ORIGINAL ARTICLE

Possible undertreatment of women with Crohn disease in Poland

A subgroup analysis from a prospective multicenter study of patients on anti–tumor necrosis factor therapy

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KEY WORDS

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ABSTRACT

INTRODUCTION In Poland, anti–tumor necrosis factor (TNF) therapy for Crohn disease (CD) is reimbursed in inflammatory disease (CD activity index [CDAI] >300 points) or perianal disease, in cases where conventional treatment has failed.

OBJECTIVES We assessed patients receiving TNF inhibitors to establish how limited access to the therapy influences the selection of the population for treatment.

PATIENTS AND METHODS Consecutive adult patients with CD starting infliximab or adalimumab in the years 2014 to 2015 were included in the study. Age at symptom onset and diagnosis of CD, disease location and behavior, previous treatment, CDAI, and body mass index (BMI) were evaluated. Subsequently, the age and sex of all patients with CD on anti-TNF therapy reimbursed by the Polish National Health Fund were analyzed.

RESULTS Among 256 patients, there were 113 women (44.1%) and 143 men (55.9%). The median time from diagnosis to enrollment was longer in women than in men (9 years vs 5.5 years; $P = 0.02$), and the proportion of women receiving TNF inhibitors for 5 years or less since diagnosis was lower than that of men (42.5% vs 57.7%; $P = 0.017$). Disease locations, behavior, and CDAI were similar between the groups, while the median BMI was lower in women than in men (20.6 kg/m^2 vs 22.6 kg/m^2; $P = 0.01$). In Poland in general, in the years 2010 to 2015, TNF inhibitors for CD were taken by fewer women than men (2208 vs 4789; 46%; 95% confidence interval, 45–48). The median age of treated women was 29 years and that of men—27 years ($P < 0.001$).

CONCLUSIONS Compared with their male counterparts, women with CD receive TNF inhibitors less frequently, at an older age, and following a longer disease duration. It is unknown whether this is a regional or more widespread phenomenon.

INTRODUCTION Anti–tumor necrosis factor (anti-TNF) antibodies improve the quality of life in patients with inflammatory bowel disease (IBD)[1] and likely modify the course of the disease via mucosal healing and a reduced rate of surgeries.[2-7] With an acceptable adverse event profile, TNF inhibitors can be considered the safest and most effective therapy for IBD.[8] The earlier in the course of the disease the anti-TNF treatment is introduced, the higher the probability of response and long-term remission.[9,10] For Crohn disease (CD), anti-TNF treatment is recommended in patients with a moderate or severe flare-up of luminal disease or perianal disease who are unresponsive or intolerant to conventional therapy, as well as a treatment of choice in extensive relapsing disease.[11]

The actual use of anti-TNF drugs depends on country-specific reimbursement regulations and varies significantly even within the European Union, with the lowest use per estimated number of patients with IBD reported in some Eastern European countries, including Poland.[12] Since 2010, the cost of infliximab or adalimumab therapy has been reimbursed by the Polish National Health Fund (Narodowy Fundusz Zdrowia [NFZ]) in patients with CD with a CD activity index (CDAI) exceeding 300 points, or with perianal fistulas, if these patients have proved resistant or intolerant to conventional therapies. Until recently, the maximum reimbursement period has been 12 months, but since 2017 the biosimilar infliximab has been reimbursed for up to 24 months and adalimumab—for up to 12 months.

Access to TNF inhibitors for patients with ulcerative colitis (UC) is even more limited, as only the biosimilar infliximab is reimbursed for up to 12 months. The cost of the newest biologic drug approved for IBD, the anti-α4β7 subunit integrin antibody vedolizumab, is not reimbursed in Poland.

The aim of this paper was to evaluate the demographic characteristics of a cohort of Polish patients with CD who were started on anti-TNF therapy. By comparing them with other cohorts reported in the literature, we aimed to establish how the limited access to TNF inhibitors in Poland influences the characteristics of the population selected for treatment.

