The effect of concomitant ankylosing spondylitis on long-term outcome of patients with inflammatory bowel disease

Kadri Atay, Hayyam Eyvazov, Selma Bozcan, Tuğçe Eşkazan, Nurhan Demir, İbrahim Hatemi, Yusuf Erzin, Aykut Ferhat Çelik

Department of Gastroenterology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey

Cite this article as: *Atay K, Eyvazov H, Bozcan S, et al. The effect of concomitant ankylosing spondylitis on long-term outcome of patients with inflammatory bowel disease. Turk J Gastroenterol 2019; 30(7): 599-604.*

ABSTRACT

Background/Aims: *The aim of the present study was to compare the demographic features and long-term outcomes of patients with inflammatory bowel disease (IBD) with or without ankylosing spondylitis (AS).*

Materials and Methods: *Among 1640 IBD (Crohn's disease and ulcerative colitis), 76 patients with IBD+AS were identified. The study group consisted of 76 patients with IBD with synchronous AS. The control group consisted of patients with only IBD, and those were selected according to their registry sequence number being the previous and next case to the diseased case with IBD+AS. The primary endpoint was to compare the rate of intestinal resections between both groups (IBD vs. IBD+AS).*

Results: *Among 76 patients with IBD+AS, 52 (68%) first presented with IBD, 11 (15%) with AS, and the remaining 13 (17%) had both diagnoses at the same time. The mean follow-up time was significantly longer in patients with IBD+AS (43.4 vs. 27.8 months; p=0.01). Twenty-two percent of patients with IBD and 14% of those with IBD+AS had an intestinal resection (p=NS). Biologic and systemic corticosteroid treatments were significantly more common among patients with IBD+AS (32% vs. 7% for biologics, p<0.0001 and 44% vs. 28% for corticosteroids, p=0.042). Age-sex-adjusted regression analysis for both groups disclosed IBD duration as the only independent predictor for resection (R2=0.178; p=0.016).*

Conclusion: *The present study shows that up to 5% of patients with IBD may have AS. Patients with IBD+AS do not have a worse disease outcome than solo patients with IBD.*

Keywords: *Ankylosing spondylitis, inflammatory bowel disease, Crohn disease, ulcerative colitis*

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders that involve different regions and layers of the gastrointestinal system. The three main subgroups of these diseases are ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (1,2). Extraintestinal manifestations (EIMs) are seen in approximately 20%-50% of patients with IBD. Musculoskeletal system-related disorders, such as peripheral arthritis, arthralgia, and spondylitis, may be seen in this patient population (3-10). Ankylosing spondylitis (AS) is reported in approximately 10% of patients with IBD, more commonly in association with CD (11-14), but data from the Middle-East region are scarce. AS activity is not typically correlated with IBD activity, and corticosteroid use or colectomy does not contribute to remission of spondylitis (9). Complex genetic, microbial, and environmental factors may be involved in the progression of IBD (15). Similarly, certain genetic and immunogenic mechanisms are known to play a role in the pathogenesis of AS (16). AS activity does not correlate with IBD activity (9), but the effect of accompanying AS on the course of IBD is not known. We wanted to test whether an additional focus (an additional load) of inflammation would worsen the disease outcome (an increase in medical treatment failure) in patients with IBD. The rationale for this idea was that whether the effect of immunosuppressives partly could be blocked by an additional inflammatory (in this case rheumatologic) process. Therefore, in the present study, the effect of concomitant AS on the course of IBD was evaluated.

MATERIALS AND METHODS

Files of all patients with IBD (n=1640, 935 with UC and 705 with CD) who were under follow-up in the gastroenterology department between 1999 and 2014 were retrospectively evaluated. Seventy-six patients with AS were compared with 152 patients with IBD who did not have AS. Patients with indeterminate colitis or patients with AS who developed intestinal inflammation under nonsteroidal anti-inflammatory drug or biologic treatment were excluded from the study.

