Female patients suffering from inflammatory bowel diseases are treated less frequently with immunosuppressive medication and have a higher disease activity

A subgroup analysis of a large multi-centre, prospective, internet-based study

I. Blumenstein a,⁎, E. Herrmann b, N. Filmann b, C. Zosel a, W. Tacke c, H. Bock c, A. Dignaß d, F. Hartmann e, S. Zeuzem a, J. Stein e, O. Schröder a

a First Department of Internal Medicine, Division of Gastroenterology, Goethe-University Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany
b Institute of Biostatistics and Mathematical Modelling, Department of Medicine, Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany
c Quality Management Group of Gastroenterologists in Hesse, Frankfurt/Main, Germany
d Division of Internal Medicine I, Agaplesion Markus Hospital, Wilhelm-Epstein-Str.2, 60431 Frankfurt/Main, Germany
e Division of Internal Medicine, St. Marien Hospital, Richard-Wagner-Strasse 14, 60318 Frankfurt/Main, Germany

Received 13 October 2010; received in revised form 18 December 2010; accepted 21 December 2010

Abstract

Background: The introduction of immunosuppressants and biologic agents has led to active debate and research about optimal therapeutic strategies considering risk factors and predictors of clinical outcome in inflammatory bowel disease (IBD). Data about gender-specific treatment differences and risk factors is lacking for IBD.

The aim of the present study was to evaluate gender-related differences in the treatment of a distinct IBD patient population treated in the Rhein-Main region, Germany.

Methods: Data about past medical history, disease status and medical treatment of 986 outpatients treated in ten gastroenterological practices and three hospitals were collected from November 1st 2005–July 31st 2007 and analyzed with regard to gender-related differences in therapy and disease management.
Results: With the exception of an extended disease duration in women, no significant gender-related differences in demographic and clinical characteristics were observed. Men showed a significantly higher remission rate than women (p=0.025), while women received significantly less immunosuppressive medication compared to men (p=0.011). In addition, treatment with immunosuppressants was not different in women with child-bearing potential compared to menopausal women.

Conclusion: Our investigation demonstrates for the first time gender-specific differences in the therapeutic management in a large cohort of IBD patients.

© 2011 European Crohn’s and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

1. Introduction

Inflammatory bowel disease (IBD) is a group of idiopathic, chronic inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). Both diseases are associated with significant morbidity, the need for medical treatment, surgery and a slightly increased mortality.1,2

CD and UC are most commonly diagnosed in the late adolescence and early adulthood (for review see1). Gender distribution in IBD appears to be dependent on the disease subtype. There is consistent data that the prevalence of females in CD is greater with gender ratios ranging from 1.1 to 1.4.3–5 On the other hand, if there is slight gender predominance in UC, it rests with males.6,7 The high prevalence in younger female patients with child-bearing potential retrieves uncertainties regarding medical treatment before and during pregnancy as well as the lactation period. Nevertheless, in contrast to other disease entities such as cardiovascular diseases,8,9 autoimmune connective tissue disorders,10 diabetes mellitus11, and cancer,12 data about gender-related differences in the management of IBD is lacking. However, there have been a few studies published on gender-specific issues with respect to the clinical course of IBD. In UC, inflammatory burden, disease extent, risk of hospitalization, or risk of colectomy were found to be independent of sex.13 In contrast, frequency of extraintestinal manifestations, and need for ileocolic resections as well as a positive family history were more often observed in females suffering from CD.14 In addition, one large outcome study demonstrated that IBD confers a lower risk of colorectal cancer to female than to male patients.15 However, the underlying reason behind the latter observations remains obscure to date.

We have previously reported on the medical diversity conducted by various health care services, e.g. gastroenterological practice vs. hospital outpatient service, in a large cross-sectional study in the Rhein-Main region in Germany.16 In the same manner, we recently also published a preliminary data analysis with respect to gender-related medical treatment in a similar patient cohort. There, we found no statistically significant discrepancies between male and female patients treated in gastroenterological practices or outpatient services of hospitals.17 Here we present data subjected to a more refined data analysis uncovering for the first time disparities in the treatment with immunosuppressive medication between male and female patients suffering from IBD.