PATIENTS AND METHODS **Patients** Data analyzed in this paper come from the SATIMOS study (Safety of Anti-tumor Necrosis Factor [TNF] Monoclonal Antibodies in Inflammatory Bowel Disease, NCT02066272), which is a prospective, multicenter, observational cohort study aimed at characterizing the safety of treatment using anti-TNF monoclonal antibodies in patients with IBD in Poland. This study was initiated by the Intestinal Section of the Polish Society of Gastroenterology.

The study enrolled consecutive patients who were started on anti-TNF treatment (infliximab or adalimumab) due to CD, UC, or indeterminate colitis between January 1, 2014, and December 31, 2015. The participating centers included gastroenterology units from both university and non-university hospitals: 14 units providing care for adult patients and 10 units—for pediatric patients.

In patients who gave informed consent, the following data were collected in an electronic database: medical history, previous treatment (aminosalicylates, corticosteroids, budesonide, azathioprine, 6-mercaptopurine, cyclosporine A, methotrexate, infliximab, adalimumab, and certolizumab), previous surgery, CDAI, disease location, indication for biological treatment, and extraintestinal manifestations. During the anti-TNF treatment, data on response to and tolerance of the treatment were also collected at each visit.

Additionally, to validate the demographic data collected in the prospective SATIMOS cohort, the analysis was extended to include the retrospective data from the NFZ on the number, age, and sex of all patients with CD who were eligible for treatment with TNF inhibitors according to the reimbursement regulations in Poland in the years from 2010 to 2015.

Data analysis The database was prepared by the Polish software company Mednet, which is also responsible for quality assurance and storage. Twice a year, the records were checked for completeness and logics, with incomplete datasets being reported to the respective data-entering persons, who were asked to complete missing data.

The present analysis of the data from the SATIMOS study is limited to adult patients with CD. The analysis of past and concomitant therapy was based on the medication therapy data sheet from the baseline visit.

Statistical analysis Variables were described by reference to frequencies, medians, and interquartile ranges (IQRs). The χ^2 test and Fisher exact test were used to compare categorical variables. Since continuous variables did not follow a normal distribution, the Mann–Whitney–Wilcoxon test was used for comparisons. A P value of less than 0.05 was considered significant. The Bonferroni correction was used for multiple comparisons. All analyses were performed with the Stata software, version 13.1 (Stata Corporation, College Station, Texas, United States).

Ethical considerations The Ethics Committee of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology approved the study (document no., 29/2013), and the Polish Inspector General for Personal Data Protection was informed about data collection.

RESULTS **Demographic characteristics of patients receiving anti-TNF treatment in Poland (SATIMOS study)** Of the 285 patients with CD registered in the database, 29 were excluded from the analysis due to incomplete records. The final sample included 256 patients (113 women [44.1%]

TABLE 1 Clinical characteristics of patients with Crohn disease in the SATIMOS study

Variable		Women n = 113 (44.1%)	Men n = 143 (55.9%)	All n = 256	*P* value
Age at symptom onset, y, median (IQR)		22 (17–31)	22.5 (18–29)	22 (17–29)	0.937
Age at diagnosis, y, median (IQR)		23 (19–34)	25 (19–31)	24 (19–32)	0.820
Age at enrollment, y, median (IQR)		31 (24–44)	31 (24–37)	31 (24–39)	0.313
Time from symptom onset to enrollment, y, median (IQR)		9 (1–52)	5.5 (1–36)	7 (1–52)	0.020
Time from diagnosis to enrollment, y, median (IQR)		7 (3–10)	5 (2–10)	5 (2–10)	0.278
Disease location, %	L1	35.2	25.5	29.8	0.275
	L2	26.1	26.4	26.3	
	L3	38.6	48.2	43.9	
Disease behavior, %	B1 (inflammatory)	55.9	52.9	54.2	0.638
	B2 (stricturing)	18.0	15.7	16.7	
	B3 (penetrating)	26.1	31.4	29.1	
Perianal disease, %	Yes	31.0	36.4	34.0	0.366
	No	69.0	63.6	66.0	
Smoking, %	Past	16.7	26.8	22.4	0.199
	Current	10.4	9.8	10.1	
	Never	72.9	63.4	67.6	
Intestinal resection, %	Yes	23.0	18.2	20.3	0.340
	No	77.0	81.8	79.7	
Perianal abscess drainage, %	Yes	12.4	16.1	14.5	0.171
	No	87.6	83.9	85.6	
Intra-abdominal abscess drainage, %	Yes	3.5	2.1	2.7	0.703
	No	96.5	97.9	97.3	
BMI, kg/m^2, median (IQR)		20.6 (19.1–23.3)	22.6 (19.4–25.5)	21.6 (19.4–24.4)	0.010

A *P* value of less than 0.05 denotes significant differences. Percentages may not total 100 because of rounding.

