

Seton drainage combined with anti-TNF therapy for perianal fistulizing Crohn's disease, single center experience

Perianal fistulizan Crohn hastalığında combine seton drenaj ve anti-TNF tedavi sonuçları, tek merkez deneyimi

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy of combined treatment with anti-tumor necrosis factor (TNF) agents, and setons for perianal fistulas in Crohn's disease.

Patients and Methods: Study included 27 consecutive patients with perianal fistulizing Crohn's disease, requiring seton drainage and anti-TNF therapy in our center from January 2013 to November 2014. All patients underwent a standardized pelvic magnetic resonance imaging (MRI) examination. Patient characteristics, follow up time, findings of pelvic MRI, colonoscopy and examination under anesthesia findings were recorded. Response to treatment was evaluated at the end of the follow up.

Results: The median follow-up after treatment was 17 months (6-32). The fistula was complex in 24 (89%) of the 27 patients. Colonoscopy revealed ileitis in 16 (59.3%) patients and active proctitis in 9 (33.3%) patients. Perianal abscess was observed in 12 (44.4%) patients. Complete response was obtained in 17 (63%) patients. Only 3 (11.1%) patients experienced recurrence abscess during the study period. We could not find any factor, which were associated with complete response.

Conclusion: Complete response was achieved in 63% of the patients, with perianal fistula formation associated with Crohn's disease, with combined seton drainage and anti-TNF therapy.

Keywords: Crohn's disease, Perianal fistula, Setons, Infliximab

ÖZ

Amaç: Bu çalışmanın amacı perianal Crohn hastalığında, kombine seton ve anti tümör nekroz faktörü (TNF) ajanlarla yapılan tedavinin etkinliğini değerlendirmektir.

Hastalar ve Yöntem: Ocak 2013 ve Kasım 2014 tarihleri arasında kombine seton drenaj ve anti-TNF tedavisi uygulanmış ardışık 27 perianal fistülizan Crohn hastası çalışmaya dahil edildi. Tüm hastalar standart pelvik manyetik rezonans görüntüleme (MRG) ile incelendi. Hasta özellikleri, takip zamanı, pelvik MRG bulguları, kolonoskopi ve genel anestezi altında rektal muayene bulguları, kaydedildi. Takip süresinin sonunda tedaviye yanıt değerlendirildi.

Bulgular: Tedavi sonrası ortalama takip süresi 17 (6-32) ay idi. Hastaların 24 (%89)'ünde fistül kompleks yapıda idi. Kolonoskopi bulgularına göre 16 (%59,3) hastada ileit, 9 (%33,3) hastada aktif proktit saptandı. On iki (%44,4) hastada perianal apse gözlemlendi. Tedaviye tam yanıt 17 hastada elde edilirken, çalışma sürecinde sadece 3 (%11,1) hastada tekrarlayan perianal apse ile karşılaşıldı. Değerlendirdiğimiz faktörlerden hiçbiri komplet yanıt ile anlamlı olarak ilişkili bulunmadı.

Sonuç: Crohn hastalığı ile ilişkili kompleks perianal fistülde kombine seton ve anti-TNF tedavi ile hastaların % 63'ünde tedaviye tam yanıt sağlanmıştı.

Anahtar kelimeler: Crohn hastalığı, Perianal fistül, Seton, Infliximab

Introduction

Perianal fistulas occur in 23-26 % of patients with Crohn's disease (CD) and can cause significant morbidity [1]. Patients with perianal fistulas can present with symptoms such as constant anal pain, especially in post-defecation, swelling around the anus, malodorous discharge of pus and/or blood from the external opening with skin irritation around the anus, fever, and even incontinence [2]. Contrary to cryptoglandular origin; the formation of perianal fistulas in CD is based on the presence of a penetrating ulcer in the

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rectal or anal mucosa, resulting in an abnormal granulating connection between the epithelial lining of the rectum or anal canal and the perianal skin [3,4].

