의학석사 학위논문

Do tumor necrosis factor-α antagonists reduce the development of advanced colonic neoplasia?

종양괴사인자 알파 길항제의 사용이 진행성 대장 종양의 발생을 줄이는가?

2015년 2월

서울대학교 대학원

임상의과학과 전공

이 준 영

A thesis of the Degree of Master of Science in Clinical Medical Sciences

종양괴사인자 알파 길항제의 사용이 진행성 대장 종양의 발생을 줄이는가?

Do tumor necrosis factor-α antagonists reduce the development of advanced colonic neoplasia?

February 2015

The Department of Clinical Medical Sciences

Seoul National University

College of Medicine

June Young Lee

종양괴사인자 알파 길항제의 사용이 진행성 대장 종양의 발생을 줄이는가?

지도 교수 김 병 관

이 논문을 의학석사 학위논문으로 제출함

2014 년 10 월

서울대학교 대학원

임상의과학과 전공

이 준 영

이준영의 의학석사 학위논문을 인준함

2015 년 1 월

위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

Do tumor necrosis factor-α antagonists reduce the development of advanced colonic neoplasia?

by

June Young Lee

A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirements for the Degree of Master of Science in Medicine at Seoul National University College of Medicine

Jan 2015

Approved by Thesis Committee:

Professor _____**Chairman**

Professor _____**Vice chairman**

Professor _____

Abstract

Background and Aim: The aim of this study was to evaluate the effect of tumor necrosis factor (TNF)-α antagonist on the development of advanced colonic neoplasia.

Methods: The study was composed of patients diagnosed with rheumatoid arthritis, ankylosing spondylitis, or psoriasis January 2005 to December 2012. Our study consisted of 67 patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriasis who underwent colonoscopies after initial diagnosis. For each patient who used TNF-α antagonists, four age- (±5 years) and sex- matched controls were identified from patients with RA, AS, or psoriasis. We compared the incidence of advanced colonic neoplasia between two groups.

Results: Two patients (3.0%) had advanced colonic neoplasia, including one colon cancer (1.5%) in patients who used TNF-α antagonists. A case-control study revealed that the odds of detecting an advanced neoplasia among patients who used TNF-α antagonist were one fourth of the age- and sex- matched controls [OR, 0.254; 95% CI, 0.059 to 1.091; P = 0.048]. Cumulative incidence was lower in the patients who used TNF-α antagonist than the control group (P = 0.037).

Conclusions: The diagnostic yield of advanced neoplasia in the patients treated with TNF-α antagonist was substantially lower than that of control group. We suggest that the risk of advanced colonic neoplasia may be decreased with the use of TNF-α antagonist.

Key words: TNF-α antagonist, adenoma, colon cancer

Student number: 2013-22607

CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Colorectal cancer is the third most common cause of cancer death worldwide with more than 550,000 annual deaths (1). It is a major health problem in most developed countries with increasing incidence during the past decades. It is widely accepted that most colorectal cancers arise from adenomas. Based on this concept, many studies were implemented to demonstrate the hypothesis that removing adenomatous polyp of colon and rectum would prevent colorectal cancer. The USA National Polyp Study showed that colonoscopic polypectomy resulted in a lower-than-expectected incidence of colorectal cancer (2). These results support current practice of removing adenomatous polyp during colonoscopy to prevent colorectal cancer.

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriasis are chronic inflammatory diseases and require medical treatment over many years. Recently, tumor necrosis factor (TNF)-α antagonists promote treatment advances for inflammatory conditions, including RA, AS, and psoriasis as well as inflammatory bowel disease (IBD). However, there exist concerns about their safety, especially associated with infections and malignancies because of its interference effect on immune system (3). The US FDA added a warning label concerning risk of malignancy to TNF-α antagonists based on completed analysis of TNF-α antagonists and reports of lymphoma and other cancers and a second analysis of post-marketing leukemia reports (4). Up to date, there are evidences both for and against increased cancer risk including colon cancer with use of TNF-α antagonists. Results from a follow-up study from DANBIO registry suggested that TNF-α antagonist therapy is associated with increased risk of

colon cancer (5). By contrast, another study suggested that TNF-α antagonist treated RA patients displayed colon cancer risk similar to RA patients without TNF-α antagonists (6). However, little information is available in regard to the risk of advanced colon adenoma with the use of TNF-α antagonists.