Abbreviations: BMI, body mass index; CD, Crohn disease; IQR; interquartile range

TABLE 2 Pharmacological treatment in patients with Crohn disease in the SATIMOS study

Variable		Women n = 113 (44.1%)	Men n = 143 (55.9%)	All n = 256	*P* value
Anti-TNF therapy started within 5 years of diagnosis, %	≤5 years	42.5	57.7	50.8	0.017
	>5 years	57.5	42.3	49.2	
History of biological treatment, %	Yes	46.0	42.7	44.1	0.591
	No	54.0	57.3	55.9	
Current immunosuppressive therapy, %	Yes	59.1	66.9	63.4	0.215
	No	41.0	33.1	36.6	
Indication for current anti-TNF therapy, %	Luminal disease	86.5	85.0	85.7	0.731
	Perianal disease	13.5	15.0	14.4	
CDAI at entry to the study in patients with predominant luminal disease, median (IQR)		334.3 (305.2–372)	336 (307–385)	334.6 (306–379)	0.970
Use of anti-TNF therapy in the current study, %	Adalimumab	61.1	57.9	59.3	0.605
	Infliximab	38.9	42.1	40.7	

Abbreviations: CDAI, Crohn disease activity index; TNF, tumor necrosis factor; others, see TABLE 1

and 143 men [55.9%]). Clinical characteristics of the study groups are presented in TABLES 1 and 2.

The median age of patients at enrollment was 31 years; at development of symptoms, 22 years; and at diagnosis, 24 years. Immunosuppressive treatment at enrollment was taken by 63.4% of the patients, while 44.1% of the patients had received anti-TNF treatment at some point in the past.

Comparison of women and men on anti-TNF treatment in Poland (SATIMOS study) Given the apparent

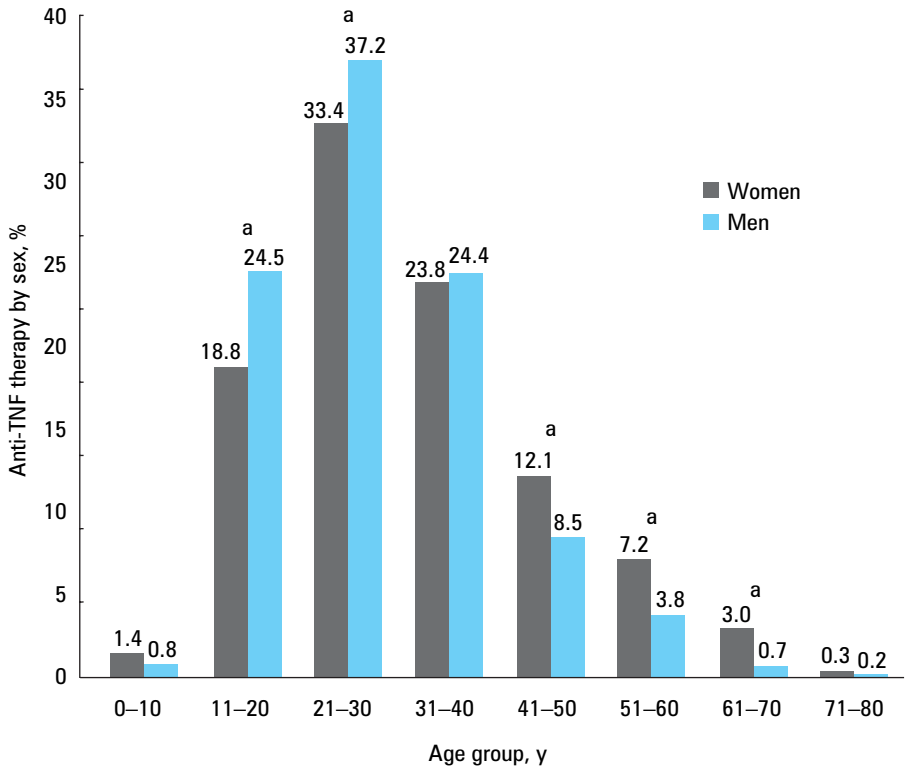

FIGURE 1 Women and men with Crohn disease receiving tumor necrosis factor (TNF) inhibitors according to the decade of life. Data are presented as percentage of the total population treated.
a *P* value <0.006

