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Research Article

Fecal Calprotectin Screening before Anti-IL17A Treatment in Patients with Psoriasis: Is there a Relationship between Fecal Calprotectin Level and Psoriasis Severity?

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Abstract

Background and objectives: Anti-IL17A treatment has been identified as exacerbating Inflammatory Bowel Disease (IBD) and leading to new-onset IBD, and Fecal Calprotectin (FCP) is a good marker of intestinal inflammation. This study aimed to evaluate the results of FCP screening and whether FCP level correlates with psoriasis severity before anti-IL17A treatment.

Methods: The present study prospectively evaluated psoriasis patients who were followed up in the outpatient dermatology & rheumatology clinic of Cerrahpasa Medical Faculty from May 2018 through December 2021. Before anti-IL17A treatment, all patients underwent an FCP test, and their PASI scores were evaluated. Patients who had pre-treatment FCP >30 µg/g or developed symptoms under anti-IL17A treatment regardless of pre-treatment FCP level consulted with gastroenterology. Eligibility criteria were used to determine which patient needed colonoscopic evaluation.

Results: 126 psoriasis patients (79 males) enrolled in this study. There was no statistically significant difference in age, pre-treatment FCP, and pre-treatment PASI scores compared to genders. No correlation was found between pre-treatment FCP and pre-treatment PASI scores. Ten patients did not undergo colonoscopy although their pre-treatment FCP >30 µg/g. Eleven patients underwent colonoscopy before or under anti-IL17A therapy because they met the eligibility criteria for colonoscopy. Among these patients, UC was detected by colonoscopy in one patient and incidental tubulovillous adenoma in the other.

Conclusions: FCP levels did not correlate with psoriasis severity in our study. In addition, FCP screening did not appear to be an efficient and cost-effective tool to predict which psoriasis patient would develop new-onset IBD under anti-IL17A therapy.

Keywords: Fecal calprotectin; Screening; Anti-IL17A; Psoriasis; Inflammatory bowel disease

Abbreviations

IBD: Inflammatory Bowel Disease; FCP: Fecal Calprotectin; PASI: Psoriasis Area Severity Index; SEC: Secukinumab; IXE: Ixekizumab; UC: Clcerative colitis; CD: Crohn's Disease; MTX: Methotrexate; CRP: C-Reactive Protein; IQR: Interquartile Range; GI: Gastrointestinal

Introduction

Psoriasis is a common chronic inflammatory skin disease with various clinical manifestations. It accounts for a significant burden on dermatology & rheumatology clinics worldwide and affects males and females equally. Peak ages for the onset of psoriasis are the fourth and sixth decades [1]. Psoriasis is also a chronic multisystem inflammatory disorder associated with much comorbidity, including IBD [2]. Ulcerative Colitis (UC) and Crohn's Disease (CD) have been reported to be more prevalent in psoriasis groups than in control groups, and CD is more strongly associated with psoriasis than UC [3,4]. Although anti-IL17A agents were considered beneficial theoretically in both psoriasis and IBD, randomized controlled trials showed no efficacy achieved by the IL 17 inhibition in patients with moderate to severely active CD [5,6]. Furthermore, paradoxical flares of IBD with IL17 inhibition prevented the use of IL17 inhibitors in UC or CD [7]. A recent meta-analysis of 21 trials reported new-onset IBD or exacerbation of IBD being uncommon in patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis treated with SEC [8].

Current guidelines are inadequate about how clinicians should act before initiating IL17 inhibitor treatment to predict which patient is at risk of new-onset IBD and which patient requires further evaluation. Moreover, the management of patients with disease exacerbation or new-onset IBD after IL17 inhibitor treatment is unclear. The present study aimed to reveal whether there is a relationship between the severity of skin inflammation caused by psoriasis and accompanying intestinal inflammation. Clarifying this may be useful in predicting patients' predisposition to IBD prior to anti-IL17A therapy, which can potentially lead to IBD. We also aimed to test the efficacy of FCP screening before anti-IL17A treatment as a result of the evaluation of patients by gastroenterology. Due to the limited knowledge and

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experience in this field, we consider that this study, which reveals the real-life experiences of multidisciplinary cooperation, will contribute to the patient management of dermatologists, rheumatologists, and gastroenterologists in anti-IL17A therapy.