Demographic characteristics, such as disease duration, age at diagnosis, smoking status, family history of IBD,

Corresponding Author: ***Kadri Atay; dr_kadrii@yahoo.com***

Received: ***June 1, 2018*** *Accepted:* ***December 29, 2018*** *Available online date:* ***February 28, 2019***

DOI: ***10.5152/tjg.2019.17291***

Table 1. Demographic characterization of patients with IBD and IBD+AS under our follow-up

Variables (n=200 patients)	Patients with IBD and IBD+AS
Age (mean±SD) (years)	44.6±13.1
Gender (female/male) (n/%)	99/101 (49.5%/51.5%)
IBD/IBD+AS (n/%)	129/71 (65%/35%)
IBD diagnosis age (year) (mean±SD)	35.3±12.8
IBD duration time (mean±SD) (months)	98.9±73.0
IBD follow-up duration (mean±SD) (months)	33.3±38.3
AS diagnosis age (year) (mean±SD)	36.2±11.2
AS duration time (mean±SD) (months)	71.6±56.0
AS follow-up duration (mean±SD) (months)	37.5±39.5
First presentation with IBD+AS (71 patients) (n/%)	
First IBD	48 (68%)
First AS	10 (14%)
At the same time IBD+AS	13 (18%)
Smoking (n/%)	
Non-smoker	126 (61%)
Active smoking	74 (37%)
Positive family history of IBD (n/%)	12 (6%)
CD location (120 patients) (n/%)	
Ileal	53 (44%)
Colonic	16 (13%)
Ileocolonic	50 (42%)
Isolated upper	1 (1%)
CD behavior (120 patients) ((n/%)	
Non-complicated	92 (77%)
Stricturing	13 (11%)
Penetran	15 (12%)
Extent of UC (80 patients) (n/%)	
Proctosigmoiditis (n/%)	26 (32%)
Left-sided UC (n/%)	27 (34%)
Extensive UC (n/%)	27 (34%)
Response to steroid treatment (67 patients) (n/%)	
Complete response	59 (88%)
Dependent	9 (12%)
Resistant	0 (0%)
The mean age of resection (years) (mean±SD)	40.5±11.0
Time between onset of IBD and resection (mean±SD) (months)	62.2±49.9
Resection rates (n/%)	16 (8%)
No. of patients with flares needing steroids (n/%)	67 (33.5%)
The average frequency of flares needing steroids (mean±SD) (months)	36±35.7
5-ASA use (n/%)	151 (75%)
Azathioprine use (n/%)	79 (40%)
Biologic use (n/%)	32 (16%)
Corticosteroid use (n/%)	67 (34%)
Extraintestinal manifestations (n/%)	46 (23%)
CD perianal fistula (n/%)	15 (12%)

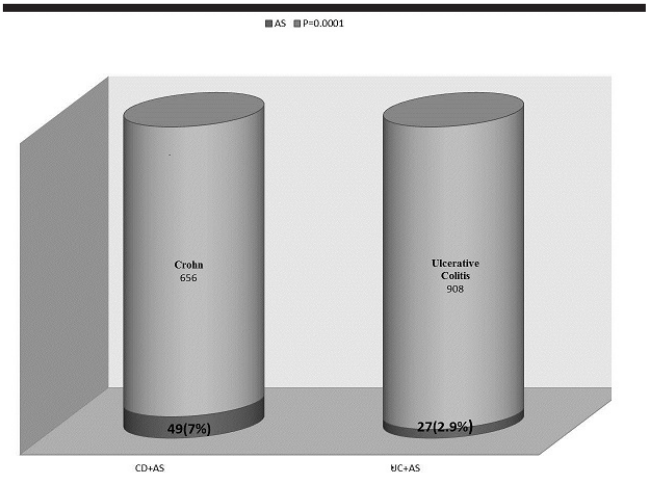

Figure 1. Frequency of ankylosing spondylitis according to IBD type

sites of involvement, behavior patterns, EIMs and types, medication history and durations, surgery history (total colectomy in UC and intestinal resection in CD), age at resection, time frame between IBD diagnosis and resection, corticosteroid-requiring disease attacks, and mean attack frequencies, were recorded for each patient. Attack frequencies and steroid responses of the patients during attacks were also assessed (Table 1). The study group consisted of 76 patients with IBD with synchronous AS. The control group consisted of patients with only IBD, and those were selected according to their registry sequence number being the previous and next case to the diseased case with IBD and AS. Therefore, patients with CD with AS were matched with the previous and next case only with CD, and patients with UC with AS were matched in the same manner with patients only with UC. The primary endpoint of the study was to compare the frequency of surgical resections being accepted as medical treatment failure. Sites of involvement were noted according to the Montreal classification (Table 3) (17). The Modified New York criteria were used to diagnose AS (18).