2. Patients and methods

2.1. Patient cohort

All patients with confirmed diagnosis (meeting the diagnostic criteria of Lennard-Jones and Truelove and Witts18,19) of IBD, receiving secondary care for IBD in one of ten gastroenterological private practices and three hospitals (one university hospital and two municipal hospitals with main focus on IBD) in the Rhein-Main region, were eligible for inclusion in the study. Data about past medical history, disease status, and medical treatment of 986 outpatients were collected from November 1st 2005–July 31st 2007. Only fully completed and consistent data sets of patients with CD or UC were included. Thus a similar, though not identical patient cohort was analyzed compared with the preliminary analysis.17

2.2. Patient data acquisition tools

The data acquisition procedure has been described previously.16 At the initial visit, data sheets were used to collect demographic patient data as well as clinical data about past medical history, actual disease status, and medication (aminosalicylates, corticosteroids, budesonide, azathioprine (AZA), 6-mercaptopurine (6-MP), cyclosporine A (CSA), methotrexate (MTX), tacrolimus and infliximab).

After data entry, completeness and logic of data was checked electronically. Incomplete data sets were highlighted and reported to the respective data entering person, who completed data sets consecutively.

2.3. Activity scores

The disease activity was determined according to the Harvey Bradshaw index (HBI) for CD20 and the Clinical activity index (CAI) for UC.21 Disease activity was classified in 3 activity groups. In the remission group patients with no disease activity (HBI ≤ 4 points or CAI ≤ 5 points) were pooled. Mild to moderate active disease was expressed as HBI 5–16 or CAI 6–10 points, respectively. Severe disease activity was thought to be present in patients with HBI > 16 or CAI > 10.

2.4. Analysis of medication therapy

Analysis of medication therapy was based on the initial visit medication therapy data sheet (cross sectional study). In total, 986 complete medication therapy data sets were available for analysis. The medication was divided into three
classes: the first group included aminosalicylates and corticosteroid medication. The second group consisted of immunosuppressive agents (e.g. AZA, 6-MP, MTX, CSA, and tacrolimus). In the third group all biologic agents (at that time only infliximab was available in Germany) were pooled.

2.5. Data analysis

All electronic patient data were transmitted online to the company IOMTech in Berlin, Germany, for quality assurance, storage, and analysis. Groups were compared with \( \chi^2 \) and Wilcoxon–Mann–Whitney U test without and with stratification (Cochran test). Note that the stratified test checks for homogeneity in the odds ratios of a variable between several groups as well as for significant difference from 1 in the overall odds ratio. All tests were two-sided and \( p \)-values below 5% were considered significant. Conditional density plots were obtained from nonparametric kernel density estimation. Statistical analysis of data was done using IBM SPSS Statistics 18 (IBM SPSS, Chicago, IL, USA) and R (R Foundation of Statistical Computing, Vienna, Austria).

2.6. Ethical considerations

The principle of an internet-based, pseudonymised documentation was approved by the Hessian bureau of data protection.

3. Results

3.1. Gender-related demographic and clinical characteristics

Demographic and clinical characteristics from 986 patients (CD=515, 52.2%; UC=471, 47.8%) treated in either one of the ten participating private practices or in one of the three hospitals were pooled (Table 1). The proportion of female patients diagnosed with CD was higher than the proportion of female patients diagnosed with UC in this patient cohort (57.9% vs. 50.7%, \( p = 0.025 \)). No significant gender-specific differences were observed in the CD and UC patient groups in terms of disease characteristics according to the Vienna classification (CD) or the Montreal classification (UC, Table 2, \( p > 0.20 \) in all cases). A trend towards a higher frequency of surgery and more extraintestinal manifestations, including about 80% musculoskeletal manifestations, in women suffering from CD was observed (\( p = 0.100 \) and \( p = 0.075 \), respectively, Table 1). The fraction of active smokers was similar in men and women (Table 1). Although no gender-specific difference in age at presentation of men and women in CD and UC patients could be observed, women with CD exhibited a statistically significant longer duration of disease (\( p = 0.004 \), Table 1). As displayed in Table 1, men showed a markedly higher remission rate than women (58.5% vs. 53.0%, \( p > 0.20 \) in CD, and 72.0% vs. 63%, \( p = 0.039 \) in UC respectively, overall \( p = 0.025 \) after stratification). In accordance, female patients were over-represented in the group of active disease.

