ARTICLE ORIGINAL

Fistules périanales complexes dans la maladie de Crohn:Traitement médico-chirurgical à base d'anti-TNF alpha avec évaluation par imagerie magnétique.

Complex perianal fistulas in Crohn's disease: An anti-TNF α based medico-surgical treatment with magnetic imaging assessment

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RÉSUMÉ

Introduction : Les anti-TNF alpha associés au drainage par setons jouent un rôle central dans le traitement des fistules de Crohn périnéales complexes (FAP). Un protocole de traitement précis fait défaut.

Objectifs: Évaluer les résultats de ce traitement combiné et identifier les facteurs prédictifs de réponse.

Méthodes: Il s'agissait d'une étude rétrospective qui a inclus tous les patients présentant une FAP complexe traitée par anti-TNF alpha.

Résultats: Nous avons inclus 49 patients, avec un âge moyen de 31, 6 ans. 17 patients avaient une atteinte rectale active. 35 patients ont été mis sous azathioprine. Après l'induction, 43 patients ont eu une réponse clinique. Le traitement d'entretien a été initié dans 45 cas. Après une médiane de 19 mois d'anti-TNF, 24 patients ont présenté une rémission clinique (avec une rémission radiologique pour 20 patients), 17 une réponse clinique partielle et 4 un échec. Les setons ont été enlevés dans tous les cas après obtention d'une rémission clinico-radiologique. et une désescalade a été réalisée. 46% des patients ayant arrêté les anti-TNF alpha Après l'obtention d'une rémission clinico-radiologique ont rechuté. L'absence d'atteinte rectale et la rémission clinique après l'induction étaient les facteurs prédictifs indépendants de l'obtention d'une rémission clinique sous traitement d'entretien par anti-TNF alpha(p = 0,016) et d'obtention d'une rémission clinicoradiologique (p = 0,028).

Conclusion: Un traitement à base d'anti-TNF? combiné à un drainage par seton lâche à long terme a contribué aux taux élevés de réponses clinique et radiologique dans cette étude. L'obtention d'une rémission clinico-radiologique «profonde» devrait être la cible du traitement. L'arrêt de l'Anti-TNF alpha devrait être évitée même après l'obtention d'une telle réponse.

Mot clés : maladie de Crohn, fistule périanale complexe, Imagerie par résonance magnétique, Anti-TNF alpha.

SUMMARY

Background: Anti-TNFα associated to seton drainage has a central role in the treatment of complex perineal Crohn's fistulas (PAF). A precise treatment protocol is lacking.

Aims: To evaluate the results of this combined treatment and identify predictive factors of response.

Methods: It was a retrospective study which included all patients with complex PAF treated with Anti-TNFα.

Results: We included 49 patients, mean age of 31.6 years. 17 patients had an active rectal involvement. 35 patients had azathioprin. After the induction, 43 patients had a clinical response. Maintenance therapy was started in 45 cases. After a median of 19 months of Anti-TNFα, 24 patients had a clinical remission (with radiological remission in 20), 17 a partial clinical response, and 4 were in failure. After clinico-radiologic remission setons were removed in all patients, 46% of patients who stopped Anti-TNFα treatment after clinico-radiologic remission relapsed. Absence of rectal involvement and Clinical remission after induction were the independent predictive factors of achieving a clinical remission under maintenance therapy with Anti-TNFα (p=0.016) and clinico-radiological remission (p=0.028).

Conclusion: An Anti-TNFα based treatment combined with long term loose seton drainage have contributed to the high rates of both clinical and radiological responses in this study. Obtaining a "deep" clinico-radiological remission should be the target of the treatment. Stopping the Anti-TNFα should be avoided even after obtaining such response.

Key words: Crohn's disease, complex perianal fistula, Magnetic resonance imaging, anti-TNF α

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INTRODUCTION

Perianal involvement is a debilitating manifestation of Crohn's disease (CD). This is due to their challenging treatment and their psychological, sexual and social impacts. Perianal fistulas (PAF) are the most common perianal manifestation and are seen in 20% to 40% of patients with CD (1–4). PAF can be classified as simple or complex according to the 2003 American Gastroenterology Association's (AGA) classification (5). Their diagnosis relies on a clinical evaluation, and is systematically supported by a radiological assessment (6–9). The treatment of complex PAF is arduous and nowadays uses a combined medico-surgical approach associating antibiotics (ATB), immunosuppressants (IS), Anti-TNFα therapy and loose seton drainage surgery (5,10,11). A precise protocol detailing the appropriate treatment associations, the modalities of the monitoring and the adjustments to undertake according to the responses is still lacking. Thus, the aims of our study were to evaluate the short and long term outcomes of a combined medico-surgical treatment and to identify predictive factors of response to Anti-TNFα treatment in complex PAF.