Statistical analysis

All analyses were made using Statistical Package for Social Sciences (SPSS version 21.0; SPSS Inc.; Chicago, IL, USA). Categorical and continuous variables were compared using χ^2 and Student's t-test, respectively. Pearson's and Spearman's correlation analyses were used to assess the correlations between variables. Regression analysis was used to further evaluate for independent indicators. Kaplan-Meier was used to analyze resection-free cumulative survival. A p value <0.05 was considered as statistically significant.

RESULTS

The frequency of AS in 1640 patients with IBD was 4.6%, and first presentation was IBD in 68% (52 patients) and AS in 15% (11 patients). The diagnosis of IBD and AS was simultaneous in 17% (13 patients). AS was significantly more frequent in patients with CD (7%, 49/705) than in patients with UC (2.9%, 27/935) (p=0.001, Figure 1).

Initially, a total of 228 patients with IBD were enrolled into the study protocol, of whom 152 had IBD and 76 had IBD+AS; 28 were excluded from the final analysis for determining resection indicators as they underwent resection before enrollment (5 from IBD+AS and 23 from IBD

Table 2. The comparison of categorical and continuous numerical variables between patients with IBD and IBD+AS groups

Variables (200 patients)		IBD (n=129)		IBD+AS (n=71)		p
Age (mean±SD) (years)		44.56	14.05	42.11	11.32	NS
Gender (female/male) (n/%)		66/63	52%/48%	33/38	46%/54%	NS
Age at onset of IBD (years) (mean±SD)		36.4	13.4	33.3	11.3	NS
IBD duration time (mean±SD) (months)		97.3	73.8	101.9	72.1	NS
IBD follow-up duration (mean±SD) (months)		27.8	34.1	43.4	43.5	0.01
Smoking (n/%)	Non-smoker	86	67%	40	56%	NS
	Active smoker	43	33%	31	44%	NS
Time between onset of IBD and resection (mean±SD) (months)		61.1	51.1	64.1	52.7	NS
Resection rates (n/%)		10	8%	6	8%	NS
Patients with flares needing steroids during follow-up (n/%)		37	29%	30	42%	0.052
Extraintestinal manifestations (n/%)		28	22%	18	25%	NS
Positive family history of IBD (n/%)		6	5%	6	8%	NS
CD perianal fistula (n/%)		11/76	14%	4/44	9%	NS
CD with internal fistula (n/%)		7/76	9%	0/44	0%	0.048
Ant-TNF use (n/%)		9/129	7%	23/71	32%	0.0001
Exposure of anti-TNF during follow-up (mean±SD) (months)		13.77	8.70	15.69	10.77	NS

Table 3. Montreal classification for patients with Crohn's disease and extent of patients with UC

Montreal classification		IBD (n=129)		IBD+AS (n=71)		p
CD location (120 patients)	Ileal (n/%)	34/76	45%	19/44	43%	NS
	Colonic (n/%)	10/76	13%	6/44	14%	NS
	Ileocolonic (n/%)	32/76	42%	18/44	41%	NS
	Isolated upper GI (n/%)	0/76	0%	1/44	2%	NS
CD behavior (120 patients)	Non-complicated (n/%)	55/76	73%	37/44	84%	NS
	Stricturing (n/%)	8/76	10%	5/44	11%	NS
	Penetran (n/%)	13/76	17%	2/44	5%	0.041
Extent of UC (80 patients)	Proctosigmoiditis (n/%)	20/53	38%	6/27	22%	NS
	Left-sided UC (n/%)	15/53	28%	12/27	44%	NS
	Extensive UC (n/%)	18/53	34%	9/27	34%	NS

CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; AS: ankylosing spondylitis