3.2. Gender-related medical treatment

In order to assess possible causal differences in treatment strategies applied to men and women, we further analyzed the data sets with complete medical history (\( n = 904; 91.7\% \) of the total study population). Table 3 summarizes the medication prescribed to men and women with CD and UC. In general, women suffering from CD were treated less frequently with IBD specific medication (\( p = 0.001 \)). On the other hand, in UC no such trend could be observed.

By taking a more detailed look into the various classes of medical therapy, another clear gender-specific treatment difference was apparent: immunosuppressive medication was prescribed less frequently to women (overall \( p = 0.011 \) after stratification, Fig. 1) and the odds ratio was not significantly different between the two disease entities. In CD, women were treated in 37.9% with immunosuppressive medications, whereas men received this class of therapy in 46.9%. Men suffering from UC were prescribed immunosuppressants in 34.3%, women only in 26.3% (Table 3).

Only about 5% of patients received anti-TNF medication. Women received anti-TNF treatment less frequently than men.

| Table 1 | Patients’ characteristics of study cohort. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Male patients   | Female patients | \( p \)          |
| No of patients (%) | 449 (45.5) | 537 (54.5) |                |
| No (% of disease group, % of gender group) of patients | 217 (48.3, 42.1) | 232 (51.7, 49.3) | 298 (55.5, 57.9) | 239 (44.5, 50.7) |                |
| Age at presentation (y) (mean SD) | 40.9 (13.7) | 45.5 (14.8) | 42.7 (13.3) | 44.1 (15.5) | \( p = 0.146 \) | \( p = 0.190 \) |
| Duration of disease (y) (mean SD) | 10.3 (9.4) | 9.0 (7.6) | 12.9 (10.0) | 11.5 (11.0) | \( p = 0.004 \) | \( p = 0.136 \) |
| Surgery (%) | 87 (42.6) | 10 (4.4) | 147 (50.5) | 14 (6.0) | \( p = 0.100 \) | \( p = 0.20 \) |
| Extraintestinal manifestations (%) | 29 (13.4) | 34 (14.7) | 58 (19.5) | 34 (14.2) | \( p = 0.075 \) | \( p = 0.20 \) |
| Active smoker (%) | 31 (17.2) | 16 (8.0) | 51 (19.7) | 15 (7.5) | \( p > 0.20 \) | \( p > 0.20 \) |
| Disease status |                |                |                |                |                |                |
| Remission (%) | 127 (58.5) | 167 (72.0) | 158 (53.0) | 150 (63.0) | \( p > 0.20 \) | \( p > 0.039 \) |
| Mild to moderate activity (%) | 34 (15.7) | 49 (21.1) | 58 (19.5) | 79 (33.2) |                |                |
| Severe activity (%) | 56 (25.8) | 16 (6.9) | 83 (27.5) | 9 (3.8) |                |                |
However, this difference did not reach statistical significance. As the total number of anti-TNF treated patients was very low, we did not further analyze the differences in anti-TNF treatment. In addition, we exploited a feasible gender-related prescription of immunosuppressants with respect to disease activity (Table 4), but did not find statistically significant differences.

