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Effects of Immunomodulators and Biologic Agents on Sexual Health in Patients With Inflammatory Bowel Disease

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Background: Although much knowledge has been gained regarding the medical and surgical management of inflammatory bowel disease (IBD), a paucity of information is available on the psychosexual issues related to IBD. The aim of this study was to evaluate the sexual health of patients with IBD who were taking immunomodulators and/or biologic agents vs patients with IBD who were not on that medication regimen.

Methods: All study participants completed a validated sexual health questionnaire, the Female Sexual Function Index or the International Index of Erectile Function, to assess their subjective perception of the effect of IBD on the different domains of sexual function during the prior 1-month time period.

Results: No statistically significant differences in any baseline demographic variables were found for either sex between the group taking immunomodulators/biologic agents and the nontreatment group. Among females and males, individual question responses, domain scores, and total scores showed no statistically significant differences between the 2 treatment groups.

Conclusion: Our data suggest that the use of immunomodulators or biologic agents does not affect female or male sexual health. However, treatment of patients with IBD must be individualized based on the aggressive nature of the disease, treatment goals, and the tolerability of various medications.

Keywords: *Adjuvants–immunologic, biological factors, inflammatory bowel diseases, reproductive health*

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INTRODUCTION

Inflammatory bowel disease (IBD) is a debilitating chronic inflammatory disease that includes both Crohn disease (CD) and ulcerative colitis (UC). Both CD and UC are increasing in prevalence globally, with as many as 1.4 million individuals in the United States and 2.2 million individuals throughout Europe affected, and the overall incidence of IBD in pediatric patients is rising worldwide as well.[1,2] Although the mainstay of therapy for CD is pharmacologic therapy, 50% of patients will undergo surgery within 10 years of diagnosis, and 80% will have surgery at some point in their lives, although surgery is not curative.[3] Similarly, pharmacologic therapy is also the mainstream treatment for UC, but up to 30% of individuals need total proctocolectomy because of refractory disease, dysplasia, or the development of cancer.[3,4] Although much knowledge has been gained regarding medical and surgical management of IBD, the psychosexual issues related to IBD have not been thoroughly addressed.

Sexuality is complex, involving psychological, biological, and social aspects. Alteration of the body in any manner may affect an individual's self-perception and may lead to difficulties in relationships and sexual health.[5] IBD is diagnosed in most patients between the ages of 15-40 years, a time when body image and exploration of sexual activity are important.[6] Marín and colleagues found that 50% of women and 33% of men reported worsening sexual function after the diagnosis of IBD.[7] A large European survey found that 40% of patients with IBD felt the disease prevented an intimate relationship.[8]

Both direct effects (eg, IBD symptoms) and indirect effects (eg, side effects of medication and consequences of surgery) of UC and CD can disrupt body image, sexual functioning, and interpersonal relationships. Among the reasons cited for decreased sexual intimacy, both males and females identified fatigue as a primary reason.[7] However, depressed mood is the strongest predictor of

lower sexual function in all analyzed domains.[9] Men tend to blame the worsening of intimacy on psychological disease–related effects (ie, reactive depression, sadness, working disability, likelihood of intestinal resection), whereas women blame decreased intimacy on disease-related symptoms (ie, abdominal pain, diarrhea, incontinence).[7]

Many patients with CD or UC are treated with immunomodulators and/or biologic agents at some point in their disease course. The treatment regimens vary based on disease type (CD or UC), severity, induction vs maintenance therapy, inpatient or outpatient, and history of remission or relapse. Depending on whether the patient has CD or UC, corticosteroids may be used as either inductive or maintenance therapy or for acute flares. Adverse effects of corticosteroids include adrenal insufficiency, weight gain, diabetes mellitus, mood changes, acne, hirsutism, and psychiatric issues, with many of these adverse effects impairing the sexual quality of life of individuals.[6] Immunomodulators such as azathioprine and 6-mercaptopurine are known for their adverse effects such as fever, rash, and arthralgias, while biologic agents, including tumor-necrosis factor antagonists, are known for infusion site reactions and risk of infections.[10] Although sexual dysfunction is not typically considered a side effect of immunomodulators/biologic agents, biologic agents and corticosteroids have been found to be independent risk factors for sexual dysfunction.[7,8] However, the surveys and methodology used for these studies had many limitations and did not prospectively evaluate patients' current pharmacologic regimen at the time they completed their validated sexual health questionnaires.[7,8] Consequently, a paucity of information is available regarding the effect of biologic agents and/or immunomodulator agents on sexual health of patients with IBD. Addressing this question is imperative because immunomodulators/biologic agents are part of mainstream IBD therapy.