numerical dominance of men receiving TNF inhibitors for CD, we analyzed sex differences in demographic and treatment characteristics of the study population (TABLES 1 and 2).

The median age at inclusion into the study of women and men was the same (31 years), and no significant differences were observed between the sexes in terms of age at disease presentation or diagnosis. However, the median time from diagnosis to age at entry to the study was significantly longer in women than in men, and the proportion of women receiving biological treatment within 5 years of diagnosis was significantly lower than that of men.

The rates of biological and immunosuppressive treatment in the past were similar in men and women. Moreover, there were no significant differences in the current use of immunosuppressive drugs, although the rate observed among men was 7.8% higher than that in women.

Disease location and behavior, as well as indications for anti-TNF treatment, were similar in both sexes. More women had undergone intestinal resections and more men were current or former smokers, but these differences did not reach significance. The severity of CD as measured by the CDAI was similar in women and men, but the median BMI at the start of treatment was significantly lower in women than in men.

Data from the Polish National Health Fund for the years 2010 to 2015 The number of women and men in every decade of life treated with TNF inhibitors in the years from 2010 to 2015 is presented in TABLE 3. Significantly more men (2581 of the total 4789 patients [54%]; 95% confidence interval [CI], 52–55) than women (2208 [46%]; 95% CI, 45–48) received anti-TNF treatment for CD. Significantly more men in their second and third decades of life received TNF inhibitors compared with women. On the other hand, in the first, fifth, sixth, and seventh decades of life, the number of women was significantly higher than that of men.

The median age of the treated women was 29 years (IQR, 22–39 years), while that of men was 27 years (IQR, 20–35 years) (*P* <0.001). The proportions of women and men with CD in each decade of life who received TNF inhibitors, out of the total population treated are shown in FIGURE 1.

DISCUSSION Our study of a national cohort of patients with CD treated with TNF inhibitors in Poland revealed that women receive anti-TNF therapy less often than men, at an older age, and following a longer disease course.

The clinical course of IBD is heterogeneous and depends on genetic, environmental, and other poorly defined factors. It is believed that all therapeutic interventions should be individualized and adapted to disease behavior and the patient's needs.[11,13] Little is known about the effect of sex on disease course and treatment strategies, especially when biological therapy is considered.

An extensive epidemiological review showed that the diagnosis of CD is not sex-specific.[14] There have been no population studies of the incidence and prevalence of CD in Poland, but according to a study analyzing national trends as regards hospitalization rates for IBD in the years 1991 to 1996 and 2003 to 2007, in 3 of the 11 years women were considerably more likely to be hospitalized for CD than men, while no difference was observed for the remaining years.[15] Therefore, it seems that the smaller number of

TABLE 3 Number of women and men in each decade of life receiving anti–tumor necrosis factor therapy in Poland in the years 2010–2015

Age group, y	Women, n	Men, n	*P* value
0–10	31	20	0.035
11–20	415	632	<0.001
21–30	738	961	<0.001
31–40	526	630	0.636
41–50	267	219	<0.001
51–60	158	97	<0.001
61–70	66	17	<0.001
71–80	7	5	0.395

Because of the Bonferroni correction, a *P* value of less than 0.006 denotes significant differences.

women treated with TNF inhibitors in our study cannot be explained by a lower prevalence of CD in this population.

