

Study of the Annual Costs Associated with the Treatment of Complex Refractory Perianal Fistulas in Patients with Crohn's Disease

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Abstract

The objective of this study is to quantify the economic impact of the treatment of Complex Perianal Fistulas (CPF) refractory to prior surgical or biological treatment in adult patients with Crohn's Disease (CD). After analysing the patient care pathway and the different treatment alternatives available, an economic model has been developed to allow for the cost estimation of the current approach to the treatment of refractory CPF in CD. In addition to the costs of each therapeutic approach, this model takes into account costs associated to disease recurrence, primary side-effects, and the impact of the disease on labour. Results of this model indicate that the estimated direct annual cost for the treatment of refractory CPF in CD is, at least, €15,241 per patient, amounting to € 21,253,374 for the total population in Spain, with an estimation of 1,395 patients. Regarding indirect costs, the impact on labour of the interventions, measured as the losses incurred as a consequence of sick leaves is estimated to be of at least €186,266 per year for the estimated population. Work absenteeism is estimated to amount to between 10 and 30 days for almost 70% of patients, incurring a total estimated annual cost of €804,599.

Keywords: Perianal Crohn's Disease; Complex Fistulas; Costs; Healthcare Resources

Abbreviations

CPF: Complex Perianal Fistulas; CD: Crohn's Disease; IBD: Inflammatory Bowel Disease; FLAP: endorectal advancement Flap; LIFT: Ligation of intersphincteric fistula tract; DRG: Diagnosis Related Groups; INE: Instituto Nacional de Estadística (National Institute of Statistics)

Introduction

A complex fistula is defined as high (high intersphincteric or high transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract), may have multiple external openings, may be associated with the presence of pain or fluctuation to suggest a perianal abscess, may be associated with the presence of a rectovaginal fistula, may be associated with the presence of an anorectal stricture, and may be associated with the presence of active rectal disease at endoscopy [1]. Clinical profile and drug utilization patterns of patients with Crohn's disease (CD).

Complex Perianal Fistulas (CPF) constitute a serious and debilitating medical complication for patients with Crohn's Disease (CD). By means of a systematic bibliographic review [2-5]. Clinical profile and drug utilization patterns of patients with Crohn's disease (CD),

the prevalence of patient's with CD presenting perianal fistulas is estimated to be of 4,55% out of the total population with CD (weighted average calculated from the cited bibliography), and, of these, approximately 80% are CPF [6-8] affects quality of life and results in an increased use of healthcare resources. Medical and surgical therapies contribute to its management. The objective of this review is to address the current understanding in the management of perianal Crohn's disease, with the main focus in reviewing pharmacological therapies, including stem cells. In complex fistulas, once local sepsis has been controlled by surgical drainage and/or antibiotics, anti-TNF drugs (infliximab, adalimumab).

Amongst the symptoms of the disease, extreme pain in defecation can be found as well as bleeding, embarrassing discharge, a strong stench as a result of the secretion of fistulas, physical impairment and impairment of sexual and psychological function. In more severe cases, faecal incontinence can occur furthering morbidity. In refractory cases, some patients face the decision of having a stoma and/or requiring proctectomy [9].

The disease poses a great personal burden for patients, significantly impacting social relationships and their overall quality of life. Furthermore, the disease has a significant impact on healthcare expenditure due to the associated surgical procedures, pharmacological treatments and medical visits that patients require [10].

The therapeutic approach for the treatment of CPF in CD relies on a combination of drug-based treatments and surgical procedures. This approach requires a multidisciplinary team made up of clinical professionals from different medical specialities, such as gastroenterologists, surgeons and radiologists [11,12].

The management of CPF in CD continues to be one of the primary challenges in the treatment of patients with Inflammatory Bowel Disease (IBD) [11].

The primary objective of this study is to quantify the economic impact of current therapeutic approaches for the treatment of refractory CPF in CD in Spain.

The study has been carried out between April and October 2018.

Methodology

For the purpose of this study, an extensive bibliographical review of the literature referencing CPF to date was carried out. Additional information was obtained from interviews, workshops and validation meetings carried out with pathology experts from Gastroenterology and General Surgery Departments of the Hospital Universitario de la Paz (Madrid).

A PubMed and Google Scholar database search were each performed to identify potentially relevant articles. Keywords included the terms "perianal Crohn's disease management", "complex perianal fistula management", "fistulizing Crohn's management", "epidemiology", "healthcare costs", "indirect costs", "side effects", "recurrence", with the search restricted to studies published between January 1999 and May 2019. This bibliographic review was completed by manual searching in scientific magazines like Gastroenterology, Journal of Gastroenterology and Hepatology, Annals of Gastroenterology, Digestive Diseases and Sciences, European Journal of Gastroenterology and Hepatology and Jama Surgery.