METHODS

Patients

We gathered retrospectively all consecutive patients with complex CD's PAF treated withAnti-TNFα in our center from January 2000 to December 2016. All patients had a certain diagnosis of CD, a follow-up duration of at least 12 months and were aged between 16 and 70 years old. We excluded patients with an unsteady follow-up or patients whointerrupted the treatment against medical advice. We analyzed the data collected from the patients' medical files including demographic features of the patients (age, sex, habits, personal and family antecedents), CD history and activity, localization and phenotype of the disease according to the Montreal classification, and CD related medical and surgical interventions.

Initial assessment

We collected data regarding the initial evaluation of the patients. Perineal examination at diagnosis (number of external orifices and their drainage by gentle finger compression and the findings of the digital rectal examination). The following biologic findings were collected: C-reactive protein (CRP), blood count and albumin. Endoscopic assessment of rectal involvement was also noted. We also collected findings of the initial radiological assessmentbased on perineal magnetic resonance imaging (MRI): location regarding the sphincters, the extension and number of fistulas' tracks, hyperintensity on T2 weighted images, the presence of abscesses or a rectal wall involvement. After this first evaluation, the PAF were classified as simple or complex according to the 2003 AGA classification (5).

Treatment protocol

The treatment was based on a protocol followed by all senior gastroenterologists in the center. It involvedan Anti-TNFα with or without azathioprin (AZA), which was either already prescribed or had previously started. A surgical loose seton drainage and a course of ATB (fluoroquinolones and metronidazole) were also prescribed at diagnosis. The dosages and duration of treatments were all noted. The Anti-TNFα treatment involved either Infliximab (IFX) or Adalimumab (ADA), the two available drugs in the center. For the initial induction phase, IFX was prescribed intravenously at weeks 0, 2 and 6 at the dose of 5mg/kg each and ADA was prescribed subcutaneously at weeks 0 (160 mg), 2 (80 mg) and 4 (40 mg). After this phase, a first clinical evaluation was done between weeks 10 and 12 after the initiation of the Anti-TNFα treatment. It was based on the fistula drainage assessment (FDA): Clinical remission was defined by the closure of all the orifices of the initially productive fistulas, partial clinical response by the closure of more than 50% of the orifices and clinical failure by the closure of less than 50% of the orifices. Afterwards, a maintenance treatment was prescribed: 5mg/kg/ 2 months for IFX and 40mg /2 weeks for ADA. We studied the clinical response based on the FDA assessment reported by the senior gastroenterologist under maintenance treatment every two months.In case of clinical remission under maintenance treatment, an MRI-based evaluation was conducted after at least 6 months since the remission was obtained. A radiological remission was defined by the absence of hyperintensity on T2 weighted imaging or gadolinium contrast enhancement, and no occurrence of new tracts or abscesses. In case of partial clinical response, the treatment was continued and a radiological assessment was only conducted if a clinical remission was obtained. In case of clinical failure, a switch to the other Anti-TNFα was conducted (IFX or ADA).

Statistical analysis

Data entry and analysis was made with Statistical Package for Social Science (SPSS) software version 21.0. A descriptive study was performed to calculate means, medians, standard deviations and percentages. A univariate analysis was then performed to identify predictive factors of response to the treatment. The comparison of qualitative variables was carried out by the chi-square test, with the Fischer test being used in cases of non-validity. Student's t-test and one-way analysis of variance (ANOVA) tests were used to compare quantitative variables. We then conducted a multivariate analysis using a model of logistic regression to identify independent predictive factors of response. Results were considered as significant when the P value was <0.05.

RESULTS

Patients' baseline characteristics and initial assessment of the PAF

Among four hundred and forty patients diagnosed with CD during the study period, 80 patients had PAF (18.18%) and 73 patients had complex PAF. Among these, 49 were treated with Anti-TNFα and 24 didn't benefit from the treatment. The main patients' and baseline PAF's characteristics are summarized in Tables 1 and 2.

Treatment

IFX was prescribed in 45 patients (92%) and ADA in 4 patients (8%). ATB were prescribed in all patients. It consisted in an association of Ciprofloxacin (mean dosage of 1.14 g/day) and Metronidazole (mean dosage of 1 g/day)with a mean duration of 3.6 months. All patients had a surgical loose seton drainage. 35 patients received AZA (76%) with a median dosage of 2.5 mg/kg/day.