Our aim was to use validated male and female sexual health questionnaires to evaluate the sexual health of patients with IBD receiving immunomodulators and/or biologic agents vs patients with IBD who were not on that regimen. We also aimed to identify other potential factors that may contribute to sexual quality of life (eg, location of disease activity, previous IBD-related surgeries). By studying these variables, our goal was to develop a strategy to provide an individualized approach to IBD management and improve the overall quality of care for patients with IBD.

METHODS

Subjects and Participants

This single-center cross-sectional study was approved by the institutional review board and conducted at an academic health system. All subjects were $\geq$18 years and provided informed consent prior to enrollment. Study participants were recruited from the general gastroenterology and IBD specialty clinic from November 30, 2013 to May 22, 2015. Consecutive patients with a diagnosis of either CD or UC, confirmed by endoscopic and histologic assessment, were eligible for enrollment.

Data Collection

We reviewed the electronic medical record of each patient to obtain demographic data and other relevant clinical information: age; sex; body mass index; smoking history; presence of chronic medical condition other than gastrointestinal disease such as obstructive sleep apnea, rheumatologic disorders (eg, systemic lupus erythematosus, rheumatoid arthritis), or mood or psychiatric disorders (eg, depression, anxiety, bipolar disorder, schizophrenia); and home medication (eg, antidepressants, anxiolytics, narcotics). Additional variables of interest included IBD-related history, such as the type of IBD (eg, UC or CD), location of disease (eg, small bowel, colon, small bowel and colon), history of IBD-related surgery, and medication for IBD treatment. For each patient, the disease activity was assessed using validated scales including the Lichtiger symptom score (LSS) for patients with UC and the Harvey-Bradshaw Index (HBI) for patients with CD. Subjects with an LSS $>$3 and an HBI $>$5 were considered to have active disease, and values less than these thresholds indicated clinical remission.

Questionnaire

All study participants received a validated sexual health questionnaire, the Female Sexual Function Index (FSFI) or the International Index of Erectile Function (IIEF), to assess the patient's subjective perception of the effect of IBD on the different domains of sexual function.[11,12] The FSFI and IIEF consist of 19 and 15 self-reported questions, respectively, that measure components of sexual function.

The FSFI measures 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The score ranges from 0 or 1 (no sexual function during the last month) to 6. Each domain score is multiplied by a domain factor to generate an overall domain score, with a minimum score of 0-1.2 (depending on domain) and a maximum domain score of 6.0 (for each domain). Subsequently, the 6 domain scores are added to obtain a total score, with a minimum score of 2 and maximum score of 36. Higher scores indicate better sexual function.

The IIEF measures 5 domains (maximum scores are shown in parentheses): erectile function (30), intercourse satisfaction (15), orgasmic function (10), sexual desire (10), and overall satisfaction (10), with higher numbers indicating less to no sexual dysfunction. Responses to each question are scaled from 0-5, with 5 indicating no sexual dysfunction. Each domain is associated with a different score range to determine the level of dysfunction, if any.

The study participants were asked to complete the FSFI (females) or the IIEF (males) questionnaire at the time of their scheduled outpatient visit. Instructions were provided, and subjects were asked to provide the best assessment of their symptoms during the previous 1-month period when answering each question.

Statistical Analysis

Frequencies and percentages are provided for categorical variables, and means and standard deviations are provided for numeric variables. Group 1 (patients taking immunomodulator/biologic agents) and Group 2 (patients not taking immunomodulator/biologic agents) were compared using the Pearson chi-square test (or Fisher exact test if some cell frequencies were small) for categorical data and the Wilcoxon rank sum test for continuous data. The level of significance was Bonferroni adjusted for multiple tests to preserve a family-wise level of significance of 5%, so a P value is significant if it is $<$0.0063 (0.05/8 tests for outcomes). All analyses were done using SAS v.9.4 or later.

