OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Medicine**

The Outcome of Anoperineal Lesions in Crohn´s Patients after Biological Treatment

Manal Cherkaoui Malki[1*], H. Elbacha[1], N. Benzzoubeir[1], I. Errabih[1]

[1]Department of Gastroentero-Hepatology and Proctology "Médecine B", Ibn Sina Hospital, University Mohamed V, Rabat, Morocco

DOI: 10.36348/sjmps.2023.v09i05.008 | **Received:** 01.04.2023 | **Accepted:** 06.05.2023 | **Published:** 26.05.2023

***Corresponding author:** Manal Cherkaoui Malki
Department of Gastroentero-Hepatology and Proctology "Médecine B", Ibn Sina Hospital, University Mohamed V, Rabat, Morocco

Abstract

Introduction*:** The development of APL is associated with a more severe prognosis of the disease, and with a significant alteration of the quality of life. For this reason, the advent of biological agents has allowed in a significant number of patients a healing of these APL. Through this work, we illustrate the evolution of these lesions by comparing patients before and after the beginning of biotherapy. ***Materials and Methods: A retrospective analytical study carried out in our department between January 2015 and January 2021 including all patients receiving biological treatment for CD with APL. ***Results*:** Among 355 patients with CD, 45 patients were on biological treatment which 32 (71%) had APL. Among these 32 patients, sex ratio (W/M) was 1.9, mean age was 37 +/- 9.3. The type of anal involvement was as follow: 20 patients (75%) had anal suppurations, 7 patients (20%) had ulcerations and 5 patients (5%) had anal stenosis. In 5% it was an isolated anal Crohn's disease, in 15% it was intestinal disease with APL, in 31% it was colonic disease with APL. 25 patients (78%) were under Infliximab and 7 (21.8%) under Adalumimab. The number of patients with APL before treatment has significantly decreased after treatment with a p=0.002, with an improvement of APL in 20 patients (60%) of under anti-TNF agent. ***Conclusion***: Anti-TNF agents allowed a better management and a favorable evolution of APL in most of our CD patients. However, to overcome the failure of anti-TNF in some of our patients, the availability of other biological molecules on the Moroccan market remains more than desirable.

Keywords: Crohn´s Disease, biological treatment, Infliximab, APL, outcome, evolution.

INTRODUCTION

Anoperineal lesions (APL) are a significant event in the evolution of Crohn's disease (CD). It may be revealing it and when it does, is associated to a poor prognosis especially in young patients. It occurs in up to 30% of individuals with luminal disease [1, 2]. APL in CD is also associated with a burden on quality in life [3]. Its management is a challenge and is particularly difficult due to tissue destruction and recurrence, and often requires multimodal therapy with surgical treatment and systemic medical therapy. Medical treatment has been dominated for decades by anti-tumor necrosis factor (TNF) therapy [4]. However, there is a wide variation in managing APL in CD, related to the fact that there are some situations which are not addressed by randomized studies. Including, alternatives for patients that are failing anti-TNF therapy. Significant advancement is under research combining surgery and local therapies, such local injections of mesenchymal stem cell that could be tomorrow´s treatment, since randomized studies shows remarkable promise [5, 6]. Our aim therefore is to illustrate the evolution of these lesions before and after anti-TNF treatment by comparing patients before and after.

MATERIAL AND METHODS

Study Population

All patients with anoperineal crohn´s disease above 18 years old admitted to our department of Gastroenteroloy Medecine B of Ibn sina hospital between January 2015- January 2021 were included. We exluded patients with incomplete data, patients with diversion ostomy and patients who were not on anti-TNF agent (Infliximab or Adalumimab). Anoperineal CD was defined as the presence of anal fistula, anal ulcer or anal stenosis. Medical records were collected and retrospectively analyzed to obtain demographic data, smoking history, familial history, and the localization of the disease according to Montreal classification. Perineal activity was assessed using the

perineal disease activity index (PDAI). Before initiating treatment, proctological examination and pelvic magnetic resonance imaging (MRI) were performed. The date of first infusions and duration of anti-TNF were collected. Infliximab (IFX) was administered initially at a dose of 5mg/kg at weeks 0, 2 and 6 as induction and then every 8 weeks for maintenance. Concomitant immunosuppressive medications and/or perianal surgery including drainage seton were also collected.

Assessment of Clinical Improvement of CD´s APL

Clinical improvement was defined as complete healing of anal fistula or at least one fistula closure, or ulcer healing, or active stenosis regression, despite the fact that anti-TNF agent in this indication is still debated. Failing anti- TNF agent was defined as the non-improvement of APL or a recurrence of one these lesions.