Materials and Methods

This prospective cohort study evaluated patients diagnosed with psoriasis and followed up in the outpatient dermatology & rheumatology clinic of Cerrahpasa Medical Faculty from May 2018 through December 2021. Patients who had various clinical manifestations of psoriasis (plaque psoriasis, nail psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis) and were verified histopathologically were included in the study. Patients who were under 18, had active arthritis at the beginning of anti-IL17A therapy, had a preexisting diagnosis of IBD, had another infectious/non-infectious inflammatory disease of the gastrointestinal tract (e.g., bacterial infections, parasite infestations, or celiac sprue), or had a gastrointestinal malignancy were excluded. All patients had been treated with Methotrexate (MTX), and twelve patients had also received anti-TNFα treatment (infliximab, etanercept, or adalimumab) due to the treatment failure or adverse effects with MTX. Treatment with an IL17 inhibitor was started because of the unresponsiveness or adverse effects of former systemic therapies. SEC or IXE were used for IL17 inhibition. The decision of which anti-IL17A agent to start was made based on expert opinion and availability of the agents. MTX was not coadministered with anti-TNFα or anti-IL17A agents. Furthermore, anti-TNFα and anti-IL17A agents were not used concurrently. The flow diagram of the study is illustrated in Figure 1.

All patients gave a fecal sample to measure FCP before anti-IL17A treatment, and this was termed pre-treatment FCP. The cut-off level for FCP was determined to be 30 μg/g. Patients who had pre-treatment FCP >30 μg/g or developed symptoms after anti-IL17A treatment regardless of pre-treatment FCP level were consulted with gastroenterology and were evaluated as follows; symptoms: 1-abdominal pain, 2-diarrhea, 3-defecating blood and/or mucus, 4-tenesmus, family history: 1-presence a relative who diagnosed with ulcerative colitis or Crohn's disease, physical examination: 1-abdominal tenderness to palpation, laboratory: 1-leukocytosis, 2-elevated CRP, 3-high sedimentation rate (Table 1). Patients who had at least one symptom and met at least one of the other criteria underwent colonoscopy to look for mucosal signs of inflammation. Biopsies were obtained when inflamed sites or polyps were detected on colonoscopy. PASI scores of all patients were assessed by an experienced dermatologist (BE) before anti-IL17A treatment, and this was termed pre-treatment PASI scores. PASI score <7 signified mild disease, score=7-15 moderate disease, and >15 severe disease [9].

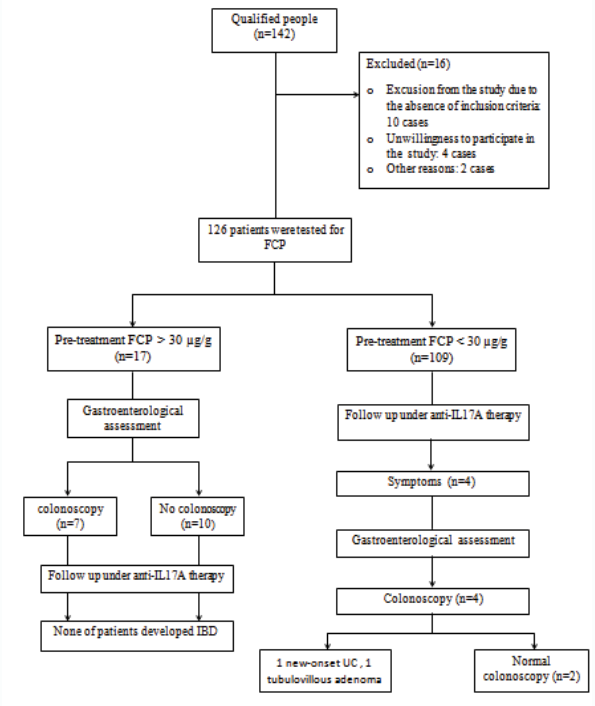


Figure 1: Study flow diagram.

Table 1: Elgibility criteria for colonoscopy†.

Symptoms
1.Abdominal pain
2.Diarrhea
3.Defacating blood and/or mucus
4.Tenesmus
Family history
1. Presence a relative who diagnosed with ulcerative colitis or Crohn's disease
Physical examination
1. Abdominal tenderness to palpation
Laboratory‡
1. Leukocytosis
2. Elevated CRP
3. High sedimentation rate

†At least one symptom and one of the other criteria are required to undergo colonoscopic evaluation

‡Presence of at least one of the laboratory criteria was considered positive.

