concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent/child (n = 49)</td>
<td>0.58 (0.10 to 1.00)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>Siblings (n = 57)</td>
<td>0.52 (0.09 to 0.96)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>Uncle-aunt/nephew-niece (n = 15)</td>
<td>0.54 (0.13 to 0.95)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>First cousins (n = 20)</td>
<td>0.72 (0.37 to 1.00)</td>
<td>&lt;0.001</td>
<td>Good</td>
</tr>
<tr>
<td>Grandparent/grandchild (n = 3)</td>
<td>Not calculated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1st degree relatives a (n = 106)</td>
<td>0.56 (0.24 to 0.88)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>2nd degree relatives b (n = 38)</td>
<td>0.63 (0.38 to 0.89)</td>
<td>&lt;0.001</td>
<td>Good</td>
</tr>
<tr>
<td>Same generation c (n = 77)</td>
<td>0.56 (0.16 to 0.95)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>Different generation d (n = 67)</td>
<td>0.55 (0.15 to 1.00)</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

a Parent/child, or siblings.
b Uncle-aunt/nephew-niece, grandparent/grandchild, or first cousins.
c Siblings or first cousins.
d Parent/child, uncle-aunt/nephew-niece, or grandparent/grandchild.
effects (availability of new drugs in recent years, different
time of follow-up, changes in recommended therapeutic
strategies, etc.) may account, at least in part, for the lack of
congruence of these evolutive issues. However, this appears
not to be the case in our patients, since the frequency of the
different items was quite similar in the senior and the junior
members of the pairs (see Tables 4 and 5).

Conceivably, the multicentric character of the study (14
hospitals) with a very long follow-up period could account in
part for the lack of phenotypic congruence. However, data
on extent/localization and clinical behaviour of the disease
are based on quite objective data which make interobserver
variability scarcely relevant. It is also not probable that
different criteria between centres in the management of
these patients could contribute to the lack of congruence in
need for therapies since, in 143/144 pairs included in the
study both members were diagnosed and treated at the
same centre.

On the other hand, differences in quitting tobacco during
follow-up in pair members could also contribute to the lack of
congruence in the outcome of the disease. Unfortunately,
data on smoking status during follow-up are not available in
ENEIDA database.

In summary, a) the prevalence of familial IBD in Spain
compares well with that reported in other Western coun-
tries, b) familial IBD is associated with diagnostic anticipa-
tion in younger individuals, both in the same and the second
generation, and c) familial history of IBD does not allow
predicting any phenotypic feature of the disease other than
the IBD type, and this only with moderate precision. Having
a relative with a severe disease course does not appear to be
per se reason enough to adopt more aggressive therapeutic
measures in IBD patients.

**Potential conflict of interests**

None of the authors have conflict of interest to declare.

**Author contributions**

Eduard Cabré conceived the study, performed data analy-
ses, and drafted the manuscript. Miriam Mañosa, Valle
García-Sánchez, Ana Gutiérrez, Elena Ricart, Maria Esteve,
Jordi Guardiola, Mariam Aguas, Olga Merino, Angel Ponferrada,
Javier P. Gisbert, Esther Garcia-Planella, Gloria Ceña, José L.
Cabriada, and Miguel Montoro participated in the acquisition of
data and revised the draft of manuscript. Eugeni Domènech
conceived the study, performed data analyses, and revised the
draft of manuscript. All authors read and approved the final
manuscript.

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ENEIDA project. The funding sources had no involvement in

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**Table 4** Phenotypic concordance in the 41 pairs concordant for ulcerative colitis.

<table>
<thead>
<tr>
<th></th>
<th>Youngest member</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E1</td>
<td>E2</td>
<td>E3</td>
<td>Total</td>
</tr>
<tr>
<td>1) Extension (E) of the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td>Oldest member</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>E2</td>
<td>11</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>E3</td>
<td>7</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>20</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>2) Extra-intestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>manifestations</td>
<td>Oldest member</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>31</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>39</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>3) Use of immuno-suppressors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oldest member</td>
<td>18</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>14</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>27</td>
<td>14</td>
<td>41</td>
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<tr>
<td>4) Use of biological agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oldest member</td>
<td>34</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>36</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>5) Need for colectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oldest member</td>
<td>35</td>
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<td>36</td>
</tr>
<tr>
<td></td>
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<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>40</td>
<td>1</td>
<td>41</td>
</tr>
</tbody>
</table>

E1 = proctitis, E2 = left-sided colitis (up to the splenic flexure), and E3 = extensive colitis (proximal to the splenic flexure).
the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.12.005.

References