The aim of this study was to evaluate the effect of TNF-α antagonists on the development of advanced colon adenoma or colon cancer.

MATERIALS AND METHODS

Patient selection and control group

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, Seoul National University Boramae Medical Center and Seoul National University Bundang Hospital. We reviewed patients diagnosed with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis at Seoul National University Hospital, Seoul National University Boramae Medical Center, and Seoul National University Bundang Hospital from January 2005 to December 2012. We enrolled consecutive patients who underwent one or more colonoscopy after initial diagnosis between January 2005 and December 2012. For each patient who used TNF-α antagonists, four age- (±5 years) and sex- matched controls were randomly identified from patients with RA, AS, or psoriasis. Patients with a history of colorectal cancer or colorectal surgery before initial diagnosis were excluded. Patients with inflammatory bowel disease and patients who underwent colonoscopy prior to initial diagnosis of RA, AS, or psoriasis were also excluded. The medical record data, including the age, sex, body mass index (BMI), family history of colon cancer, laboratory findings and drug history were obtained by reviewing the information in the electric medical recording system.

Colonoscopy

We only included the patients who had received a colonoscopy after initial diagnosis. All colonoscopies (CF-H260, Olympus, Tokyo, Japan) were performed by board-certified gastroenterologists. All polypoid lesions detected during examination were biopsied, and endoscopic mucosal resection was performed when the polyp size was greater than 5mm. Polyp or mass size was measured by comparing with the open width of the biopsy forceps and it was remeasured by pathologists after fixation. Advanced colonic neoplasia included advanced adenomas and primary colorectal cancers. Advanced colonic adenoma was defined as an adenoma ≥ 10mm size or as an adenoma with villous component or high-grade dysplasia. Colorectal cancer was defined as invasion of malignant cells beyond the muscularis mucosa. Non-advanced neoplasia were defined as adenomas less than 10mm in size with low-grade dysplasia. Nonspecific lesions and hyperplastic or inflammatory polyps were considered as non-neoplastic lesions.

Statistical analysis

Continuous variables were expressed as means±SD and analyzed using Student's t-test. Categorical variables were expressed as numbers (percentages) and compared with the chi-square test and Fisher's exact test. Univariate and multivariate logistic regression models were used to estimate the odds of advanced colonic neoplasia. The multivariate model included the variables which were considered statistically significant in the univariate model. Cumulative incidence was calculated with the Kaplan-Meier method,

and the difference among two groups was analyzed using log-rank test. Results were considered statistically significant for P-value < 0.05. Statistical analysis was performed with SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Sixty-seven patients who used TNF-α antagonists for the treatment of RA, AS, or psoriasis were identified. We identified 268 age- and sex- matched controls from patients who did not use any TNF-α antagonists for the treatment of RA, AS, or psoriasis. The mean age was 56.7±11.85 years and 56.5±11.49 years in the TNF group and control group, respectively. Male patients were 50.7% and female patients were 49.3% in both groups. The mean BMI was 23.6±3.45 kg/m2 and 23.9±3.46 kg/m2 in the TNF group and control group, respectively. Patients in two groups were similar in average age, sex, BMI, history of smoking and alcohol use, family history of colon cancer, and indication for colonoscopy.

In the TNF group, patients diagnosed with RA, AS, and psoriasis were 26 (38.8%), 29 (43.3%), and 12 (17.9%), respectively. In the control group, patients diagnosed with RA, AS, and psoriasis were 120 (44.8%), 66 (24.6%), and 82 (30.6%), respectively. More patients in the TNF group used methotrexate, azathioprine and sulfasalazine than patients in the control group (62.7% vs 43.7%, 9.0% vs 2.6%, and 46.3% vs 29.5%, respectively). (Table 1).