Characteristics of patients who underwent colonoscopy are given in Table 2. Patients' ages, pre-treatment FCP, and pre-treatment PASI scores were compared according to their genders. And the correlation between pre-treatment FCP and pre-treatment PASI scores was assessed. The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was received from all of the patients, and the study was approved by the independent ethics committee of Cerrahpasa Medical Faculty.

Statistical analysis

All analyses were performed with the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive characteristics of patients are presented as mean ± Standard Deviation (SD), median (Interquartile Range [IQR]), or frequency (%). Student's t-test method was used to evaluate patients' ages within the groups. Mann Whitney U test was used to compare continuous variables. Pearson's correlation analysis was used to evaluate the correlation between the two data sets. P<0.05 was regarded as statistically significant.

Results

The present study enrolled 126 patients with psoriasis (79 males and 47 females). While 45 (36%) of patients used SEC, 81 (64%) used IXE. Age, pre-treatment FCP, and pre-treatment PASI scores were compared according to patients' genders (Table 3). The mean age was 40.7 ± 11.5 in males and 45.06 ± 12.8 in females (p=0.048). Pre-treatment FCP median was 18 (IQR: 12-28) in males and 16 (10-26) in

Table 2: Characteristics of patients who underwent colonoscopy

Gender	Age†	Anti-IL17A agent	Pre-treatment PASI score‡	Pre-treatment FCP§	Eligibility criteria for colonoscopy	Colonoscopic findings	Histopathology
Male	42	SEC	15	40	2 symptoms+physical examination	None	No taken biopsy
Male	38	SEC	15	100	1 symptom+physical examination	None	No taken biopsy
Male	33	SEC	17	78	1 symptom+2 laboratory	None	No taken biopsy
Male ¶	44	SEC	24	28	2 symptoms+2 laboratory	A polyp	Tubulovillous adenoma
Male	28	IXE	30	212	2 symptoms+physical examination+1 laboratory	None	No taken biopsy
Female	24	IXE	20	48	2 symptoms+physical examination	None	No taken biopsy
Female	54	IXE	25	60	1 symptom+physical examination	None	No taken biopsy
Female ¶	25	IXE	18	24	1 symptom+physical examination	Fragile rectal mucosa	Proctitis of UC
Female ¶	45	IXE	15	20	Family history+ 1 laboratory	None	No taken biopsy
Female ¶	58	IXE	25	12	1 symptom+physical examination	None	No taken biopsy
Female	32	IXE	17	100	1 symptom+2 laboratory	None	No taken biopsy

FCP: Fecal Calprotectin; PASI: Psoriasis Area Severity Index; SEC: Secukinumab; IXE: Ixekizumab

†Age, mean±SD: 38.5 (±11.3), ‡Pre-treatmentPASI Score Median (IQR:25-75): 18 (15-25), §Pre-treatment FCP Median (IQR:25-75): 48 (24-100)

¶These patients underwent colonoscopyunder anti-IL17A therapy.

Table 3: Comparison of age, pre-treatment FCP, and PASI scores according to patients' genders

	Male, n=79	Female, n=47	P value
Age, mean ± SD†	40.7 (± 11.5)	45.06 (± 12.8)	0.048
Pre-treatment FCP Median(IQR:25-75)	18 (12-28)	16 (10-26)	0.297
Pre-treatment PASI Score Median(IQR:25-75)	19 (15-24)	20 (17-23)	0.49

FCP: Fecal Calprotectin; PASI: Psoriasis Area Severity Index

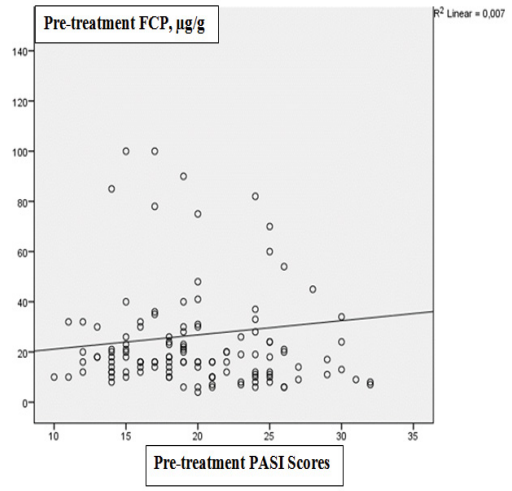
†Patients' age was not correlated with pre-treatment FCP or pre-treatment PASI scores.