Statistical Analysis

Statistical analyses were performed by using SPSS Software version 20 .0. Quantitative variables were described as mean ± standard deviations or median and percentile (interquartile range [IQR], 25% and 75%). Categorical variables were presented as counts and percent. Variable normality was analyzed using Kolmogorov-Smirnov test and comparison of continuous variables between groups before and after treatment was performed using t-student test and between counts using McNemar test. A p value <0.05 was considered to be statistically significant.

RESULTS

1- Characteristics of the Population

Among 355 Crohn´s diseases treated in our department during this period of time, 45 (12%) were under anti- TNF agent, and after excluding patients without APL, only 32 patients where left with APL (Figure 1). This tiny rate is explained by the fact that multiple patients have a lack of resources, and could not afford anti-TNF costs. The baseline characteristics are listed in Table 1. Of these patients, 21 (65.7%) were female. The mean age at diagnosis was 37 ± 9.3 and the median duration of CD follow-up 82weeks (IQR, 48-115). According to the Montreal classification, localization of CD was as followed 5(15%) ileal, 15(45%) colic, 10(31%) ileocolic and 2(5%) upper CD. Before starting treatment, mean PDAI was 10,2 ± 3.3. 62,5% had perianal fistula, 21,8% had anal ulcer and 5% had stenosis. Median duration of anti-TNF was 120 weeks (IQR 48-115) and 78% were on Infliximab and 22% on Adalimumab. Seton drainage was done in 80,3% of perianal fistula, and concomitant immunosuppressants was association to anti-TNF in 74,6% of the cases.

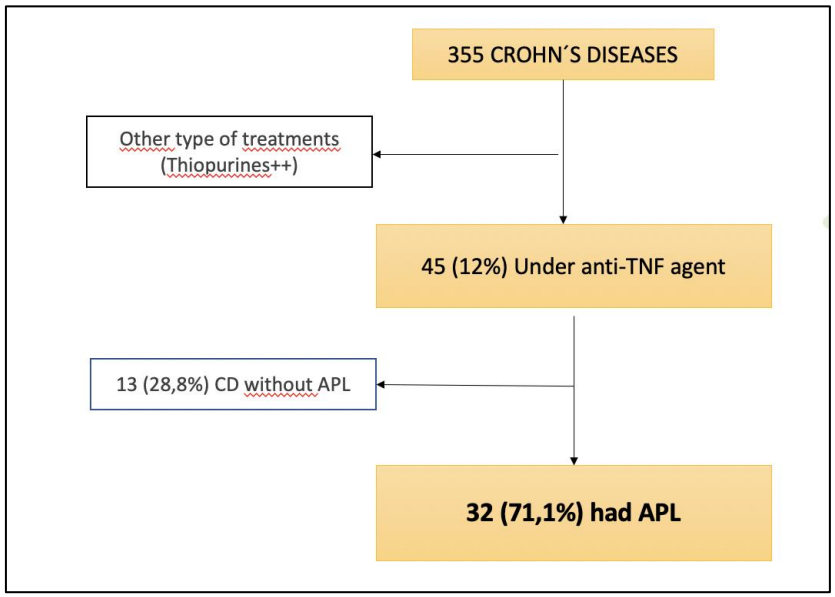

Figure 1: The sample included in our study

Table 1: Baseline Characteristics

Variable	**n =32**
Age (yr), mean (SD)	37 ± 9.3
Sex Male Female	 11(34.3%) 21 (65.7%)
Localization (Montreal classification) L1 L2	 5(15%) 15(45%)

L3 L4	10(31%) 2(5%)
Duration of follow-up in weeks, median (IQR)	82 (48-115)
Duration of anti-TNF in weeks, median (IQR)	120 (48-115)
Anti-TNF agent IFX ADA	 25(78%) 7 (22 %)
PDAI, mean (SD)	10,2 ± 3.3
Concomitant measures Immunosuppressant Seton drainage	 26(80%) 23(74,6%)

2- Comparison between groups before and after anti-TNF agent

2-1- PDAI

Of the 32 patients who had APL, before debuting anti-TNF, mean PDAI was 10,2 ± 3.3, this score has significantly decreased to 3,6± 1.3 after a median duration of 120 weeks of anti-TNF, with a p of 0.007.