Table 1. Demographic, clinical characteristics of patients who treated with anti-TNF-α agents and age- and gender-matched controls

Variables	Patient with Anti-TNF-α (N=67)	Controls (N=268)	*p*-value
Age(years)			
Mean±SD	56.7±11.85	56.5±11.49	0.932
Range	33-81	29-84	
Gender			1.0
Female	33 (49.3%)	132 (49.3%)	
Male	34 (50.7%)	136 (50.7%)	
BMI (kg/m^2)	23.6±3.45	23.8±3.46	0.717
Underlying disease			0.006
RA (%)	26 (38.8%)	120 (44.8%)	
AS (%)	29 (43.3%)	66 (24.6%)	
Psoriasis (%)	12 (17.9%)	82 (30.6%)	
History of smoking			0.759
Nonsmoker (%)	42 (62.7%)	180 (67.2%)	
Current smoker (%)	11 (16.4%)	36 (13.4%)	
Past smoker (%)	5 (7.5%)	23 (8.6%)	
History of alcohol use			0.448
Nondrinker (%)	38 (56.7%)	177 (66.0%)	
< 4/week (%)	14 (20.9%)	53 (19.8%)	
≥ 4/week (%)	3 (4.5%)	6 (2.2%)	
Diabetes mellitus at initial diagnosis	7 (10.4%)	47 (17.5%)	0.148
Immunosuppressant at time of colonoscopy			
MTX (%)	42 (62.7%)	117 (43.7%)	0.005
Azathioprine (%)	6 (9.0%)	7 (2.6%)	0.027
Sulfasalazine (%)	31 (46.3%)	79 (29.5%)	0.009
Steroid (%)	42 (62.7%)	140 (52.2%)	0.125

NSAID (%)	56 (83.6%)	201 (75.0%)	0.137
FHx of colorectal cancer	2 (3.0%)	4 (1.5%)	0.323
Indication for colonoscopy			0.162
Gastrointestinal symptom (%)	19 (28.4%)	70 (26.1%)	
Screening or surveillance (%)	29 (43.3%)	154 (57.5%)	
Anemia (%)	6 (9.0%)	18 (6.7%)	
Gastrointestinal bleeding (%)	11 (16.4%)	23 (8.6%)	
Stool occult blood (%)	1 (1.5%)	3 (1.1%)	
Laboratory tests			
Hemoglobin (g/dl)	12.9±2.34	13.2±2.45	0.479
Cholesterol (mg/dl)	174.7±35.91	182.4±39.17	0.145
Albumin (g/dl)	4.1±0.57	4.2±0.49	0.154
Total bilirubin (mg/dl)	0.8±0.53	0.8±0.39	0.745

Table 2. Summary of anti-TNF-α therapy

Variables	**N=67**
Types	
Etanercept (%)	47 (70.1%)
Infliximab (%)	8 (11.9%)
Adalimumab (%)	12 (17.9%)
Duration	
≤ 1 year	27 (40.3%)
1 year ~ 3 year	24 (35.8%)
> 3 year	16 (23.9%)

TNF-α antagonist treatment

Etanercept was used in 47 patients (70.1%) and infliximab in 8 patients (11.9%), adalimumab in 12 patients (17.9%), respectively. Median duration of TNF-α antagonists use was 23.7±19.95 months, range from 1 to 74 months. Patients who used TNF-α antagonist for more than 3 years were 16 (23.9%). 24 (35.8%) and 27 (40.3%) patients used TNF-α antagonist for 1 ~ 3 years and less than 1 year, respectively (Table 2).

Colonoscopy Findings

Two patients (3.0%) were diagnosed with advanced colonic neoplasia, including one colon cancer (1.5%) and one advanced adenoma (1.5%) in the TNF group. Additionally, 29 patients (10.8%) were diagnosed with advanced colonic neoplasia, including 10 (3.7%) colon cancers and 21 (7.8%) advanced adenomas in the control group. Two patients in the control group had both colon cancer and advanced adenoma. The risk of advanced colonic neoplasia was reduced in patients used TNF-α antagonist, but the difference was not statistically significant (OR, 0.254; 95% CI, 0.059 to 1.091; P = 0.048). Less patients were diagnosed with advanced adenoma, colon cancer in the TNF group than in the control group, but the differences were not statistically significant (OR 0.178; 95% CI, 0.024 to 1.349; P = 0.093 and OR 0.391; 95% CI, 0.049 to 3.108; P = 0.700, respectively).

Twenty patients (29.9%) were diagnosed with nonadvanced adenoma in the TNF group and 83 patients (31.0%) were diagnosed with nonadvanced adenoma in the control group (OR 0.948; 95% CI, 0.529 to 1.701, P = 0.859) (Table 3).