Table 1. Female Demographics by Treatment Group

Variable	Group 1 – On Immunomodulators/Biologic Agents n=13	Group 2 – Not on Immunomodulators/Biologic Agents n=10	Overall	*P* Value
Anxiety				
No	7 (53.8)	5 (50.0)	12 (52.2)	1.00
Yes	6 (46.2)	5 (50.0)	11 (47.8)	
Comorbid disease				
No	4 (30.8)	4 (40.0)	8 (34.8)	0.69
Yes	9 (69.2)	6 (60.0)	15 (65.2)	
Depression				
No	6 (46.2)	3 (30.0)	9 (39.1)	0.67
Yes	7 (53.8)	7 (70.0)	14 (60.9)	
IBD disease				
Active	7 (53.8)	5 (50.0)	12 (52.2)	1.00
Inactive	6 (46.2)	5 (50.0)	11 (47.8)	
Disease complications				
No	6 (46.2)	3 (30.0)	9 (39.1)	0.67
Yes	7 (53.8)	7 (70.0)	14 (60.9)	
IBD effects				
No	5 (38.5)	4 (40.0)	9 (39.1)	1.00
Yes	8 (61.5)	6 (60.0)	14 (60.9)	
Disease location				
Colon	7 (53.8)	2 (20.0)	9 (39.1)	0.25
Small bowel and colon	3 (23.1)	5 (50.0)	8 (34.8)	
Small bowel	3 (23.1)	3 (30.0)	6 (26.1)	
Medications				
No	4 (30.8)	3 (30.0)	7 (30.4)	1.00
Yes	9 (69.2)	7 (70.0)	16 (69.6)	
Sexual assault				
No	9 (69.2)	9 (90.0)	18 (78.3)	0.34
Yes	4 (30.8)	1 (10.0)	5 (21.7)	
Smoking status				
No	8 (61.5)	8 (80.0)	16 (69.6)	0.41
Yes	5 (38.5)	2 (20.0)	7 (30.4)	
Surgical intervention				
No	8 (61.5)	5 (50.0)	13 (56.5)	0.69
Yes	5 (38.5)	5 (50.0)	10 (43.5)	
Type of disease				
Crohn disease	9 (69.2)	10 (100.0)	19 (82.6)	0.12
Ulcerative colitis	4 (30.8)	0 (0)	4 (17.4)	

IBD, inflammatory bowel disease.
Data are presented as n (%).

RESULTS

A total of 23 females met inclusion criteria and completed the FSFI survey, 13 on immunomodulators or biologic agents (Group 1) and 10 not on immunomodulators or biologic agents (Group 2), with mean ages of 43.6 and 53.0 years (P=0.051), respectively. A total of 19 males met inclusion criteria and completed the IIEF survey, 10 on immunomodulators or biologic agents (Group 1) and 9 not on immunomodulators or biologic agents (Group 2), with mean ages of 37.5 and 40.7 years (P=0.775), respectively.

Table 2. Male Demographics by Treatment Group

Variable	Group 1 – On Immunomodulators/Biologic Agents n=10	Group 2 – Not on Immunomodulators/Biologic Agents n=9	Overall	*P* Value
Anxiety				
No	8 (80.0)	7 (77.8)	15 (78.9)	1.00
Yes	2 (20.0)	2 (22.2)	4 (21.1)	
Comorbid disease				
No	5 (50.0)	4 (44.4)	9 (47.4)	1.00
Yes	5 (50.0)	5 (55.6)	10 (52.6)	
Depression				
No	8 (80.0)	5 (55.6)	13 (68.4)	0.35
Yes	2 (20.0)	4 (44.4)	6 (31.6)	
IBD disease				
Active	5 (50.0)	5 (55.6)	10 (52.6)	1.00
Inactive	5 (50.0)	4 (44.4)	9 (47.4)	
Disease complications				
No	5 (50.0)	4 (44.4)	9 (47.4)	1.00
Yes	5 (50.0)	5 (55.6)	10 (52.6)	
IBD effects				
No	7 (70.0)	4 (44.4)	11 (57.9)	0.37
Yes	3 (30.0)	5 (55.6)	8 (42.1)	
Disease location				
Colon	8 (80.0)	4 (44.4)	12 (63.2)	0.17
Small bowel and colon	2 (20.0)	5 (55.6)	7 (36.8)	
Medications				
No	3 (30.0)	3 (33.3)	6 (31.6)	1.00
Yes	7 (70.0)	6 (66.7)	13 (68.4)	
Sexual assault				
No	10 (100.0)	9 (100.0)	19 (100)	-
Smoking status				
No	7 (70.0)	9 (100.0)	16 (84.2)	0.21
Yes	3 (30.0)	0 (0)	3 (15.8)	
Surgical intervention				
No	6 (60.0)	5 (55.6)	11 (57.9)	1.00
Yes	4 (40.0)	4 (44.4)	8 (42.1)	
Type of disease				
Crohn disease	4 (40.0)	6 (66.7)	10 (52.6)	0.37
Ulcerative colitis	6 (60.0)	3 (33.3)	9 (47.4)	

IBD, inflammatory bowel disease.
Data are presented as n (%).