2-2- APL Improvement

Fistula rate has significantly decreased from 62.50% to 18% with a p of 0.002, whether it was complete healing or one fistula closure (Figure 2). Rate of anal ulcer has significantly decreased from 21.80% to 6% with a p of 0.001. However, the comparison of anal stenosis rate did not show any significant decrease in our group of patients (Figure 3).

After subtracting failure rate from these results, we found that there were 55.5% of anal fistula that hadn´t improved.

Figure 2: An example of a patient who improved after one year of Infliximab combined to seton drainage

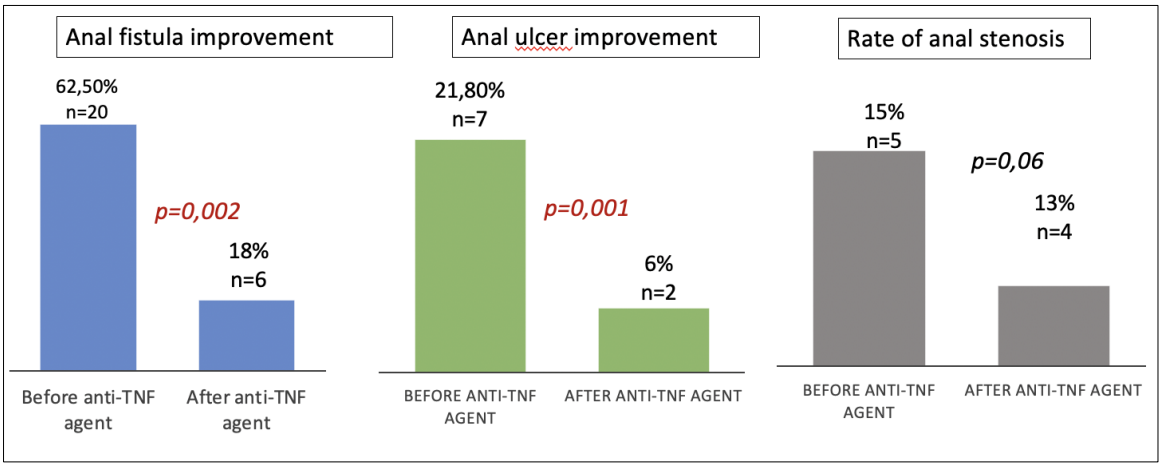

Figure 3: Comparison between groups according to anal fistula, anal ulcer et anal stenoses rates before and after anti-TNF agent

DISCUSSION

Perianal fistulas can be a devastating complication of Crohn's disease, and patients often require aggressive medical and surgical therapy. Perianal CD encompasses primary lesions or type 1: anal fissures, deep anal canal ulcers, and skin tags, secondary lesions or type 2: fistulas, rectovaginal fistulas, and abscesses and type III are lesions resulting from the long-term inflammatory process (including anorectal stenosis and/or carcinoma) [7]. Perianal fistulas are the most common manifestation of fistulizing CD [8]. The prevalence of perianal involvement in patients with CD reaches 20%, with permanent or relapsing disease in approximately 30% of the cases [8, 9]. Perianal lesions are predictors of aggressivity of the disease with a strong impact of patients 'quality of life and risk ana anal canal carcinoma. Consequently, adequate management is important. Therapies that have proved efficiency are anti-TNF agents especially following abscess drainage when needed, and in combination with thiopurines and/ or antibiotics [8-10]. Infliximab has been recognized to be an effective treatment for active perianal lesions [11, 12]. Adalimumab is also used in perianal CD, although levels of evidence are weaker [13, 14]. Nevertheless, not all patients achieve remission. In a randomized controlled trial for fistulas in CD, receiving Infliximab showed efficiency in 55% of patients compared to 13% of the placebo group [15], it´s a good rare, but the 45% left, haven´t showed efficiency. These results agree with our, where efficiency has been seen only in 44.5% of anal fistulizing CD after a median of 120 weeks of treatment. Yarur, A. J. *et al.,* [16] showed levels of infliximab significantly associated with fistula healing / closure. Our results support the value of anti-TNF in the treatment of complex perianal Crohn's disease fistulas; however there´s still an important rate of failure. Reasons of failing in literature could be primary nonresponse, loss of response, or intolerance [17-19]. Therapeutic armamentarium is currently rapidly growing in inflammatory bowel disease, new biologic agents, with alternative modes of action, may bring new opportunities for pCD management. Ustekinumab is an interleukin (IL) 12 and 23 inhibitor, approved since 2016 for luminal CD. In refractory CD, studies indicated encouraging results regarding ustekinumab efficacy and safety [20, 21]. However, data for perianal CD are not efficient. A recent study of CERTIFI, UNITI-1, and UNITI-2 suggested that Ustekinumab therapy might be effective in perianal fistulas [22]. But no definite conclusions can be retained. A multicenter cohort from the GETAID showed that Ustekinumab success in perianal CD was reached only in 38.5 % of patients [23]. For Vedolizumab, no dedicated randomized controlled trials have assessed the efficacy of vedolizumab for perianal Crohn's disease, and clinical data have shown limited benefit [24]. *Mesenchymal stem cell therapy*, its exact mechanism that leads to the efficacy in the treatment of perianal Crohn's disease is not known, it likely relates to their ability control the local inflammatory response and allow for fistula healing [25]. A placebo- controlled randomized trial found a single dose (120 million cells) of intralesional injection of adipose derived allogeneic cells to the fistula tract in patients with perianal Crohn's disease who were refractory to medical therapy achieved clinical and radiographic remission in 56% of patients compared to 39% in the placebo group after 12 months [26]. So this will likely remain an important therapeutic option to consider when it widely available. Temporary fecal diversion studies in the re-biologic era suggested it was highly efficacious, with response rates reported to occur in over 80% of individuals in the short term [27, 28].