The mean duration of the Anti-TNFα treatment was *24 months*. After the induction phase, 43 patients (88%) had a clinical response which consisted in a clinical remission in 28 cases (57%) and a partial clinical response in 15 patients (31%). A primary failure was observed in 6 patients (12%).

Maintenance therapy was started in 45 patients. IFX was prescribed for 41 patients (91%) and ADA for 4 patients (9%). Among these patients, 26 were in clinical remission after induction, 15 patients in partial clinical response and 4 patients in primary failure. After a median of 19 months of Anti-TNFα treatment, 24 patients (53%) had a clinical remission, 17 patients (38%) a partial clinical response, and the 4 patients (9%) in primary failure maintained the same response.

T**able1.** Patients' baseline characteristics.

Patients' characteristics	Patients : N=49
Age at diagnosis of CD (years)	27.36
Age at diagnosis of PAF (years)	31.6
Sex Ratio (men/women) 23/26	0.88
Active smoking (n,%)	12 (24%)
Family history of CD (n,%)	6 (12%)
Extra intestinal manifestations (n,%)	10 (20%)
Previous digestive resection (n,%)	14 (28%)
CD localization according to the Montreal classification	
L1 (n,%)	11 (23%)
L2 (n,%)	17 (34%)
L3 (n,%)	25 (52%)
Disease behavior	
Inflammatory	24 (48%)
Stricturing	7 (15%)
Penetrating	18 (37%)
Previous flares	1.31
Treatment at inclusion	
Aminosalicylates (n,%)	6 (12%)
Corticosteroids (n,%)	5 (10%)
Azathioprin (n,%)	11 (23%)
Anti-TNF alpha (n,%)	1 (2%)
CRP (mg/l)	50
Albumin (g/l)	33.5
Hemoglobin (g/dl)	11
Leucocytes (el/mm^3)	8276
Platelets (el/mm^3)	382 000

CD : Crohn's disease ; PAF : perianal fistula ; CRP: C-reactive protein

Table 2: Clinical, radiological and endoscopic baseline characteristics of the perianal fistulas.

PAF characteristics	Patients : N=49
Mean number of perianal orifices	2
Abcess of the anal margin (n,%)	4 (8%)
Associated anoperineal lesions	24 (21%)
Anal ulceration (n,%)	5 (10%)
Anal fissure (n,%)	16 (32%)
Anal stricture (n,%)	3 (6%)
Active rectal involvement at endoscopy (n,%)	17 (34%)
MRI findings :	
Hyper-intensity on T2 weighted images (n,%)	49 (100%)
Enhancement after gadolinium injection	49 (100%)
Trans-sphincteric (n,%)	18 (39%)
Inter-sphincteric (n,%)	10 (20%)
Supra-sphincteric (n,%)	6 (13%)
Extra-sphincteric (n,%)	1 (2%)
Horseshoe (n,%)	8 (16%)
Recto or Ano-vaginal (n,%)	6 (12%)
Perineal abscess (n,%)	9 (19%)

PAF : perianal fistula ; MRI: magnetic resonance imaging

Patients in clinical remission under maintenance treatment:

Twenty-four patients (53%) were in clinical remission. Among these patients, 17 (71%) were under AZA in addition to the Anti-TNFα. All 24 patients in clinical remission had an MRI to evaluate the radiological response. The MRI was performed after an average duration of 10 months after the clinical remission.20 patients (44%) had a complete clinical and radiological response. In this case, the setons were removed after a medium duration of drainage of 22 months. The Anti-TNFα was stopped after a mean duration of 24 months for 13 patients (65%) while AZA was maintained. During the follow up, 6 of these patients (46%) that benefited from this de-escalation relapsed after a median of 16 months period. For the 7 remaining patients that continued the Anti-TNFαtreatment without AZA, a loss of response occurred in 2 of them. For the 4 patients with no radiological remission, the Anti-TNFαwas maintained and all patients presented a loss of response.

Patients in partial clinical response under maintenance treatment:

Anti-TNFαtreatment was carried out in all 17 cases. 14 patients were already on AZA, the remaining 3 were prescribed AZA in addition to the Anti-TNFα. A loss of response was noted in 13 patients **(76%).**

Patients in clinical failure:

The 4 patients already in clinical failure after the induction phase maintained the same response under maintenance therapy. They were all under IFX and AZA. They were switched to ADA and a partial clinical response was obtained in all cases after the induction phase.