3.3. Age-related prescription of immunosuppressants in women

Women suffering from IBD are often in their reproductive years. This represents a possible obstacle for the prescription of immunosuppressive medication, as some immunosuppressants (e.g., MTX) are absolutely contraindicated during the peri-conceptional period and pregnancy. For this purpose we assessed the influence of female patient age on the prescription of immunosuppressants. Neither in CD nor in UC a significant difference was detectable with respect to medication prescribed to women aged 18–42 or >42 years. Surprisingly, a non-significant trend towards no medication in both CD and UC in women aged >42 years was apparent (9.8% vs. 17.2% in CD, p = 0.132; 4.5% vs. 7.6% in UC, p = 0.20, Table 5).

3.4. Gender-related medical management depending on disease duration

As women in our patient cohort showed a significantly extended duration of disease, we further investigated the medical management of women and men in dependence of the duration of the disease. The probability to receive no IBD specific medication increased with the duration of disease for both men and women (data not shown). In accordance, the probability for the use of immunosuppressive medication in patients with CD...
declined over time for both sexes (Fig. 2A and B). Importantly, the probability of remission remained unchanged (data not shown). Corresponding results were obtained for UC (data not shown).

4. Discussion

The introduction of immunosuppressive therapies and biologic agents within the last decade has made the treatment of IBD increasingly complex. These new options have led to active debate and research about various important topics including the optimal time point when to use such therapies during the course of the disease as well as predictors of clinical outcome. In contrast, gender-specific issues in the treatment of IBD have yet not been in the focus of such research despite the high prevalence in younger patients with child-bearing potential evoking uncertainties due to the limited clinical data about the use of immunosuppressive and biologic drugs in pregnant and lactating patients.

The present prospective investigation provides data about gender-specific differences in the treatment of IBD for the first time. Our results were obtained in a study cohort comprising patients attending different forms of health care services in a metropolitan area of Germany and clearly demonstrate that women showed a lower remission rate than men, especially in patients with UC. This unfavourable outcome for women was accompanied by an infrequent use of immunosuppressive agents in the female gender. The reason behind these findings remains to be obscure but may involve 1) a higher risk of developing more severe disease in males, 2) a lower compliance to corticosteroids and/or aminosalicylates in males, and/or 3) an avoidance of the use of immunosuppressive agents in females of child-bearing age.

In accordance to recent epidemiological data, we found a predominance for female CD patients in our study cohort, whereas in UC the men to women ratio was almost equal to 1. Female CD patients, however, exhibited marked but not statistically significant differences in certain patient characteristics, e.g. a higher rate of extraintestinal manifestations and active smoking habit as well as an extended disease duration. A clear association of a more severe disease status in active smoking CD patients has been shown, and might explain, at least in part, the detected gender-specific differences in remission rates observed in our study cohort. Concerning dissimilarities in the frequency of extraintestinal manifestations and disease duration, published data is scarce. In one small study examining amyloidosis as a very rare but serious complication of inflammatory bowel disease, a striking male preponderance among patients with CD, was reported. In addition, primary sclerosing cholangitis in IBD is also well known to be associated with the male gender. In our study population, due to low numbers no difference between men (n=5) and women (n=3) suffering from primary sclerosing cholangitis was observed.

There is limited data with respect to the demographic factors influencing adherence to medical treatment in IBD. Earlier studies predominantly indicated that non-adherent patients to medical treatment are more likely to be male. Most of those data referred to incompliance to aminosalicylates. According to the current "step up" approach in the medical management of IBD these findings in general could explain the more common use of immunosuppressive drugs and, since immunosuppressants are more effective than aminosalicylates, consequently explain the higher remission rates among male patients in our study population. Nevertheless, a recently published systematic review questions conclusions of earlier reviews in terms of demographic factors influencing non-

### Table 4  Imunosuppressive medication vs. disease activity.

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>58.2</td>
<td>65.6</td>
</tr>
<tr>
<td>Active disease (%)</td>
<td>41.8</td>
<td>34.4</td>
</tr>
</tbody>
</table>