All information gathered has been subject to a deep review and analysis in order to develop the economic model for the estimation of the costs associated with the management of refractory CPF in patients with CD in Spain, in accordance with standard clinical practices at the date of the study (Standard of Care or SoC).

Epidemiological data of the disease

To calculate the total estimated number of CD patients with refractory CPF, the prevalence tree represented by figure 1 has been applied.

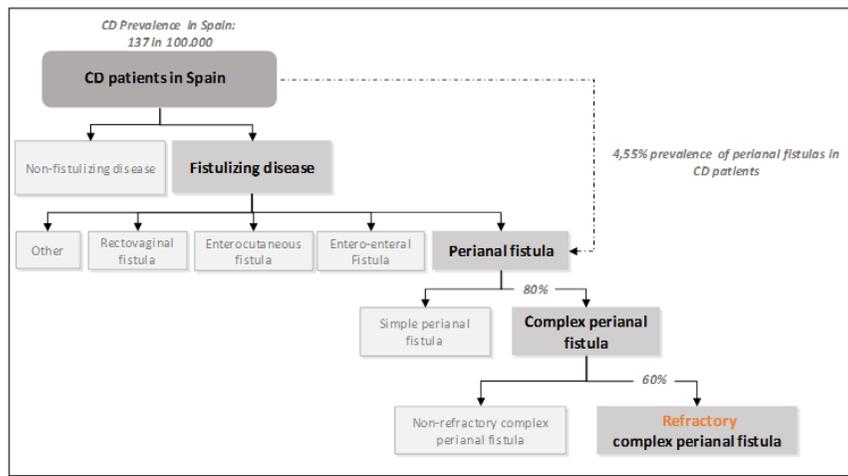


Figure 1: Prevalence Tree for Refractory Complex Perianal Fistulas in Crohn's Disease in Spain. [1-7,12-14].

Taking into account the percentages shown in figure 1 and the official population data from the National Institute of Statistics (Instituto Nacional de Estadística or INE), the total number of CD patients with refractory CPF in Spain is estimated to be 1,395 patients [2-8,13-15].

Care process

For this study, we have considered the patient care pathway that starts when the CD patient with refractory CPF visit the gastroenterologist for evaluation of the perianal disease, until the follow-up visits following the surgical procedures (Figure 2). The outline of this patient care pathway has been developed according to the 2017 ECCO 2017 guides [16], in addition to the opinions of the expert which have participated in this study.