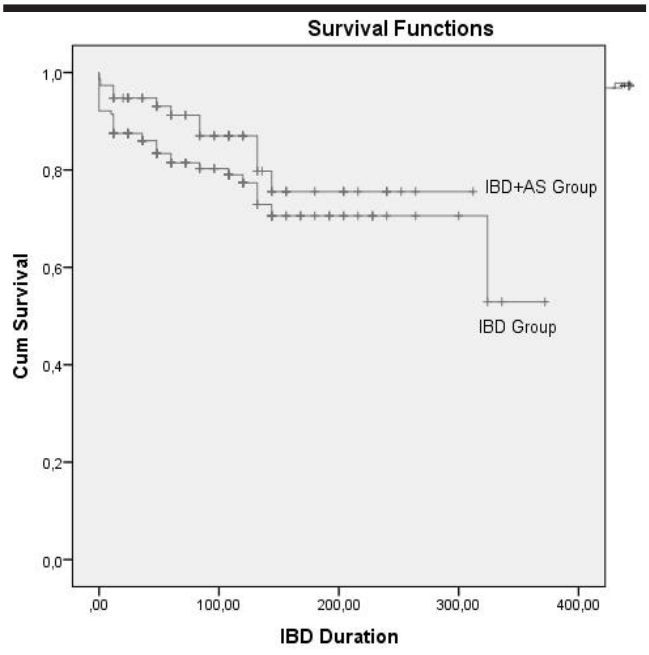

Figure 2. Resection-free cumulative survival of patients with IBD and IBD+AS

groups). However, they were included in the statistical analyses regarding the comparison of resection frequency between the groups.

Analyses revealed frequencies of resection as 22% (33/152) and 14% (11/76) in the IBD and IBD+AS groups, respectively (p=NS). The remaining 200 patients, 129 with IBD (65%) and 71 with IBD+AS (35%), were evaluated separately to determine the factors that affected resection. Of these patients, 49.5% were women (99 patients), and 50.5% were men (101 patients). The mean age of the patients was 44.69±13.17 years. The general features are presented in Table 1.

The comparisons of categorical and continuous variables between the groups are presented in Tables 2 and 3. Follow-up durations were longer in the IBD+AS group than in the IBD group (43.4 vs. 27.8 months; p=0.01). The frequency of resection during follow-up was similar between the groups (8% in both groups, Figure 2). Fistulas internal fistula frequency was 0% in the CD+AS group and 9.2% in the isolated CD group (p=0.048).

Age-sex-adjusted regression analysis for both groups disclosed IBD duration as the only independent predictor for resection (R^2=0.178; p=0.016). When the IBD+AS group (n=71) was evaluated, factors that were significantly associated with resection were CD behavior type (r=0.373; p=0.013) and azathioprine use (r=0.3; p=0.034). The only independent factor in the multivariate logistic regression analysis was behavior type (shifting from inflammatory- to penetrating-type, R^2=0.15, p=0.04). Correlation analyses in the IBD group (n=129) revealed that CD involvement sites (r=0.2; p=0.046), CD behavior pattern (r=0.4; p<0.001), presence of intestinal fistula (r=0.3; p=0.07), azathioprine use (r=0.2; p=0.03), and presence of EIF (r=0.2; p=0.045) affected the primary endpoint, surgical resection. Multivariate logistic regression analysis using these factors (R^2=0.19) revealed that CD behavior (shifting from inflammatory- to penetrating-type) was the only independent indicator for resection (p=0.026).

DISCUSSION

We aimed to evaluate whether concomitant AS in patients with IBD had any effect on increased inflammatory burden and IBD prognosis. According to our results, the overall frequency of AS was 4.6% in 1640 patients with IBD, 7% in CD, and 2.9% in UC. When patients who had resection during follow-up (200 patients) were evaluated, the frequency was similar and 8% in both groups of IBD and IBD+AS. Age-sex-adjusted regression analysis for both groups disclosed IBD duration as the only independent predictor for resection. When the two groups were evaluated separately, the regression analyses for primary endpoint of surgical resection revealed that CD behavior pattern (shifting from inflammatory- to penetrating-type) was the only independent factor associated with resection in patients with IBD+AS and also in patients with IBD without AS.

The effect of demographic characteristics and relevant behavior patterns on IBD course has been evaluated (14). However, the effect of accompanying AS has drawn less interest, if any. AS activity does not correlate with IBD activity (9), but the effect of accompanying AS on the course of IBD is not known. Although the clinical characteristics of patients with IBD with AS have been reported (14, 19), to our knowledge, no comparative analyses have been performed in patients IBD with and without AS. Therefore, we aimed to compare patients IBD with and without AS.

Various frequency rates have been reported for AS in patients with IBD. Betty et al. reported that frequency of AS in IBD is 3.9% (19). Palm et al. (13) reported AS rates as 6% and 2.6% in CD and UC, respectively; we found similar rates in our study. However, in a previous study from Turkey by Ozin et al. (20), AS rates were reported as

1% and 3.6% in UC and CD, respectively. These rates are nearly half the rates in our study, and presumably related with the geographic distribution of the patients, of whom 70% were from Middle Anatolia, in which the rate of AS is relatively lower than from western regions of Turkey (21).