Pelvic magnetic resonance imaging (MRI) is accurate in determining the exact location of the fistula, differentiating between a fibrotic and septic fistula and locating abscesses [5]. Anorectal endoscopic ultrasound (EUS) is equivalent to pelvic MRI, with less cost, but it requires expertise [6]. Examination under anesthesia (EUA) has the advantage of the possibility of concomitant drainage of abscesses and placement of non-cutting setons. The random combination of two of three methods (MRI, EUS and EUA) resulted in a 100% correct classification of perianal fistulizing Crohn's disease (PFCD) [7].

Perianal fistulas are classified according to Parks classification [8]; this is also useful for CD, although more complicated tracts can occur in a CD patient. Furthermore, this system does not include other perianal manifestations of CD (e.g. abscesses or strictures). According to the classification of the American Gastroenterological Association (AGA) [4] a simple anal fistula is defined as having a single low transsphincteric track without abscess formation, stenosis or anorectal inflammation. All other forms are classified as complex and comprise the majority of lesions.

The treatment of PFCD is based on surgical fistula drainage, fecal diversion, antibiotics, immunosuppressant drugs, and anti-tumor necrosis factor (TNF) agents. All fistulas are potential sources of sepsis; therefore, obtaining drainage is fundamental in all locations to prevent abscess formation. Since anal continence mechanism may be damaged, perineal interventions have limited role. In the case of perianal fistulas, non-cutting loose seton drainage is the method of choice to prevent recurrent abscesses and anal continence. The timing of the removal of seton drains varies between centers, as controlled data are lacking [9]. Surgical diversion of the fecal stream by a stoma often allows healing; however, many patients find a stoma to be undesirable, and the benefit of this approach is unlikely to maintain after bowel continuity is restored [10].

Perianal fistulizing Crohn's disease is accepted as an indication of therapy with a monoclonal chimeric antibody to TNF- α : infliximab. The effectiveness of this treatment has been established first by Present et al. [11] and then confirmed in the ACCENT II trial [12]. Another anti-TNF agent, adalimumab is also shown as an efficacious and safe treatment for PFCD in patients who have failed infliximab treatment [13].

The optimal clinical approach in the treatment of PFCD,

however, has yet to be defined, and a satisfactory treatment algorithm is lacking. The aim of this study was to evaluate the efficacy of combined treatment with anti-TNF agents and setons for PFCD.

Patients and Methods

Our study included 27 consecutive PFCD patients requiring seton drainage and anti-TNF therapy in a tertiary center from January 2013 to November 2014. We excluded patients who had a follow-up of less than 6 months. A written informed consent was obtained from all patients who had participated study. A retrospective analysis of collected data from medical files was performed to describe. Patient's characteristics, demographic data, pelvic MRI, colonoscopy and EUA findings (number, type, and location of fistulas tracts, presence or not of abscess), response to therapy were noted from medical files, and analyzed retrospectively.

All patients underwent a standardized pelvic MRI examination with a 1.5 Tesla magnetic resonance imaging system (Magnetom Symphony; Siemens, Munich, Bavaria, Germany) with use of an intravenous contrast agent. Gastrointestinal radiologists evaluated the images and a detailed report was created including the amount of fistulas (single, single branched, or multiple), location (extrasphincteric, intersphincteric, transsphincteric, or suprasphincteric), extension (supra or infralevatoric), presence of a collection, and rectal wall involvement (normal, thickened).

All patients underwent surgical drainage of abscess (when existent) and seton placement, accompanied by a 2-week course of antibiotics (metronidazole and/or ciprofloxacin), and followed by infliximab induction treatment (three i.v.; administrations at 5 mg/kg at week 0, week 2, and week 6). Seton removal was planned when fistulous output was reduced after third infliximab injections. A patient was considered as a responder in the absence of drainage from all fistulas despite gentle finger compression with or without cicatrization of the external fistula orifice [12]. Factors were investigated, such as age, gender, CD duration, ileitis, proctitis, perianal abscess, fistula multiplicity, type of fistula, and follow up time, which may affect the response of combined therapy on PFCD.

Statistical Analysis

For each, data median and range were calculated. Comparison of patients according to the response to combined treatment

was made by Chi square test or Fisher's Exact test for qualitative and by Student's t-test or Mann Whitney U test for quantitative variables. Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA) for Windows, version 17. All tests were two-sided and p-values below 0.05 were considered statistically significant.