Patients in loss of response:

In total, a loss of response occurred in 19 patients (42%) during the follow up. It was noted 15 months on average after obtaining a clinical response. 12 patients (63%) were on AZA in addition to the Anti-TNFα.Among the 21 patients in clinical response without clinico-radiological remission, 17 (85%) presented a loss of response.

An optimization of the treatment was undertaken in 16 patients. It consisted in shortening the injections' intervals in 7 cases (44%), increasing the doses in 4 cases (25%) and both approaches in 5 cases (31%). 6 patients (37%) presented a clinical remission, 3 patients (19%) a partial clinical response and 7 patients (44%) didn't respond to the optimization.

Predictive factors of response and loss of response to Anti-TNFα treatment

Univariate analysis:

**Predictive factors of response to the induction phase of Anti-TNFα:* In univariate analysis, the absence of rectal involvement (66% vs. 34%, p=0.005) and a negative CRP level after the induction phase (68% vs. 32%, p=0.047) were significantly associated with obtaining a clinical remission after the induction. A negative CRP level was associated with obtaining a partial clinical response (21% vs. 79%, p=0.029). The absence of rectal involvement was associated with a clinical response (remission and partial response) after the induction (69% vs. 31%, p=0.011).

**Predictive factors of response to the maintenance treatment:*A clinical remission after induction (81% vs. 19%, p<0.0001), a negative CRP level after induction (84% vs. 16%, p=0.03) and a negative CRP after one

year of Anti-TNFα treatment (87% vs 13%, p=0.009) were significantly associated with a clinical remission under maintenance treatment. Associating AZA to the Anti-TNFα was not predictive of obtaining a clinical remission after maintenance treatment (53% vs. 47%, p=ns). Conversely, the presence of a recto-vaginal fistula (0% vs. 100%, p=0.04) and a partial clinical response after the induction phase (20% vs. 80%, p=0.002) were predictive of not achieving clinical remission.

The absence of rectal involvement (93% vs. 7%, p=0.011), a clinical remission after induction (100% vs. 0%, p<0.0001) and a negative CRP level after maintenance treatment (96% vs. 4%, p=0.006) were predictive of achieving a clinical response after maintenance treatment.

A clinical remission after induction treatment (71% vs. 19%, p=0.002), a negative CRP after maintenance treatment (61% vs. 39%, p=0.028) and a platelets count inferior to 250 000 elements /mm3 (64% vs. 36%, p=0.038) were significantly associated with achieving a clinico-radiological response. Contrariwise, an age inferior to 31 years (18% vs. 82%, p=0.002) and a partial clinical response after induction treatment (10% vs. 90%, p=0.005) were both predictive of failure to achieve this response.

An age inferior to 31 years (56% vs. 44%, p=0.045) and a partial clinical response after the induction phase (54% vs. 46%, p=0.044) were predictive of a loss of response to Anti-TNFα.

Multivariate analysis

After the multivariate analysis, the absence of rectal involvement was the only independent predictive factor of achieving a clinical remission under maintenance therapy with Anti-TNFα (p=0.016). A clinical remission after the induction phase was the only independent predictive factor of a clinico-radiological remission under maintenance treatment (p=0.028).

DISCUSSION

PAF are a recurrent manifestation of CD with a frequency of 18.18% in our center. The baseline demographic and CD characteristics of the patients were comparable to those of other studies (12–16). The classification of the PAF as complex relied on the 2003 AGA classification based on the clinical assessment and on the MRI, which was systematically done in this study. In fact, the MRI enables the precise description of the fistulas' tracks and overrules the presence of clinically silent abscesses with a precision close to 100% (6,17–19). Such abscesses were found in 19% of the patients in this study. Other studies have also shown that an MRI assessment resulted in a change of the type of the intended surgical procedure in10--15% of the patients (8,19,20).

The role of Anti-TNFα treatment in complex PAF of CD was first established by the ACCENT II trial (21). Other studies and latest guidelines have adopted a combined medico-surgical approach as in the 2016 ECCO guidelines where the Anti-TNFα treatment has the main role (10,22,23). In this study, 24 patients didn't receive an Anti-TNFα treatment due to a lack of health insurance. IFX was prescribed in 92% of cases in this study. In fact, the role of ADA was controversial in the beginning of the use of this molecule for the treatment of PAF (24–26).