CONCLUSION

Anti-TNF agents are the first line in managing APL CD. However there´s still an important failure rate (about a half) making it a challenging management.

Other biological treatments have not shown good success rate in APL CD, for those further studies are needed.

REFERENCES

1. Mak, W. Y., Mak, O. S., Lee, C. K., Tang, W., Leung, W. K., Wong, M. T., ... & Ng, S. C. (2018). Significant medical and surgical morbidity in perianal Crohn's disease: results from a territory-wide study. *Journal of Crohn's and Colitis*, *12*(12), 1392-1398.
2. Brochard, C., Rabilloud, M. L., Hamonic, S., Bajeux, E., Pagenault, M., Dabadie, A., Seyrig, J. A. … & Groupe ABERMAD. (2022). Natural History of Perianal Crohn's Disease: Long-term Follow-up of a Population-Based Cohort. *Clinical Gastroenterology and Hepatology*, *20*(2), e102-e110.
3. Adegbola, S. O., Dibley, L., Sahnan, K., Wade, T., Verjee, A., Sawyer, R., ... & Hart, A. L. (2020). Burden of disease and adaptation to life in patients with Crohn's perianal fistula: a qualitative exploration. *Health and Quality of Life Outcomes*, *18*(1), 1-13.
4. Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., Van Hogezand, R. A., ... & Van Deventer, S. J. (1999). Infliximab for the treatment of fistulas in patients with Crohn's disease. *New England Journal of Medicine*, *340*(18), 1398-1405.
5. Panés, J., García-Olmo, D., Van Assche, G., Colombel, J. F., Reinisch, W., Baumgart, D. C., Danese, S. … & ADMIRE CD Study Group Collaborators. (2016). Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *The Lancet*, *388*(10051), 1281-1290.
6. Barnhoorn, M. C., Wasser, M. N., Roelofs, H., Maljaars, P. J., Molendijk, I., Bonsing, B. A., ... & van der Meulen-de Jong, A. E. (2020). Long-term