Another possible reason for the lower use of TNF inhibitors in women with CD could be a milder course of the disease, but again, the review of the literature does not seem to confirm this hypothesis. A recent study assessing sex differences among 5782 adolescents hospitalized for CD showed that, as compared with men, women were slightly more likely to have anemia, infection, and mood disorders, as well as had more blood-product transfusions. Other therapeutic procedures were performed both in men and women with a similar frequency.[16] Such sex-related differences have not been described among adult patients with IBD. Although sex hormones influence systemic and mucosal immunity, as well as intestinal permeability, this is probably only reflected in some variations in the clinical course of IBD during pregnancy and the menstrual cycle.[17] However, it should be noted that some differences in the occurrence of extraintestinal manifestations have been described. Data from a Swiss IBD cohort study regarding disease phenotype and its clinical manifestations showed that female sex is a risk factor for developing axial or peripheral inflammatory articular disease.[18] There also seems to be a higher prevalence of eye and skin involvement in women. As regards environmental factors, there is some evidence that smoking is associated with a higher risk of disabling CD among women, while it has also been suggested that the use of antibiotics and appendectomy are more closely associated with the development of CD in women.[17] In summary, the course of CD would seem to be similar in women and men, with the former manifesting a higher occurrence of several extraintestinal manifestations. Therefore, there are no data to justify a less aggressive treatment in women with CD.

We analyzed the available cohort studies on adult patients receiving TNF inhibitors to compare the demographic characteristics of our cohort with those of patients from other countries. In a Belgian cohort of 720 patients with CD treated with adalimumab,[19] the median age at diagnosis was 24 years and the median disease duration was 11 years, while the rates of previous anti-TNF treatment and surgery for CD were 64.7% and 41%, respectively. Concomitant immunosuppressive drugs were taken by 41% of patients. Compared with these adalimumab-treated patients, the Polish infliximab- or adalimumab-treated patients were younger, had a shorter disease duration, and received previous anti-TNF therapy less frequently, but were characterized by a higher rate of concomitant use of immunosuppressive drugs. Women comprised 61% of the Belgian cohort, which is 15% more than in our population. In a Swiss cohort of 146 patients with CD treated with infliximab, the mean age at diagnosis was 27 years and the mean disease duration was 9 years, also making the Swiss cohort older than the Polish one.[20] Immunosuppressive therapy was administered in 44% of the Swiss patients. This cohort again had a higher prevalence of women (55%). In an older single-center cohort of 614 infliximab-treated patients from Leuven in Belgium,[21] the median age at diagnosis was 22.8 years and the median disease duration prior to the first use of infliximab was 7.6 years. In this cohort, women represented 61% of the total population. None of the above studies were subject to any further sex-specific analyses.

We may thus conclude that Polish patients with CD resemble their counterparts in Western countries in that they are selected for anti-TNF at a similar stage of the disease, or even slightly earlier. A high CDAI (the cutoff level required for treatment administration in Poland) is most often seen in the early phases of CD in young people, which may be the reason for the lower median age of the Polish cohort. Unfortunately, Polish women have lower chances of receiving TNF inhibitors than Polish men, and also lower than their counterparts in other countries. Except for a registry study from the Netherlands reporting that almost 70% of the 131 patients with IBD treated with biological drugs were men,[22] we did not identify studies showing a lower rate of anti-TNF use in women than in men. A recent cross-sectional study from the United States, which included 5782 hospitalized adolescent patients with CD, showed that the rates of using biologics were almost identical in women and men (16% vs 15%, respectively).[16]

Similarly, there is some evidence suggesting sex differences in the use of thiopurines, methotrexate, and calcineurin inhibitors for CD or UC. In a large cohort of German patients with CD or UC participating in a multicenter, prospective, internet-based study, immunosuppressive drugs were prescribed significantly more often among men.[23] The authors also showed that, in general, women with CD received IBD-specific medications less frequently, with the phenomenon of no treatment in IBD also being noted more often among female patients.[23] Furthermore, in a retrospective Asian cohort study, Law et al[24] reported a delayed use of immunosuppressive therapy

in women, particularly those younger than 40 years. Our study also revealed that immunosuppressive drugs are currently prescribed more often in men than in women, although the difference was not significant. Interestingly, in their cross-sectional analysis of 1409 pediatric patients with IBD, Lee et al[25] found no significant differences in medical therapy, including infliximab, between girls and boys.