No statistically significant differences were found between groups in any of the female demographics (Table 1) or male demographics (Table 2).

Among females, none of the individual question responses for the FSFI survey showed a significant difference between Group 1 and Group 2 (Table 3). Similarly, none of the FSFI domains showed a statistically significant difference between groups (Table 4). Among males, no significant differences were found in individual IIEF responses between Group 1 and Group 2 (Table 5), nor were any differences found in domain differences between the 2 groups (Table 6). The FSFI assessment includes the sum of the individual domain scores as a total score (maximum of 36). Female patients in Group 1 had a higher mean total score than patients in Group 2, but the difference was not significant (Table 4). Although the IIEF does not base a

Table 3. Female Sexual Function Index Responses by Treatment Group

Domain/Question	Group 1 – On Immunomodulators/Biologic Agents n=13	Group 2 – Not on Immunomodulators/Biologic Agents n=10	*P* Value
Desire			
1	2.46 ± 1.27	2.30 ± 1.46	0.78
2	2.39 ± 1.45	2.30 ± 1.64	0.90
Arousal			
3	1.69 ± 2.02	1.10 ± 1.92	0.48
4	1.85 ± 1.91	1.00 ± 1.76	0.29
5	1.92 ± 1.93	1.10 ± 1.91	0.32
6	1.77 ± 1.79	1.10 ± 1.91	0.40
Lubrication			
7	2.54 ± 2.03	1.40 ± 2.12	0.20
8	2.77 ± 2.05	1.10 ± 2.08	0.07
9	2.08 ± 2.29	0.90 ± 1.73	0.18
10	2.92 ± 2.14	2.10 ± 2.51	0.41
Orgasm			
11	2.38 ± 1.89	1.30 ± 1.89	0.19
12	2.31 ± 1.80	1.40 ± 2.12	0.28
13	2.62 ± 2.02	1.30 ± 2.06	0.14
Satisfaction			
14	2.62 ± 2.06	1.20 ± 1.99	0.11
15	2.38 ± 1.85	2.10 ± 1.85	0.72
16	1.85 ± 1.99	1.80 ± 1.69	0.95
Pain			
17	1.46 ± 1.94	1.20 ± 2.10	0.76
18	1.38 ± 1.94	1.10 ± 2.08	0.74
19	1.54 ± 2.11	1.10 ± 2.08	0.62

Data are reported as mean ± SD. Higher scores indicate better sexual function.

clinical interpretation on the sum of the domain scores, we listed the sums in Table 6 for the sake of comparison.

DISCUSSION

Our aim was to evaluate the sexual health of patients with IBD receiving immunomodulators and/or biologic agents (Group 1) vs those not on that regimen (Group 2) by using validated male and female sexual health questionnaires. Our results suggest that immunomodulator/biologic agent use does not specifically hinder the sexual well-being of patients with IBD. Although the sexual health scores in 2 domains—intercourse satisfaction and overall satisfaction—were lower among males taking immunomodulators and/or biologic agents, the difference between groups was not significant. Interestingly, among females, Group 1 reported higher scores in all 6 domains compared to Group 2, but again, these differences were not significant.

Prior studies have shown that roughly two-thirds of women and almost half of men with IBD want information about the impact of IBD on intimacy and sexuality, and they reported that this information should be given at the initial disease diagnosis encounter.[6] However, most quality-of-life questionnaires do not address sexuality, and many physicians do not routinely address relationship or sexual concerns with their patients, even in the presence of known pathology.[5] Many patients do not raise sexual health issues at the initial diagnosis but wait until complications arise or even until after surgical intervention.