Analyses of resection rates, which also included patients who had resection before our follow-up period (a total of 228 patients), revealed that the overall resection rate was 19% (44/228). When patients with CD and UC were evaluated separately, resection rates were 28.6% and 2.5%, respectively. When IBD durations of 83.4±77.1 months for CD and 107.5±72.8 months for UC were taken into account, the resection rates were lower in our study group than the rates of Western populations, which were reported as 40% and 10% in the initial 10 years of CD and UC, respectively (22). This finding supports our clinical observation that IBD course is milder in developing countries.

When the 28 patients who underwent resection before the follow-up period were excluded, the resection rates were 8% in each of the IBD-only and IBD+AS groups. We performed a Kaplan-Meier analysis for resection-free survival because the follow-up periods were significantly longer in the IBD+AS group, which revealed that concomitant AS did not influence this outcome (Figure 2). In view of these findings, we suggest that concomitant AS did not predict a worse prognosis for IBD.

The past decade has seen major changes in the therapeutic armamentarium available for management of IBD. Infliximab, a drug against tumor necrosis factor-alpha (TNF-α), was first approved for treatment of IBD in 1998 (23); subsequently adalimumab (anti-TNF) (24) became available for induction and maintenance of remission in IBD. Since anti-TNF drugs are available, these biologic agents have been shown to decrease the need for resections in patients with IBD (25-27). In our study, we found that the resection rates were 8% in both IBD-only and IBD+AS groups, although the IBD+AS group had a significantly longer mean follow-up time nearly (44.49 vs. 28.6 months; p=0.01). In addition with the fact that biologic use was significantly more common in our IBD+AS group, one could speculate that these treatments might have lowered the resection rate in this group. However, although the rate of anti-TNF use was higher in patients with IBD with AS, the duration of anti-TNF use was not different between patients with IBD+AS and IBD. Thus, we cannot speculate that a worse outcome in patients with IBD+AS could have been masked by anti-TNF use.

One of the behavior patterns of CD is the penetrating one, which may exhibit aggressive characteristics, such as transmural involvement, fistulization to the surrounding structures, progression of intraabdominal abscess, and peritonitis. These complications are among the most problematic ones and increase the need for surgical resection (28). In our patients who underwent resection during follow-up, 15 of the 16 patients had CD. When the IBD-only and IBD+AS groups were evaluated separately, regression analyses in these groups revealed that only CD behavior pattern (progression from inflammatory- to penetrating-type) was an independent indicator of resection. Additionally, when the solo IBD and IBD+AS groups were evaluated together, regression analysis disclosed IBD duration as the only independent predictor for resection, which is a well-known risk factor.

The number of attacks requiring steroid use was significantly higher in the IBD+AS group than in the IBD-only group (p=0.03), but this might be associated with the longer follow-up period in this group (p=0.01). In accordance with this result, the average frequency of attacks was not different between these groups. At first sight, these finding suggest that concomitant AS does not influence the disease course of IBD.

The limitations of our study include its retrospective nature and limited sample size. Additionally, 228 patients were enrolled in the study, but 28 patients were excluded from the final analyses because they had undergone resections before their admission to our clinic. Thus, only 16 patients who underwent resection during follow-up were eligible for final analyses. Furthermore, 15 of these patients had CD, and only 1 had UC. Consequently, we could not perform regression analysis for resection indicators in patients with UC.

In conclusion, IBD has increasing prevalence and incidence rates, and they are important health problems because of relatively high resection rates. Scrutinizing clinical characteristics and other accompanying inflammatory diseases in these disorders may provide new information about disease progression and novel treatment options. According to the findings of this retrospective study, we suggest that concomitant AS does not influence the disease course of IBD, in particular resection rates. We think that further prospective studies are needed to draw firm conclusions about the exact impact of concomitant AS on the disease course of IBD.