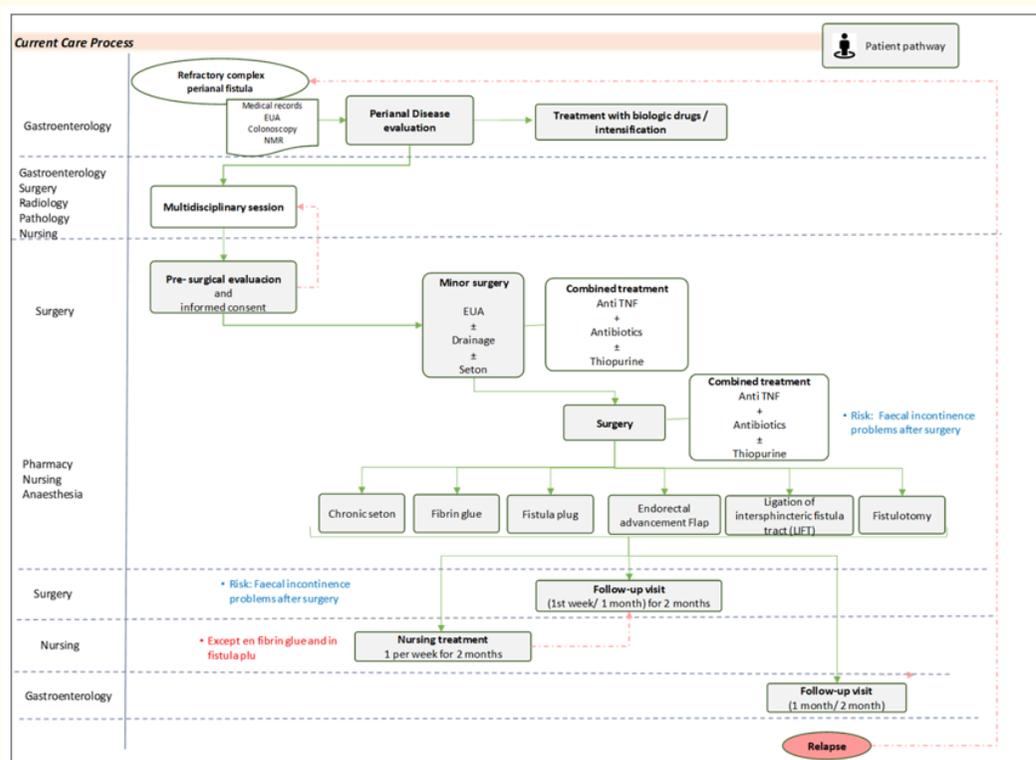


Figure 2: Current Care Process for Complex Perianal Fistulas in Refractory CD.

Hypothesis and criteria included in the development of the model

This model is defined by a timeframe of 52 weeks.

The different treatment options and the cost structure of the model are shown in figure 3. The percentages of application in routine clinical practice for each of the treatment alternatives have been calculated and are represented in the model following the indications given by the experts. Thus, patients with CPF in refractory CD may follow 3 different patient routes depending on their medical situation and on any prior treatments received:



Figure 3: Model hypothesis for the study of the costs associated with the therapeutic approach for the treatment of Refractory Complex Perianal Fistulas in patients with Crohn’s Disease.

Patients already treated with Anti-TNF drugs for their basal disease (CD):

- Anti-TNF dosage intensification to avoid surgery, or Surgical approach following recurrence after the first line of treatment.
- Patients not subject to prior Anti-TNF treatment:
- Treatment with Anti-TNF to avoid surgery.

Direct Costs

In the following section, the elements which have been taken into account to quantify direct costs are shown:

- Costs per treatment with anti-TNF and surgical procedure. According to the experience of the experts that have participated in this study and the bibliography, it is estimated that 40% of patients with refractory CPF are treated through surgical procedures [17]. Another 40% are treated by intensifying the dosage of anti-TNF that they receive as treatment for their basal disease (CD). The remaining 20% of patients have not received any prior treatment with anti-TNF and start treatment with biologic drugs for the treatment of the refractory CPF.
- The surgical interventions taken into account in this study are: chronic seton, fistulotomy, fibrin glue, fistula plug, endorectal advancement Flap (FLAP) and ligation of intersphincteric fistula tract (LIFT). According to the experience of the experts, stome and protectomy are not relevant at this moment of the disease process.

To estimate the average cost of each surgical procedure, we have used the costs per Diagnosis Related Groups (DRG) corresponding to 2017 and published by the Spanish Ministry of Health, Consumer Affairs and Social Welfare. DRG have been assigned to the different procedures according to their degree of severity (Figure 4).

| DRG code | Description | Average cost | Assignment of DRGs according to the interervention degree of severity: |
|------------------|----------------------------|--------------|--|
| DRG 226 -1 (NS1) | Anal procedures severity 1 | 1.790,75 € | Abcess drainage, Seton |
| DRG 226 -2 (NS2) | Anal procedures severity 2 | 2.921,74 € | Fibrin glue, Fistula plug, Fistulotomy |
| DRG 226 -3 (NS3) | Anal procedures severity 3 | 5.823,45 € | Endorrectal advancement flap, LIFT |
| DRG 226 -4 (NS4) | Anal procedures severity 4 | 9.967,11 € | Ostomy |

Figure 4: Costs per DGR and assignment to procedures.

The cost of treatment with anti-TNF has been calculated taking into account a posology 5 mg/kg for the standard dose (infliximab data sheet) and of 10 mg/kg for the strengthened dose [18] and the Infliximab public sales price in Spain.

b) Side Effects. Incontinence is one of the primary side effects of the surgical interventions for the treatment of refractory CPF in CD patients [19]. To calculate direct treatment costs of incontinence, the costs indicated in the bibliography have been used [11,(20,21)]. Additionally, data on the percentage rates of incontinence of the different surgical procedures were collected from the bibliography and are outlined as follows: chronic seton 24%, fibrin glue 0%, fistulotomy 40%, fistula plug 0%, FLAP 30% and LIFT 6%. These rates have been taken from bibliography and validated by the experts who have participated in the study [21-26].