According to the Polish data from the NFZ, women receiving TNF inhibitors for CD were significantly older than men (29 years vs 27 years). This is in line with the analysis of the SATIMOS cohort, which showed that a significantly smaller proportion of women received the treatment within 5 years of CD diagnosis, as compared with men.

One possible explanation for the observed differences in the onset of anti-TNF therapy between men and women is that the use of immunosuppressive and biological drugs is generally avoided in women of childbearing age. In our analysis, a significantly higher number of men receiving TNF inhibitors in the second and third decades of life may support this hypothesis. Although TNF inhibitors and thiopurines are generally considered safe during pregnancy (and only TNF inhibitors should be stopped in the third trimester), with the risk of miscarriage and other obstetrical complications rather being increased by disease activity itself as opposed to the medications used to sustain remission, there is still a high risk of treatment discontinuation among pregnant women.[26] Moreover, in Poland, the NFZ has declared pregnancy a contraindication to biological therapy, with reimbursement regulations providing that the therapy must be stopped in women who become pregnant while receiving TNF inhibitors. This might be the reason why women are less likely to receive biologics early in the course of the disease.

Our data thus demonstrate an alarming trend, given a strictly defined window of opportunity in biological therapy in IBD, during which the use of TNF inhibitors is the most effective and safe.[27] Post-hoc analyses from large clinical trials have shown that patients with a shorter disease duration had a better response to anti-TNF therapy than those with a longer disease duration.[6] Recently, Papamichael et al[10] have shown that a shorter period between diagnosis of CD and the start of anti-TNF therapy is associated with long-term remission (a median period of approximately 10 years) after discontinuation of infliximab on achieving clinical remission.[10] Thus, the observed delay in the anti-TNF therapy administration in Polish women may compromise the chances for good outcomes.

In our study, we also observed a lower median BMI in women starting anti-TNF treatment as compared with men (20.6 kg/m^2 vs 22.6 kg/m^2). This difference cannot be explained by demographic trends alone because, according to a recent pooled analysis of population studies from 200 countries (including Poland), the age-standardized mean BMI in Polish women in 2014 was 25.8 kg/m^2 (95% CI, 25.1–26.5), which is 1.1 kg/m^2 lower than in Polish men (26.9 kg/m^2; 95% CI, 26.3–27.7).[28] As weight loss is one of the key symptoms of CD activity, our results may indicate that women have a more serious disease than men at the start of anti-TNF therapy, which is a novel finding. As concerns the CDAI, we did not observe sex-related differences, but, as noted above, the CDAI must exceed 300 points in Poland for the treatment to be started unless the indication for treatment is refractory perianal disease.

Our study has several limitations. First, the study sample was relatively small, as compared with cohorts from other countries. However, to our knowledge, our cohort study was the first to describe the use of TNF inhibitors in a country with a limited access to biologics. To validate the SATIMOS study data on the age and sex of patients, we retrieved the NFZ data, which confirmed our results. Second, we did not collect data on past pregnancies and deliveries in our female patients, which might otherwise have helped us explain the observed differences in therapy between women and men. Third, we lacked data on the patients' involvement in treatment decision making, so we could not consider this factor in our analysis. However, one of the possible explanations for our results might be that women are less frequently willing to give consent to a more aggressive treatment, as compared with men.

In conclusion, we showed that women with CD in Poland are less likely to receive TNF inhibitors than men, and receive them at a stage of the disease that is already so advanced as to possibly compromise treatment outcomes. There have been single reports in the literature suggesting that female sex might also be associated with a more limited use of immunosuppressive and biological drugs in other countries. We do not know whether this merely reflects a limited access to TNF inhibitors or is associated with some other cultural or physician- or patient-related factors. More prospective studies are thus needed to explore this important phenomenon, with a view to optimizing therapy outcomes in patients with IBD regardless of sex.