evaluation of allogeneic bone marrow-derived mesenchymal stromal cell therapy for Crohn's disease perianal fistulas. *Journal of Crohn's and Colitis*, *14*(1), 64-70.
7. Sandborn, W. J., Fazio, V. W., Feagan, B. G., & Hanauer, S. B. (2003). AGA technical review on perianal Crohn's disease. *Gastroenterology*, *125*(5), 1508-1530.
8. Gecse, K. B., Bemelman, W., Kamm, M. A., Stoker, J., Khanna, R., Ng, S. C., ... & D'Haens, G. (2014). A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut*, *63*(9), 1381-1392.
9. Gomollón, F., Dignass, A., Annese, V., Tilg, H., Van Assche, G., Lindsay, J. O., ... & Ecco. (2017). 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *Journal of Crohn's and Colitis*, *11*(1), 3-25.
10. Dewint, P., Hansen, B. E., Verhey, E., Oldenburg, B., Hommes, D. W., Pierik, M., ... & van der Woude, C. J. (2014). Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut*, *63*(2), 292-299.
11. Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., Van Hogezand, R. A., ... & Van Deventer, S. J. (1999). Infliximab for the treatment of fistulas in patients with Crohn's disease. *New England Journal of Medicine*, *340*(18), 1398-1405.
12. Bouguen, G., Siproudhis, L., Gizard, E., Wallenhorst, T., Billioud, V., Bretagne, J. F., ... & Peyrin–Biroulet, L. (2013). Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clinical Gastroenterology and Hepatology*, *11*(8), 975-981.
13. Colombel, J. F., Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Panaccione, R., ... & Pollack, P. F. (2007). Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*, *132*(1), 52-65.
14. Colombel, J. F., Schwartz, D. A., Sandborn, W. J., Kamm, M. A., D'Haens, G., Rutgeerts, P., ... & Pollack, P. F. (2009). Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut*, *58*(7), 940-948.
15. Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., Van Hogezand, R. A., ... & Van Deventer, S. J. (1999). Infliximab for the treatment of fistulas in patients with Crohn's disease. *New England Journal of Medicine*, *340*(18), 1398-1405.
16. Yarur, A. J., Kanagala, V., Stein, D. J., Czul, F., Quintero, M. A., Agrawal, D., ... & Abreu, M. T. (2017). Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Alimentary pharmacology & therapeutics*, *45*(7), 933-940.
17. Sands, B. E., Anderson, F. H., Bernstein, C. N., Chey, W. Y., Feagan, B. G., Fedorak, R. N., ... & van Deventer, S. J. (2004). Infliximab maintenance therapy for fistulizing Crohn's disease. *New England Journal of Medicine*, *350*(9), 876-885.
18. Bouguen, G., Siproudhis, L., Gizard, E., Wallenhorst, T., Billioud, V., Bretagne, J. F., ... & Peyrin–Biroulet, L. (2013). Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clinical Gastroenterology and Hepatology*, *11*(8), 975-981. e1–4.
19. Colombel, J. F., Schwartz, D. A., Sandborn, W. J., Kamm, M. A., D'Haens, G., Rutgeerts, P., ... & Pollack, P. F. (2009). Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut*, *58*(7), 940-948.
20. Feagan, B. G., Sandborn, W. J., Gasink, C., Jacobstein, D., Lang, Y., Friedman, J. R., ... & Rutgeerts, P. (2016). Ustekinumab as induction and maintenance therapy for Crohn's disease. *New England journal of medicine*, *375*(20), 1946-1960.
21. Wils, P., Bouhnik, Y., Michetti, P., Flourie, B., Brixi, H., Bourrier, A., ... & Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID). (2018). Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Alimentary Pharmacology & Therapeutics*, *47*(5), 588-595.
22. Battat, R., Bessissow, T., Strohl, M., Kopylov, U., Bitton, A., Cohen, A., ... & Afif, W. (2017). P626 Ustekinumab for the treatment of perianal fistulas in patients with Crohn's disease. *Journal of Crohn's and Colitis*, *11*(suppl_1), S400-S401.
23. Chapuis-Biron, C., Kirchgesner, J., Pariente, B., Bouhnik, Y., Amiot, A., Viennot, S., ... & GETAID BioLAP Study Group. (2020). Ustekinumab for perianal Crohn's disease: the BioLAP multicenter study from the GETAID. *Official journal of the American College of Gastroenterology| ACG*, *115*(11), 1812-1820.
24. Feagan, B. G., Schwartz, D., Danese, S., Rubin, D. T., Lissoos, T. W., Xu, J., & Lasch, K. (2018). Efficacy of vedolizumab in fistulising Crohn's disease: exploratory analyses of data from GEMINI 2. *Journal of Crohn's and Colitis*, *12*(5), 621-626.
25. Carvello, M., Lightner, A., Yamamoto, T., Kotze, P. G., & Spinelli, A. (2019). Mesenchymal stem cells for perianal Crohn's disease. *Cells*, *8*(7), 764.
26. Panés, J., García-Olmo, D., Van Assche, G., Colombel, J. F., Reinisch, W., Baumgart, D. C., & Guadalajara, H. … & ADMIRE CD Study Group Collaborators. (2018). Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. *Gastroenterology*, *154*(5), 1334-1342.
27. Edwards, C. M., George, B. D., Jewell, D. P., Warren, B. F., Mortensen, N. M., & Kettlewell, M.

G. W. (2000). Role of a defunctioning stoma in the management of large bowel Crohn's disease. *British journal of surgery*, *87*(8), 1063-1066.

28. Yamamoto, T., Allan, R. N., & Keighley, M. R. (2000). Effect of fecal diversion alone on perianal Crohn's disease. *World journal of surgery*, *24*, 1258-1263. discussion 1262-3.