Results

This study included 27 consecutive patients with PFCD requiring seton drainage and anti-TNF therapy in our center from January 2013 to November 2014. The median age of the study cohort was 38 years (20-70) and 17 (63%) were male patients.

The first symptom of CD was perianal fistula in 6 (22.2%) patients. Fistula was diagnosed in the other 21 patients at median time of 5.5 (1-30) years after the diagnosis of CD. Median follow up time for the study cohort was 17 (6-32) months.

Colonoscopy before seton insertion revealed ileitis in 16 (59.3%) patients and active proctitis in 9 (33.3%) patients. Only one patient exhibited both conditions. Perianal abscesses were observed in 12 (44.4%) patients. Pelvic MRI before treatment revealed the median number 1 (1-4) of fistulas (Table I). Total amount of fistulas, which were detected with MRI were 41 in 27 patients. The majority (70.7%) of the fistulas were transsphincteric and suprasphincteric (Table II). Four (14.8%) patients had horseshoe fistula. According to (AGA) classification 3 (11.1%) had simple while 24 (88.9%) had complex fistula.

Table I. Patients' characteristics

Age	38	(20-70)
Gender		
Male	17	(63%)
Female	10	(37%)
Duration between CD diagnosis and PFCD (year)	5.5	(1-30)
Number of fistulas (MRI)		
1	17	(63 %)
2	6	(22 %)
3	2	(7 %)
4	1	(4 %)
Median number of fistulas	1	(1-4)
Perianal abscess	12	(%44.4)
Proctitis	9	(%33.3)
Ileitis	16	(%59.3)

CD: Crohn's Disease, PFCD: Perianal Fistulizing Crohn's Disease, MRI: Magnetic Resonance Imaging

Table II. Types of fistula according to MRI results

	N (%)
Intersphincteric	10 (24.4)
Transsphincteric	19 (46.3)
Suprasphincteric	7 (17.1)
Extrasphincteric	1 (2.4)
Horseshoe	4 (9.8)
Total fistula number (27 patients)	41 (100)

Twenty-one (77.7%) patients were treated with infliximab, because of drug intolerance or resistance, and six (22.2%) patients were treated with adalimumab. Nineteen patients (70.4%) had an initial response at week 6 after the third injection of anti-TNF agent. Setons were removed in 10 (37%) patients. Only 3 (11.1%) recurrent perianal abscesses were observed during follow up period. Two of these patients had abscesses at eighteen and nineteen months after initial response and seton removal. They were successfully treated with repeat drainage, seton replacement and anti-TNF agents. Among 17 (63%) patients who are still have seton only one patient developed recurrent abscess during follow up. Diverting colostomy was performed for this patient.

After combined therapy of anti-TNF agents and seton insertion, a complete response was obtained in 17 (63%) patients by the end of the study period. When patients with clinical response were compared to those without, there were not any significant difference between the two groups regarding age, gender, CD duration, ileitis, proctitis, perianal abscess, fistula multiplicity, type of fistula, and follow up time (Table III).

Table III. Comparing the characteristics of the patients according to the outcome of the treatment

Variable	Responder patients (n= 17)	No responder patients (n= 10)	P value
Age (year)	38 (20-70)	34 (20-55)	0.45
Gender			
Male	11 (65%)	6 (60%)	
Female	6 (35%)	4 (40%)	1
CD duration (year)	4 (0-30)	3 (0-14)	0.84
Ileitis	10 (59%)	6 (60%)	1
Proctitis	6 (35%)	3 (30%)	1
Perianal abscess	7 (41%)	5 (50%)	0.71
Fistula multiplicity	6 (35%)	3 (30%)	0.78
Type of fistula (AGA classification)			
Simple	2 (14%)	1 (10%)	
Complex	15 (88%)	9 (90%)	1
Follow up time	17 (3-29)	8 (3-27)	0.24

CD: Crohn's Disease, AGA:American Gastroenterological Association

Discussion

Achieving rapid and sustained fistula healing is challenging in CD patients. Choosing criteria of complete response is important because radiologic response rates, as previously reported, are not at a level high enough to evaluate treatment. Radiologic healing of PFCD was achieved in only one quarter of the patients with clinical response [14]. Present et al., defined a complete response in PFCD means absence of drainage from all fistulas with or without cicatrization of the external fistula orifice [11]. Almost all studies about PFCD have used the Present's criteria for complete response.