Table 3. Diagnostic yield of advanced neoplasia between patients with or without anti-TNF-α agents

	Cases (n=67) No. of Patients (%)	Controls (n=267) No. of Patients (%)	Odds ratio (95% CI)	*p*-value
Advanced neoplasia[†]	2 (3.0%)	29 (10.8%)	0.254 (0.059-1.091)	0.048
Advanced adenoma[‡]	1 (1.5%)	21 (7.8%)	0.178 (0.024-1.349)	0.093
Colon cancer	1 (1.5%)	10[§] (3.7%)	0.391 (0.049-3.108)	0.700
Non advanced adenoma	20 (29.9%)	83 (31.0%)	0.948 (0.529-1.701)	0.859

[†] Advanced adenoma or primary colon cancer. Metastatic lesion of primary cancer including direct invasion was not detected.

[‡] Advanced adenoma is defined as an adenoma ≥ 10mm size or as an adenoma with villous component or high-grade dysplasia. These patients had no malignant lesion.

[§] 2 patients also had advanced adenoma.

Univariate and multivariate analyses for risk factors of advanced colonic neoplasia

In the univariate analysis, age, smoking and gastrointestinal bleeding were associated with the increased risk for advanced colonic neoplasia. We next performed multivariate analysis to estimate the odds of advanced colonic neoplasia. The use of TNF-α antagonist was an independent preventive factor for advanced colonic neoplasia (OR 0.20; 95% CI, 0.04 to 0.95, P = 0.043). Age, smoking, and gastrointestinal bleeding were independent risk factors for advanced colonic neoplasia (Table 4).

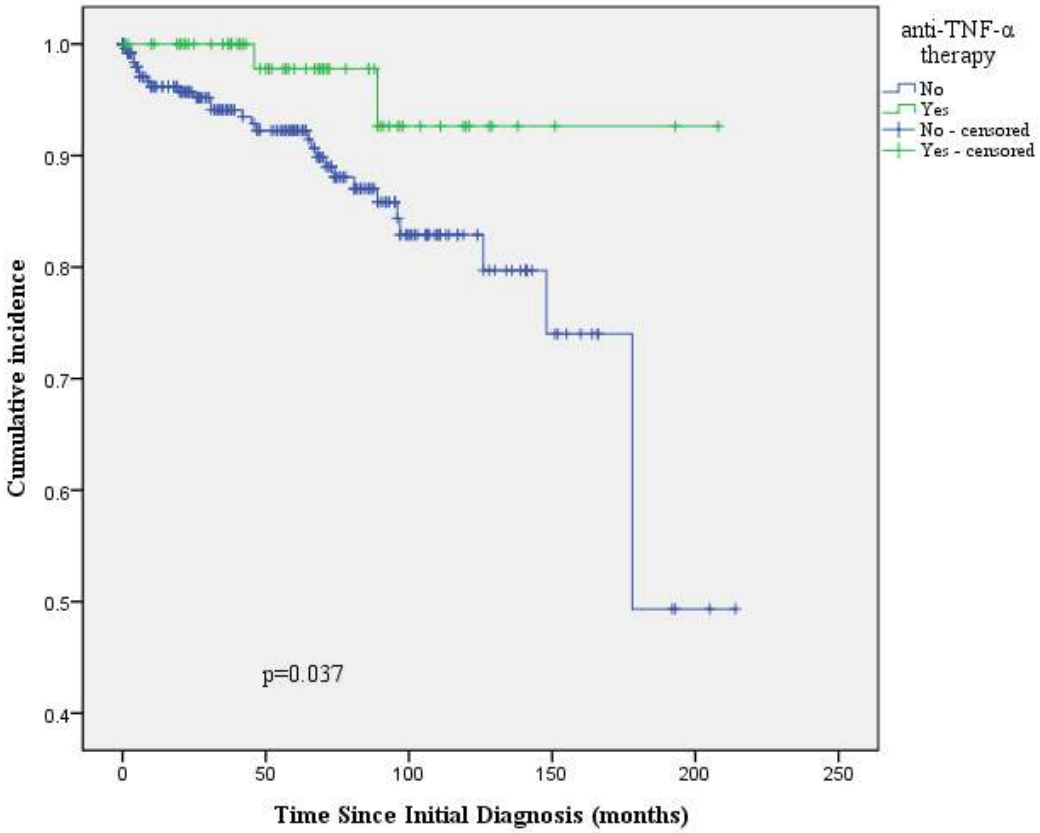
Cumulative incidence of advanced colonic neoplasia

The Kaplan-Meier curves of cumulative incidence of overall advanced colorectal neoplasia according to the use of TNF-α antagonists showed significant difference between two groups. Cumulative incidence was lower in the TNF group than the control group (P = 0.037) (Figure 1).