### Table 5  Medication of female patients dependent on age.

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women aged 18–42</td>
<td>Women aged &gt;42</td>
</tr>
<tr>
<td>No medication (%)</td>
<td>9.8</td>
<td>17.2</td>
</tr>
<tr>
<td>Group 1 (%)</td>
<td>70.3</td>
<td>60.2</td>
</tr>
<tr>
<td>corticosteroids ±5-ASA</td>
<td>36.3</td>
<td>38.1</td>
</tr>
<tr>
<td>Group 2 (%)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>immunosuppressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>biologicals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
adherence to medical treatment of IBD. Furthermore, it appears to be unreasonable to believe that gender-related adherence to various drugs utilized in IBD may be different. In favor of the latter assumption Mantzaris et al. reported that male gender was associated with non-adherence of treatment with AZA in patients with CD in long-term remission. Thus, if there was female predominance in medical adherence it rather argued for a better outcome of women compared to men.

As already pointed out, the lower use of immunosuppressive therapy in females might also be explained by uncertainties in the prescription for women of child-bearing potential. However, an age-related analysis (women age 18–42 vs. >42 years) did not reveal any difference in the treatment of women in either CD or UC between both age groups. A therapy with AZA/6-MP, the most commonly used immunosuppressant in IBD, is generally considered to be of low risk during pregnancy. However, the relative contraindication for peri-conceptional use of thiopurines is still mentioned by the manufacturer in the patient information sheet. This provokes considerable confusion in patients with an active desire to conceive, possibly reducing the otherwise high adherence to medication of these patients. On the other hand, the effect of azathioprine/6-MP therapy in men who wish to conceive has been also under controversial discussion: while the large experience in male transplant population as well as a single IBD study did not show increased adverse effects regarding pregnancy outcome, a small study reported a significantly increased incidence of pregnancy-related complications when fathers used 6-MP within 3 months of conception. While MTX is absolutely contraindicated in the peri-conceptional period and during pregnancy restricting its use not only in women but also in men, little information is available regarding the use of other immunosuppressants such as CSA and tacrolimus in IBD during pregnancy.

The importance of conception plans for the therapeutic management of IBD patients has been demonstrated by Zelinkova et al. in a recently published study: within a cohort of 61 IBD patients (51 females, 40 with CD, 21 with UC) about one-third had to change the medication due to active reproductive plans. Nevertheless, it should be kept in mind that the risk of complications during pregnancy seems to be primarily related to disease activity and not to specific medication.

Our analysis revealed another possible explanation for the observed gender-related differences. Both women and men showed a marked decrease in prescriptions in general and immunosuppressants in particular with longer disease duration. Nevertheless, this cannot be explained by a less active disease as remission rates were nearly unchanged over time. As women were diagnosed earlier and displayed a longer disease duration, one might hypothesize that these patient characteristics might illustrate most of the observed differences in the use of immunosuppressants in women and men.

Overall, typical population characteristics as well as local health care supply in the Rhein-Main region cannot automatically be projected to the entire German population or other European nations. Furthermore, the cross sectional study design limits interpretation of the general patient management quality and long term outcome. Thus, larger prospective multi-centre longitudinal studies are warranted to reappraise our findings of disparities in the treatment with immunosuppressive medication between male and female patients suffering from IBD.

**Acknowledgements**

We thank the study nurses P. Altmann, D. Bratic, L. Fouta, E. Kretzschmar, M. Paterakis, D. Rompel, N. Schieferdecker, S.
Spielberg, S. Steckhan, and S. Weber for the excellent data entry and cooperation. We thank T.L. Chung and Y. Asai for their excellent support in the statistical analysis.

IB participated in the study design, carried out the studies and data analysis and drafted the manuscript. EH, NF, and CZ performed the statistical analysis. EH helped draft the manuscript. HB participated in the study design, carried out the studies and data analysis. WT, AD and FH included patients in the database. SZ participated in the data analysis and drafted the manuscript. JS conceived of the studies and participated in its design and coordination. OS participated in the design and coordination of the studies, took part in the data analysis and drafted the manuscript. All authors read and approved the final manuscript.

References