Ethics Committee Approval: Ethics Committee Approval has received for this study from the Ethics Committee of Cerrahpaşa School of Medicine Clinical Research.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.E., K.A.; Design - A.F.Ç.; Supervision - Y.E., K.A.; Materials - İ.H., H.E.; Data Collection and/or Processing - S.B., N.D.; Analysis and/or Interpretation - K.A., Y.E.; Literature Search - K.A., Y.E.; Writing Manuscript - K.A., Y.E.; Critical Review - Y.E., K.A., T.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004; 126: 1504-17. [CrossRef]
2. JB K. Overview of etiology, pathogenesis and epidemiology of inflammatory bowel disease. In: Haubrich WS SF, Berk JE editor. Bockus Gastroenterology. 5th ed. Philedelphia; 1995.
3. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2011; 7: 235-41.
4. Juillerat P, Mottet C, Pittet V, et al. Extraintestinal manifestations of Crohn's disease. Digestion 2007; 76: 141-8. [CrossRef]
5. Felekis T, Katsanos K, Kitsanou M, et al. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease: a prospective single-center study. Inflamm Bowel Dis 2009; 15: 29-34. [CrossRef]
6. Wright R, Lumsden K, Luntz MH, Sevel D, Truelove SC. Abnormalities Of The Sacro-Iliac Joints And Uveitis In Ulcerative Colitis. Q J Med 1965; 34: 229-36.
7. Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin North Am 2002; 31: 307-27. [CrossRef]
8. Tavarela Veloso F. Review article: skin complications associated with inflammatory bowel disease. Aliment Pharmacol Ther 2004; 20(Suppl 4): 50-3. [CrossRef]
9. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut 1998; 42: 387-91. [CrossRef]
10. Fornaciari G, Salvarani C, Beltrami M, Macchioni P, Stockbrugger RW, Russel MG. Muscoloskeletal manifestations in inflammatory bowel disease. Can J Gastroenterol 2001; 15: 399-403. [CrossRef]
11. Bjarnason I, Helgason KO, Geirsson AJ, et al. Subclinical intestinal inflammation and sacroiliac changes in relatives of patients with ankylosing spondylitis. Gastroenterology 2003; 125: 1598-605. [CrossRef]
12. Maksymowych WP. Update on the treatment of ankylosing spondylitis. Ther Clin Risk Manag 2007; 3: 1125-33.
13. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). J Rheumatol 2002; 29: 511-5.
14. Dekker-Saeys BJ, Meuwissen SG, Van Den Berg-Loonen EM, De Haas WH, Meijers KA, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. III. Clinical characteristics and results of histocompatibility typing (HLA B27) in 50 patients with both ankylosing spondylitis and inflammatory bowel disease. Ann Rheum Dis 1978; 37: 36-41. [CrossRef]
15. Goyette P, Labbe C, Trinh TT, Xavier RJ, Rioux JD. Molecular pathogenesis of inflammatory bowel disease: genotypes, phenotypes and personalized medicine. Ann Med 2007; 39: 177-99. [CrossRef]
16. van der Linden S, van der Heijde D. Ankylosing spondylitis. Clinical features. Rheum Dis Clin North Am 1998; 24: 663-76, vii. [CrossRef]
17. Satsangi J, Silverberg MS, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55: 749-53. [CrossRef]
18. Moll JM, Wright V. New York clinical criteria for ankylosing spondylitis. A statistical evaluation. Ann Rheum Dis 1973; 32: 354-63. [CrossRef]
19. Dekker-Saeys BJ, Meuwissen SG, Van Den Berg-Loonen EM, De Haas WH, Agenant D, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. II. Prevalence of peripheral arthritis, sacroiliitis, and ankylosing spondylitis in patients suffering from inflammatory bowel disease. Ann Rheum Dis 1978; 37: 33-5. [CrossRef]
20. Ozin Y, Kilic MZ, Nadir I, Cakal B, Disibeyaz S, Arhan M, et al. Clinical features of ulcerative colitis and Crohn's disease in Turkey. J Gastrointestin Liver Dis 2009; 18: 157-62.
21. Baser O, Burkan A, Baser E, Koselerli R, Ertugay E, Altinbas A. Health care costs associated with ankylosing spondylitis in Turkey: an analysis from nationwide real-world data. Int J Rheumatol 2013; 2013: 139608. [CrossRef]
22. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol 2012; 107: 1228-35. [CrossRef]
23. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337: 1029-35. [CrossRef]
24. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132: 52-65. [CrossRef]
25. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008; 135: 1493-9. [CrossRef]
26. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005; 128: 862-9. [CrossRef]
27. Rizzo G, Pugliese D, Armuzzi A, Coco C. Anti-TNF alpha in the treatment of ulcerative colitis: a valid approach for organ-sparing or an expensive option to delay surgery? World J Gastroenterol 2014; 20: 4839-45. [CrossRef]
28. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010; 4: 28-62. [CrossRef]