We recommend that clinicians be proactive and initiate the discussion about sexual health–related issues at the time of the initial diagnosis. For example, routine discussions about sexual health might help ease the fear of infertility among childbearing women with IBD, as approximately 42% of patients with IBD described some fear of infertility.[13] Marín et al showed that 18% of CD and 14% of UC patients chose voluntary childlessness compared to 6% in healthy controls.[7] The presence of active disease may cause lower rates of fertility, but when the disease is in remission, fertility is similar to those without IBD.[14,15] Patients must understand that the risk of passing IBD to an offspring ranges from 1.6%-5.2% if one parent has the disease and up to 36% when 2 parents have the

Table 4. Female Domain and Total Scores by Treatment Group

Domain	Group 1 – On Immunomodulators/Biologic Agents n=13	Group 2 – Not on Immunomodulators/Biologic Agents n=10	*P* Value
Desire	2.91 ± 1.45	2.76 ± 1.84	0.83
Arousal	2.17 ± 1.96	1.29 ± 2.25	0.33
Lubrication	3.09 ± 2.29	1.50 ± 2.17	0.11
Orgasm	2.92 ± 2.22	1.60 ± 2.41	0.19
Satisfaction	3.26 ± 2.14	2.04 ± 1.92	0.17
Pain	1.75 ± 2.37	1.36 ± 2.50	0.70
Total	16.11 ± 10.28	10.55 ± 11.99	0.25

Data are reported as mean ± SD. Higher scores indicate better sexual function.

disease.[16,17] Only one of the commonly used medications for IBD, methotrexate, is category X and should be avoided during pregnancy.[15]

Another consideration is the finding that a major factor affecting sexual activity is concomitant depressed mood rather than disease activity,[9] reinforcing the recommendation that discussions pertaining to secondary medical issues, such as depression and infertility, must be performed—and performed early in the disease course—by the gastroenterology physician.

Limitations of our study include the limited sample size and the enrollment of patients from a single academic medical center. We also had no demarcation between patients who were taking corticosteroids at the time of the study or in the past. Although not statistically significant, the mean baseline age of women in Group 1 and Group 2 differed by almost a decade. Effects on patients nearing or in menopause should be further analyzed. Our study did, however, use validated sexual health surveys with prospective consented patients and delineated numerous patient

Table 5. International Index of Erectile Function Responses by Treatment Group

Domain/Question	Group 1 – On Immunomodulators/Biologic Agents n=10	Group 2 – Not on Immunomodulators/Biologic Agents n=9	*P* Value
Erectile function			
1	3.20 ± 1.99	3.11 ± 2.20	0.93
2	3.40 ± 2.01	3.67 ± 1.94	0.77
3	3.70 ± 2.06	3.67 ± 2.12	0.97
4	3.40 ± 1.96	3.44 ± 2.07	0.96
5	3.40 ± 1.96	3.11 ± 2.42	0.78
15	3.80 ± 1.14	3.22 ± 1.86	0.42
Intercourse satisfaction			
6	1.90 ± 1.85	2.44 ± 1.74	0.52
7	2.50 ± 2.12	4.11 ± 1.62	0.08
8	2.90 ± 1.92	3.44 ± 2.07	0.60
Orgasmic function			
9	3.50 ± 2.12	3.44 ± 2.07	0.96
10	3.00 ± 2.11	2.67 ± 2.00	0.74
Sexual desire			
11	3.70 ± 1.57	3.56 ± 1.59	0.84
12	3.70 ± 1.57	3.44 ± 1.42	0.72
Overall satisfaction			
13	2.90 ± 1.45	3.33 ± 1.50	0.53
14	3.10 ± 1.60	3.11 ± 1.54	0.99

Data are reported as mean ± SD. Higher scores indicate better sexual function.

Table 6. Male Domain and Total Scores by Treatment Group

Domain	Group 1 – On Immunomodulators/Biologic Agents n=10	Group 2 – Not on Immunomodulators/Biologic Agents n=9	*P* Value
Erectile function	20.60 ± 10.48	20.22 ± 11.71	0.94
Intercourse satisfaction	7.30 ± 4.99	10.00 ± 4.90	0.25
Orgasmic function	6.50 ± 4.12	6.11 ± 2.89	0.82
Sexual desire	7.40 ± 3.13	7.00 ± 2.83	0.78
Overall satisfaction	6.00 ± 3.02	6.44 ± 2.83	0.75
Total	47.80 ± 22.14	49.78 ± 18.57	0.84

Data are reported as mean ± SD. Higher scores indicate better sexual function.

demographic criteria. Also, the patients' use of immunomodulators/biologic agents corresponded to when they completed the surveys, thereby providing an assessment of their prior 1 month of sexual health.

CONCLUSION

Our data suggest that the use of immunomodulator or biologic agent therapy does not affect female or male sexual health. Further studies are needed to assess other potential variables that may hinder the sexual health in patients with IBD. Treatment must be individualized based on the aggressive nature of the patient's disease, treatment goals, and the patient's tolerability of various medications.

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