females (p>0.05). Pre-treatment PASI Score median was 19 (IQR: 15-24) in males and 20 (IQR: 17-23) in females (p>0.05). Pre-treatment PASI score was >15 in 98 (77%) patients and 7-15 in 28 (23%) patients. Patients' age was not correlated with pre-treatment FCP levels or pre-treatment PASI scores. Furthermore, no correlation was found between patients' pre-treatment FCP levels and pre-treatment PASI scores (Table 4). After the gastroenterological assessment, there were ten patients who did not undergo colonoscopy, although their pre-treatment FCP >30 µg/g based on the criteria mentioned above. Patients who did not undergo colonoscopy after gastroenterological assessment did not develop new-onset IBD during their follow-ups (median 20 months [IQR: 13-38]). In total, eleven patients underwent colonoscopy before or under anti-IL17A therapy because they met the above criteria. The mean age was 38.5 ± 11.3, the pre-treatment FCP median was 48 (IQR: 24-100), and the pre-treatment PASI Score median was 18 (IQR: 15-25) in patients who underwent colonoscopy. Characteristics of patients who underwent colonoscopy are given in Table 2. Seven patients were consulted with gastroenterology because they had pre-treatment FCP >30 µg/g. They also met the above criteria, so they were further evaluated colonoscopically. None of them had gross signs of mucosal inflammation, so the biopsy was not performed, and anti-IL17A treatment was started. None of them developed any adverse effects during their follow-ups (median 23 months [IQR: 9-31]). Four patients who had pre-treatment FCP <30 µg/g developed symptoms under anti-IL17A treatment, so they consulted with gastroenterology, and the above criteria were applied. Thereby, it was decided to continue further examination with colonoscopy in all of them. Acute phase elevation was present in 46% of the patients who underwent colonoscopy, and FCP was found to be high in 3(60%) of them. Colonoscopy revealed pathological findings of mucosal inflammation in one patient and a polyp in the other. The rest of the patients had a normal colonoscopy. Mucosal biopsies were performed in the first patient, and proctitis of UC was detected histopathologically with cryptic distortion and neutrophilic abscesses. Thus, the incidence of new-onset UC was 0.7% in our study. Polypectomy was performed on the second patient, and histopathological examination revealed tubulovillous adenoma. Therefore, anti-IL17A treatment was discontinued in both patients. Proctitis of UC spontaneously resolved without recurrence in the first patient.

Discussion

IL-17A agents (SEC and IXE) have been shown to be substantially effective in psoriasis with a rapid-onset of action [10-12]. However, dermatologists and rheumatologists may be hesitant when starting these agents because of their potential risk of exacerbating IBD or causing new-onset IBD [8]. And, current guidelines remained inadequate to aid clinicians in dealing with this issue. To our knowledge, it is not well defined how IL17 inhibition triggers an IBD exacerbation or leads to new-onset IBD. However, IL-17 plays a crucial role in maintaining intestinal wall integrity, and its inhibition may have deleterious effects with worsening inflammation, reduced barrier function, and increased susceptibility to infections [8,13].

Table 4: Correlation graph comparing FCP and PASI scores.



In this study, most of the patients used IXE (n=81, 64%). While the majority of patients had severe disease (PASI score >5), the remainder had the moderate disease (PASI score =7-15) [9]. According to the baseline demographic data of our study, female patients were significantly older than male patients (p=0.048). Pre-treatment FCP and PASI scores did not significantly differ between genders (p=0.29 and p=0.49, respectively). There was no correlation between pre-treatment FCP and pre-treatment PASI scores. In addition, approximately half of the patients who underwent colonoscopy had acute phase elevation (n=5, 46%), and FCP was found to be high in most of these patients (n=3, 60%).Considering the MTX and TNFα inhibitors are taking place in IBD treatment, and all the patients had been treated with at least one of these agents, patients' pre-treatment FCP levels may have been measured less than expected [14]. Thus, this situation possibly affected the correlational relationship between pre-treatment FCP and pre-treatment PASI scores in our study.