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Contribution statement EZ, PE, JK, MK, and MW-J conceived the idea for the study. PE, MK, MW-J, RT-W, DM, ID-K, AŚ, AL, MB, and MG collected the data and critically reviewed the manuscript. PE and EZ drafted the manuscript. EZ is the guarantor of the article and approved the final manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest PE received lecture fee(s) from Abbvie; other conflict, Astellas. MK received lecture fee(s) from Abbvie, Alvogen, and Takeda; other conflict, Ferring, Alvogen, and Abbvie. RT-W received lecture fee(s) from Abbvie and Takeda; other conflict, Ferring. ID-K: other conflict, Astellas, Ferring, Abbvie, MSD, and Takeda. JK received lecture fee(s) from Egis and Abbvie. MB: other conflict, Olympus. EZ received lecture fee(s) from Egis; other conflict, Astellas, Takeda, and Jannsen-Cilag.

REFERENCES

1 Vogelaar L, Spijker AV, van der Woude CJ. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. Clin Exp Gastroenterol. 2009; 2: 101-109.

2 Peyrin-Biroulet L, Harmsen WS, Tremaine WJ, et al. Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970–2004). Am J Gastroenterol. 2012; 107: 1693-1701.

3 Vester-Andersen MK, Prosberg MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. Am J Gastroenterol. 2014; 109: 705-714.

4 Molander P, Sipponen T, Kemppainen H, et al. Achievement of deep remission during scheduled maintenance therapy with TNFalpha-blocking agents in IBD. J Crohns Colitis. 2013; 7: 730-735.

5 Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012; 61: 1619-1635.

6 Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol. 2014; 12: 929-934.

7 Eder P, Linke K, Witowski J. Update on the mechanisms of action of antiTNF-alpha antibodies and their clinical implications in inflammatory bowel disease. Pol Arch Med Wewn. 2016; 126: 772-780.

8 Trivedi I, Hanauer SB. Balancing the risks and benefits of biologic therapy in inflammatory bowel diseases. Expert Opin Drug Saf. 2015; 14: 1915-1934.

9 Oussalah A, Evesque L, Laharie D, et al. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol. 2010; 105: 2617-2625.

10 Papamichael K, Vande Casteele N, Gils A, et al. Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission. Clin Gastroenterol Hepatol. 2015; 13: 1103-1110.

11 Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017; 11: 3-25.

12 Rencz F, Pentek M, Bortlik M, et al. Biological therapy in inflammatory bowel diseases: Access in Central and Eastern Europe. World J Gastroenterol. 2015; 21: 1728-1737.

13 Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012; 6: 991-1030.

14 Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012; 142: 46-54.

15 Jakubowski A, Zagorowicz E, Kraszewska E, et al. Rising hospitalization rates for inflammatory bowel disease in Poland. Pol Arch Intern Med. 2014; 124: 180-190.

16 Dotson JL, Bricker JB, Kappelman MD, et al. Assessment of sex differences for treatment, procedures, complications, and associated conditions among adolescents hospitalized with Crohn's disease. Inflamm Bowel Dis. 2015; 21: 2619-2624.

17 Zelinkova Z, van der Woude CJ. Gender and Inflammatory Bowel Disease. J Clin Cell Immunol. 2014; 5: 4.

18 Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011; 106: 110-119.

19 Baert F, Glorieus E, Reenaers C, et al. Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients. J Crohns Colitis. 2013; 7: 154-160.

20 Juillerat P, Pittet V, Vader JP, et al. Infliximab for Crohn's disease in the Swiss IBD Cohort Study: clinical management and appropriateness. Eur J Gastroenterol Hepatol. 2010; 22: 1352-1357.

21 Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut. 2009; 58: 492-500.

22 Lesuis N, Befrits R, Nyberg F, et al. Gender and the treatment of immune-mediated chronic inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease and psoriasis: an observational study. BMC Med. 2012; 10: 82.

23 Blumenstein I, Herrmann E, Filmann N, et al. 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. J Crohns Colitis. 2011; 5: 203-210.

24 Law ST, Li KK. Gender-related differences in clinical course of Crohn's disease in an Asian population: a retrospective cohort review. Arq Gastroenterol. 2014; 51: 90-96.

25 Lee GJ, Kappelman MD, Boyle B, et al. Role of sex in the treatment and clinical outcomes of pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2012; 55: 701-706.

26 van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis. 2015; 9: 107-124.

27 Magro F, Eliakim R. Are we on our way to change our mode of thinking and treating inflammatory bowel disease patients? Ann Gastroenterol. 2014; 27:424-426.

28 NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016; 387: 1377-1396.