Table 4. Univariate and multivariate analysis for advanced colonic neoplasia in patients with RA, AS, and psoriasis

	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value
Age	1.10 (1.05-1.14)	< 0.001	1.11 (1.05-1.16)	< 0.001
Anti-TNF-α	0.25 (0.06-1.09)	0.065	0.20 (0.04-0.95)	0.043
History of smoking		0.030		0.003
Past smoker	3.78 (1.42-10.08)	0.008	6.40 (1.97-20.89)	0.002
Current smoker	1.35 (0.48-3.84)	0.574	4.24 (1.21-14.79)	0.024
Colonoscopy indication		0.048		0.010
Screening or surveillance	2.04 (0.66-6.28)	0.216	1.51 (0.45-5.07)	0.507
Anemia	3.04 (0.63-14.61)	0.166	1.92 (0.32-11.32)	0.473
Gastrointestinal bleeding	6.54 (1.82-23.47)	0.004	12.60 (2.73-58.11)	0.001

Figure 1. A Kaplan-Meier analysis on the cumulative incidence of overall advanced colorectal neoplasia according to the use of anti-TNF-α agents



DISCUSSION

Our multicenter study, which enrolled patients who was diagnosed with RA, AS, or psoriasis and subsequent colonoscopy, investigated the risk of advanced colon adenoma or colon cancer with the use of TNF-α antagonists. Of the 67 patients who used TNF-α antagonists, two patients had advanced colonic neoplasia including one colorectal cancer. However, 29 patients had advanced colonic neoplasia in patients who did not use TNF-α antagonists. In addition, the use of TNF-α antagonist was an independent preventive factor for advanced colonic neoplasia in a multivariate analysis (OR 0.20; 95% CI, 0.04 to 0.95, P = 0.043).

Tumor necrosis factor (TNF) was recognized for its ability to mediate endotoxin-induced tumor necrosis in mouse models (7). This ability of TNF-α against tumors raises the concern that TNF-α inhibition may increase the risk of malignancy. Initial concern occurred from post-marketing reports to the US FDA which showed 26 cases of lymphoma among patients with RA or Crohn's disease treated with TNF-α antagonists (4). However, previous studies mostly analyzed the risk of overall cancer, not colon specific and did not include advanced colon adenoma (8-12). But in some studies, the risk of site-specific cancer was reported. Results from a follow-up study from DANBIO registry suggested that TNF-α antagonist therapy is associated with increased risk of colon cancer (5). By contrast, another study suggested that TNF-α antagonist treated RA patients displayed colon cancer risk similar to RA patients without TNF-α antagonists (6). To our knowledge, no studies about the risk of advanced colon adenoma with the use of TNF-α antagonists were made. Therefore, we performed a study to determine

association of the use of TNF-α antagonist and risk of advanced colonic neoplasia. The diagnostic yields of advanced neoplasia in the TNF group and the control group were 3.0% and 10.8%, respectively. The odds of detecting an advanced neoplasia among patients who used TNF-α antagonist were one fourth of the age- and sex- matched controls. Moreover, the use of TNF-α antagonist was an independent preventive factor for advanced colonic neoplasia in a multivariate analysis. Based on this data, we suggest that the risk of advanced colonic neoplasia may be decreased with the use of TNF-α antagonists. To our knowledge, this is the first study to show the chemopreventive effect of TNF-α antagonist on advanced colonic neoplasia. Further study is needed to demonstrate this chemopreventive effect of TNF-α antagonist in high risk patients such as familial adenomatous polyposis.