A large SEC safety analysis across 21 clinical trials of 7355 patients found that both SEC-related exacerbations and new-onset IBD cases were uncommon [8]. In this study, the psoriasis cohort included 5181 patients. Of 5 (0.1%) patients with CD and 10 (0.19%) patients with UC, 2 CD and 4 UC patients had experienced disease exacerbation during therapy. While 3 (0.06%) patients had developed new-onset CD, 10 (0.19%) patients had developed new-onset UC and 1 (0.02%) patient new-onset IBD unclassified (IBDU) [8]. In our study, the incidence of new-onset UC was 0.7%, and there was no new-onset CD or IBDU. Thus our study results regarding the low rates of new-onset IBD in psoriasis patients who received IL17 inhibitor therapy were consistent with previous studies.

FCP is a promising non-invasive marker of histologic activity in UC, and a clear correlation has been found between histologic activity and FCP levels in adult patients with UC in a large systematic review [15]. Furthermore, it has been proposed that FCP level 72-250 μg/g predicts the histologic activity of UC, although a validated cut-off has not been established yet [15]. However, in this study, we observed that although the susceptibility to IBD was increased in patients with psoriasis, psoriasis severity and FCP levels were not correlated. Fauny et al. [7] outlined an algorithm based on the experience of authors. They recommended measuring FCP after searching for family history and gastrointestinal symptoms. According to this algorithm, patients who have FCP >250 μg/g should be consulted with gastroenterology and be assessed for the need for complementary procedures (e.g., colonoscopy) [7]. In our study, we evaluated patients without prior history of IBD and requested FCP testing from all patients regardless of the presence of family history or symptoms. In contrast to the algorithm mentioned above, we determined the cut-off FCP level as 30 μg/g, much lower than proposed. Since IBD has been reported to be more common in psoriasis patients, we aimed to increase the sensitivity of testing and decrease the probability of skipping patients who had underlying intestinal inflammation [3,4]. Because the using upper limit of the "normal range" (usually 50 μg/g as the threshold) for referring patients for colonoscopy will result in large numbers of unnecessary procedures, we also applied comprehensive criteria to select eligible patients for colonoscopy [16]. However, we observed new-onset IBD only in one patient who had pre-treatment FCP <30 μg/g and used IXE. This situation made us discourage the measuring pre-treatment FCP to predict which patient would develop new-onset IBD with anti-IL17A treatment. Although FCP screening is a useful tool to determine the need for colonoscopic evaluation in patients with symptoms or signs attributable to IBD, our study has shown that FCP screening is of no value in predicting the development of inflammatory bowel disease in every psoriasis patient who will be initiated on anti-IL17A therapy [17]. Moreover, there is no current comperative analysis regarding the IBD development risk of both investigational agents, namely SEC and IXE. Nonetheless, we consider that the patients' prior therapies (MTX and anti-TNFα agents) may have affected the outcomes of our study. AK et al. [18] proposed that developing a scoring system comprising family history, GI symptoms, previous autoimmune attacks, elevated FCP, and serum markers may be useful to determine which patients could be at high risk for developing IBD. We also consider that it would be useful to develop a scoring system to refer patients to further investigations before and during anti-IL17A therapy or to predict which patient should be followed more closely for IBD under IL 17A inhibition. However, according to our study, the value of FCP screening is not promising for this purpose. We suggest that such a scoring system should include gastrointestinal symptoms, family history, physical examination findings, and serum markers of inflammation.

The most important limitation of this study is the absence of a control group. In addition, the eligibility criteria for colonoscopy used in this study need to be validated in a larger patient population. Although we initially excluded patients with active psoriatic arthritis, as we thought this might be a confounding factor in this study, the investigation of FCP levels in patients with active arthritis with similar PASI scores may be the subject of a different study. However, prospective real-life data with anti-IL17A agents will improve our approaches in clinical practice, which is important for IL17 inhibitor-related IBD because of the limited knowledge in this field.

Conclusions

According to this study, there was no correlation between the psoriasis severity and pre-treatment FCP, a marker of intestinal inflammation. In addition, FCP screening did not appear to be efficacious and cost-effective in predicting which psoriasis patient will develop new-onset IBD under anti-IL17A therapy. Well-developed scoring systems or criteria are needed in the management of patients who are started on IL-17 inhibitor therapy, and more studies should be conducted on this subject.

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