Seton drainage combined with infliximab treatment has shown promising results. The ACCENT II trial, which is a cornerstone study about PFCD treatment, has shown that infliximab treatment is superior to a placebo. The initial response was 64%, however complete response rate decreased to 36% in 54 weeks [12]. In similar fashion; Haennig et al., recently reported initial response and complete response rates as 88 % and 75% respectively [15]. This was related with late recurrences, which were unnoticed in early periods of treatment. In our study, initial response rate was 70.4%. Only two patients experienced recurrences near 1.5 years after their initial response. These two patients were accepted as non-responders, although they had complete response after second seton insertion and anti-TNF treatment. Clinicians and patients should be aware of late recurrences, because perianal abscess may be even mortal in an immune compromised patient unless urgent drainage is done.

Studies, which investigated the results of combined seton and anti-TNF treatment for PFCD, reported a great range of complete response rate between 18-75% (Table IV) [11, 12, 15-24]. Table IV was meticulously prepared only for PFCD. Patients with other manifestations of CD or undergone other treatment modalities were extracted as much as possible. This discrepancy of the results may be related with varied follow up times, heterogeneity and extent of CD and other local or systemic immunosuppressive agents used. A 63% complete response rate, achieved in our study, is acceptable for a 17-month follow up time.

In 20–45% of the CD patients a perianal fistula developed before or at the time of CD diagnosis [1]. Consistently, the first presentation was perianal fistula in 6 (22.2%) patients in our series. The combination of two of three methods (MRI, EUS and EUA) is recommended for correct classification of PFCD. Pretreatment MRI showed that the most common type of fistula in PFCD is transsphincteric fistula. It is compatible

with previous studies [7]. Preoperative characterization of PFCD is important, because an overlooked fistula tract can cause treatment failure during EUA. In our opinion, surgeon would be aware of complex or multiple fistulas owing to preoperative MRI, and it indirectly increases the success of the treatment.

Table IV. Some of the previous studies investigating the efficacy of combined seton and infliximab treatment

Year	Author	Number of patients (N)	Follow up time (months)	Complete response rate (%)
1999	Present et al. [11]	56	3	46
2003	Topstad et al. [16]	29	9	29
2004	Sand et al. [12]	89	13	36
2005	Talbot et al. [18]	21	20	47
2006	Hyder et al. [19]	22	21	18
2008	Guidi et al. [20]	9	19	55
2009	Tougeron et al. [17]	28	58	42
2009	Bouguen et al. [21]	31	43	54
2012	Duff et al. [22]	52	66	42.3
2013	Antakia et al. [23]	48	20	29
2013	Bouguen et al. [24]	97	55	60
2015	Haennig et al [15]	81	64	75
	Present study	27	17	63

The best time for removal of the seton is controversial [9]. An early seton removal may increase the risk of perianal infection because of inadequately drained collection during anti-TNF treatment. On the other hand, prolonged stay can result in maturation of the fistulous track, leading to persistence incapability to heal after seton removal. Although it is widely believed that setons protect the patients from perianal abscess, we observed recurrence abscess in one patient with seton. Only this patient (3.7%) required diverting stoma. In our opinion, removal of the setons needs to be considered after infliximab infusion based on both clinical and MRI evaluation of perianal region.

Female gender, complex fistula formation, active intestinal and rectal diseases were reported as factors independently associated with failure of combined treatment [16, 17]. Any factor, which significantly related to complete response, could not be found in the study. This could be due to relatively small size of this study and/or great heterogeneity of PFCD patients.

This study has some limitations in need of acknowledgment. First, this was a retrospective study and does not have control arm, and study includes a small number of patients for evaluating the previous known predictors.

Second, seton removal time is not standard but based on clinical response. This study does not include information about optimal seton removal time.

In conclusion, we reported a group of PFCD patients treated with seton drainage and anti-TNF agents with 63% complete response rate in 17 month follow up time. Although, a high rate of complete response has been achieved in this study, a considerable rate of patients (37%) did not respond well to the current treatment. New or additional treatment modalities should be investigated with randomized controlled studies in the future.

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