After the induction phase, 88% of the patients had a clinical response. This is superior to the 68% of patients presenting such a response as reported in ACCENT II (29). In other "real life" case series, the rates of clinical remission varied from 60 to 88% using a combined medico-surgical protocol (30–35). Under maintenance treatment, 53% of our patients were in clinical remission and 38% in partial clinical response, resulting in a rate of clinical response of 91%. This number also coincides with the upper limits of the range of results in the previously cited studies (41 to 89.3%).

These high numbers reported in our study may be due to a longer follow-up period than other studies. Additionally, the systematic seton drainage and its late removal (medium duration of drainage of 22 weeks), the systematic prescription of antibiotics for a relatively long period (mean duration of 3.4 months in our study) along with a high rate of prescription of AZA (76%) may have improved the outcomes. In fact, loose seton drainage avoids the deleterious effect of infection on the sphincter and allows the progressive transformation of the inflammatory tissue into fibrous scar tissue. As for ATB, they potentiate the effect of the Anti-TNFα by controlling the local sepsis. This was proven for ciprofloxacin with both IFX and ADA (36,37). As for Metronidazole, it has a historical role in the treatment of PAF (38) and potentiates the effects of ciprofloxacin (39). On the other hand, the combination therapy with immunosuppressants has proven its efficacy by enhancing the results of the Anti-TNFαtreatment

(40,41). This wasn't specifically investigated in PAF but was found in sub-groups analyses. In a French cohort that included 906 patients (MICISTA registry), the combination therapy was superior to the monotherapy for both IFX and ADA and both luminal and anoperineal CD (42). This was not found as a predictive factor of clinical response after a one-year maintenance treatment in our study (53% vs 47%, p=ns), potentially because of the smaller number of patients included.

In this study, all of the patients in clinical remission were evaluated by an MRI. Until recently, the criteria for remission under maintenance treatment were exclusively clinical. However, judging the efficacy of anti-TNFα treatment solely on clinical remission was associated with a high rate of PAF recurrence. In a study by Rasul & al evaluating the radiological response of CD's PAF to IFX, it was demonstrated that at week 48, patients who discontinued anti-TNFα while in clinical remission but in incomplete radiological response were at high risk of early relapse (43). In this study, 85% of patients in clinical response without radiological remission presented a loss of response. Also, in our study, the radiological evaluation was performed after a mean duration of 10 months after clinical remission. This choice was based on the delay observed between clinical and radiological remissions. In fact, some studies have shown that a radiological remission was seen with a delay varying between 10 and 21 weeks after clinical remission (31,44).

In our study, 44% of the subjects presented with both clinical and radiological remissions and we observed that all patients with no radiological remission had a loss of response. For comparison, a study by Thomassin & al found a loss of response in one third of patients(45). Also, obtaining a clinical remission after the induction phase was the only independent predictive factor of achieving a clinical and radiological response. In contrast, obtaining a partial clinical response was predictive of failure to obtain clinical or clinico-radiological remission and was associated with a greater risk of loss of response (OR = 4.3), as 73% of those patients presented a secondary failure. This suggests that an early optimization of the Anti-TNFα treatment in case of partial clinical response after the induction phase is an option that should be studied, the aim of this approach being the achievement of clinico-radiological remission.

De-escalation of the treatment in CD is an option that is often considered given the risk of severe adverse effects, the cost of the treatments, and also the patients' wishes. The data regarding this matter is still scarce and no study has prospectively evaluated the outcomes of de-escalation of the treatment specifically in the case of PAF, but their presence is often reported as a predictive factor of relapse (46). In this study, a relapse after discontinuation of the Anti-TNFα was seen in 46% of the patients after 16 months. These findings question the feasibility of the discontinuation of the Anti-TNFα treatment in case of complex PAF.

In conclusion, an Anti-TNFαbased treatment combined with long term loose seton drainage (mean duration: 22 weeks) may have contributed to the high rates of both clinical and radiological responses in this study. Controlling any active rectal involvement is a fundamental variable as it appeared as an independent predictive factor of response. Obtaining a "deep" clinico-radiological remission is a main target of the treatment, as 85% of the patients without such outcome displayed a loss of response. An early optimization of the Anti-TNFα in case of partial clinical response after the induction phase is an alternative that should be studied as it was an independent predictive factor of clinic-radiological remission. Lastly, de-escalating the treatment in case of PAF by stopping the Anti-TNFα came with a high rate of recurrence in this cohort and should be studied specifically in the case of perineal involvement.

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