It is known that there are two stages in colon carcinogenesis, initiation and promotion/progression stages. Because inflammation process play a role in the promotion/progression stage, many studies were carried out to prove chemopreventive effect of anti-inflammatory agents (13-15). TNF-α was initially identified for its ability to induce necrosis of cancers, but evidences suggesting that TNF might stimulate tumor growth arose (16). TNF-α is one of the major inflammatory mediators by mediating its effects through two receptors: TNF-α receptor I and II. TNF-α exposed cells activate NF-κB, leading to the expression of inflammatory genes and NF-κB signaling is a key mediator of tumor promoting activity of inflammatory cytokines (17, 18). Moreover, macrophage-induced angiogenesis is mediated by TNF-α (16). Based on this information, trials using TNF-α antagonists as cancer treatment were carried out (19, 20). A mouse study showed that blocking TNF-α in mice had reduced colorectal carcinogenesis associated with chronic colitis (21). In our study, there was no difference

in the incidence of nonadvanced adenoma between the TNF group and the control group. However, the incidence of advanced colonic neoplasia was lower in the TNF group than the control group. This result may be due to anti-inflammatory effect on promotion/progression stage and anti-angiogenic effect of TNF-α antagonist.

Our data showed a slightly higher prevalence of advanced colonic neoplasia in the control group compared to previous studies. A meta-analysis of 18 studies about prevalence of adenomas and colorectal cancer in average risk individuals reported the pooled prevalence of advanced colonic neoplasia as 6.0% with older cohorts reporting higher prevalence rates (22). And another retrospective prevalence study involving 1177 persons reported the prevalence of advanced colonic neoplasia as 7.4% (23). There may be several reasons for this. First, we excluded patients who underwent colonoscopy prior to initial diagnosis of RA, AS, or psoriasis. Second, substantial portion of patients in our study underwent colonoscopy because of gastrointestinal symptom, anemia, gastrointestinal bleeding, and stool occult blood, not because of screening. Actually, a study involving 5486 persons reported the prevalence of advanced colonic neoplasia as about 10% (24). Therefore, prevalence of advanced colonic neoplasia can vary according to study design and we think that our data provide a reasonable prevalence of advanced colonic neoplasia.

Our study has several strengths compared to previous studies. To our knowledge, this was the first study to evaluate the risk of advanced colonic neoplasia with the use of TNF-α antagonists in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis. Previous studies mostly analyzed the risk of overall cancer, not colon specific. Some studies included incidences of site specific cancers including colon cancer, but did not include advanced colonic neoplasia (5, 6). Second, through the multi-center study

design, we were able to minimize the bias arising from a single center study design. Finally, this study showed decreased risk of advanced colonic neoplasia with the use of TNF-α antagonists, which was contrary to previous concept of TNF-α antagonist that it may increase the risk of malignancy.

Our study has several limitations. First, its retrospective study design is a limitation. Second, not all patients diagnosed with RA, AS, or psoriasis underwent colonoscopy, which may have affected the precise prevalence of advanced colonic neoplasia. Third, relatively small numbers of patients were enrolled, considering low prevalence of advanced adenoma and colon cancer. Therefore, patients diagnosed with advanced colonic neoplasia were not sufficient enough. Finally, we might have selected a higher portion of patients with advanced colonic neoplasia in the control group because of selection bias. However, we believe that we minimized bias by providing a precise prevalence of advanced colonic neoplasia and by exclusively enrolling patients who underwent colonoscopy in both groups. Nevertheless, because of retrospective design of our study, cautious interpretation of our data should be required. A large prospective cohort study for a lengthy period of time is needed to determine risk of advanced colon adenoma or colon cancer with use of TNF-α antagonists.

In conclusion, the diagnostic yield of advanced neoplasia in the patients treated with TNF-α antagonist was substantially lower than that of control group. We suggest that the risk of advanced colonic neoplasia may be decreased with the use of TNF-α antagonists.

REFERENCES

1. Bretthauer M. Colorectal cancer screening. J Intern Med. 2011 Aug;270(2):87-98.

2. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. The New England journal of medicine. 1993 Dec 30;329(27):1977-81.

3. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. Jama. 2012 Sep 5;308(9):898-908.

4. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis and rheumatism. 2002 Dec;46(12):3151-8.

5. Dreyer L, Mellemkjaer L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Annals of the rheumatic diseases. 2013 Jan;72(1):79-82.

6. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Annals of the rheumatic diseases. 2005 Oct;64(10):1421-6.

7. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proceedings of the National Academy of Sciences of the United States of America. 1975 Sep;72(9):3666-70.

8. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 2006 May 17;295(19):2275-85.

9. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Annals of the rheumatic diseases. 2011 Nov;70(11):1895-904.

10. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiology and drug safety. 2011 Feb;20(2):119-30.

11. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. Journal of the American Academy of Dermatology. 2011 Jun;64(6):1035-50.

12. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis and rheumatism. 2011

Jun;63(6):1479-85.

13. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer research. 1999 Feb 1;59(3):597-601.

14. Reddy BS, Hirose Y, Lubet R, Steele V, Kelloff G, Paulson S, et al. Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib, administered during different stages of carcinogenesis. Cancer research. 2000 Jan 15;60(2):293-7.

15. Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. The New England journal of medicine. 2000 Jun 29;342(26):1960-8.

16. Leibovich SJ, Polverini PJ, Shepard HM, Wiseman DM, Shively V, Nuseir N. Macrophage-induced angiogenesis is mediated by tumour necrosis factor-alpha. Nature. 1987 Oct 15-21;329(6140):630-2.

17. Sethi G, Sung B, Aggarwal BB. TNF: a master switch for inflammation to cancer. Frontiers in bioscience : a journal and virtual library. 2008;13:5094-107.

18. Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, et al. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature. 2004 Sep 23;431(7007):461-6.

19. Madhusudan S, Foster M, Muthuramalingam SR, Braybrooke JP, Wilner S, Kaur K, et al. A phase II study of etanercept (Enbrel), a tumor necrosis factor alpha inhibitor in patients with metastatic breast cancer. Clinical cancer research : an official

journal of the American Association for Cancer Research. 2004 Oct 1;10(19):6528-34.

20. Brown ER, Charles KA, Hoare SA, Rye RL, Jodrell DI, Aird RE, et al. A clinical study assessing the tolerability and biological effects of infliximab, a TNF-alpha inhibitor, in patients with advanced cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2008 Jul;19(7):1340-6.

21. Popivanova BK, Kitamura K, Wu Y, Kondo T, Kagaya T, Kaneko S, et al. Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis. The Journal of clinical investigation. 2008 Feb;118(2):560-70.

22. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2009 Dec;7(12):1272-8.

23. Strul H, Kariv R, Leshno M, Halak A, Jakubowicz M, Santo M, et al. The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40-80 years. The American journal of gastroenterology. 2006 Feb;101(2):255-62.

24. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME, Colorectal Cancer Study G. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. The New England journal of medicine. 2004 Dec 23;351(26):2704-14.

국문 초록

서론: 본 연구는 류마티스 관절염, 강직성 척추염, 그리고 건선 환자에서 종양괴사인자 알파 길항제의 사용이 진행성 대장 선종과 대장암에 끼치는 영향을 평가하기 위하여 시행되었다.

방법: 2005년 1월부터 2012년 12월까지 류마티스 관절염, 강직성 척추염, 그리고 건선으로 진단되었고 진단 이후에 대장 내시경을 시행한 환자를 대상으로 하였다. 종양괴사인자 알파 길항제를 사용한 환자 67명 각각에 대하여 류마티스 관절염, 강직성 척추염, 건선으로 진단되고 대장 내시경을 시행한 네 명의 연령(±5세), 성별이 일치하는 대조군을 선정하여 양 군의 진행성 대장 종양의 발생률을 비교하였다.

결과: 종양괴사인자 알파 길항제를 사용한 67명 중 2명 (3.0%)에서 진행성 대장 종양이 확인되었고 그 중 1명 (1.5%)은 진행성 대장 선종, 1명 (1.5%)은 대장암이었다. 환자-대조군 연구의 결과 종양괴사인자 알파 길항제를 사용한 환자에서 진행성 종양이 발생한 비율은 대조군의 1/4 이었다 [승산비, 0.254; 95% 신뢰구간, 0.059 – 1.091; P = 0.048]. 종양괴사인자 알파 길항제를 사용한 환자에서 누적 발생률은 대조군에 비해 낮았다 (P = 0.037).

결론: 종양괴사인자 알파 길항제를 사용한 환자에서 진행성 대장 종양의 진단율은 대조군에 비해 낮았다. 본 연구진은 종양괴사인자 알파 길항제의 사용이 진행성 대장 종양의 발생을 낮출 가능성이 있음을 보고한다.

주요어: 종양괴사인자 알파 길항제, 대장 선종, 대장암

학 번: 2013-22607