On the other hand, treatment with infliximab may lead to certain side effects which include a 10-15% risk of developing abscesses [28-29]. Direct costs of abscesses treatment have been calculated using the corresponding DRG (Figure 4). Published evidence shows that infliximab exposure increases the risk of other serious infections, like pneumonia, peritonitis or sepsis, and haematological conditions in CD patients [30].

According to the experience of the experts that have participated, only the costs of incontinence (surgeries) and abscesses (anti-TNF) have been included in this study.

c) Recurrence. The model takes into account the percentage rates of disease recurrence within a period of 52 weeks following treatment and considers a maximum of 1 additional surgical intervention to treat said recurrence in that period. The recurrence percentage ranges by procedure used in this model have been as follows: chronic seton 28%, fistulotomy 7%, fibrin glue 90%, fistula plug 71%, FLAP 57%, LIFT 60%, Anti-TNF and intensifications 44%. These rates have been taken from bibliography and validated by the experts who have participated in the study [23,25,27,31-3pain, discharge of pus and blood. Treatment of this benign disease can affect faecal continence, which may, in turn, impair quality of life (QOL3,37].

Indirect costs

This model also takes into account, as indirect costs, the impact on labour resulting from sick leave associated with the treatment.

To calculate the economic impact due to sick leaves resulting from the different interventions, estimated employment rates of patients with perianal disease were collected from the reviewed bibliography [34]. Average wage in Spain (obtained from *INE data 2017: 23,646 €/year*) and the clinical practices as indicated by the experts who participated in this study were also taken into account. The number of days on sick leave following the different interventions was calculated as follows: 3 days for the chronic seton, 30 days for a fistulotomy, 3 days following the fibrin glue, 3 days for the fistula plug, and 30 days for the FLAP and LIFT procedures.

On the other hand, the labour absenteeism and the overall has been estimated according to the reviewed bibliography [35].

Results

The estimated direct annual cost for the treatment of refractory CPF in CD patients in Spain is of, at least, 21,253,374 € (15,241 €/patient) for an estimated population of 1.395 patients (Figure 5). Of the total cost, 79.8% (16,961,154€, 12,163€/patient) corresponds to anti-TNF drugs; 6.37% (1,354,551€, 971€/patient) corresponds to surgery costs; 8.37% (1,779,658€, 1,276€/patient) corresponds to disease recurrence and 5.45% (1,158,011€, 830€/patient) corresponds to treatment-associated side effects. In surgical patients (40% of the total), the estimated average cost of each surgical intervention is 2,428€/patient (Figure 5).

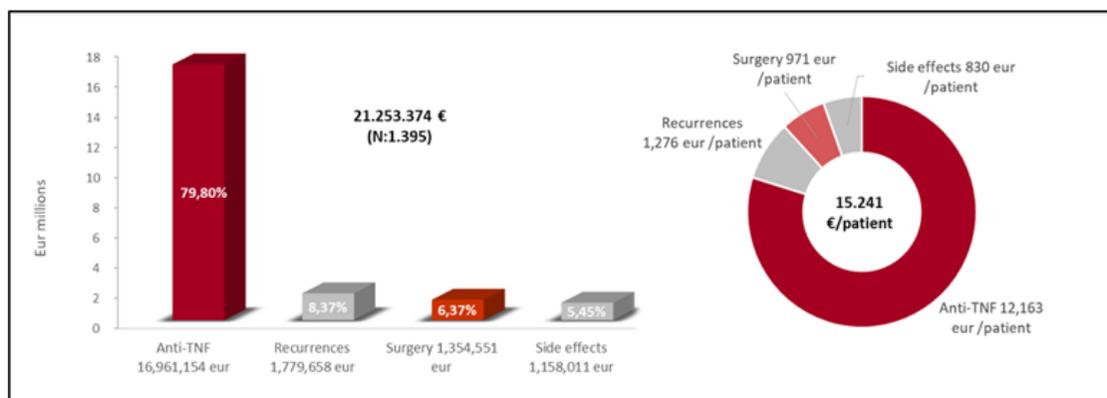


Figure 5: Estimated Annual Direct Cost for the treatment of CPF in CD in Spain: 21,253,374 € (estimated population: N=1,395) & direct annual Costs per patient: 15,241 €.

With regards to indirect costs, the impact on labour as a consequence of associated sick leaves is estimated to be of, at least, 186,266 € per annum (134 €/ patient) in Spain. Work absences as a consequence of the disease are estimated to be within the range of 10 and 30 days for nearly 70% of all patients, according to data extracted from the bibliography [35], resulting in an estimated annual cost of 804,599 € (577 €/ patient).

Discussion

This study provides an economic model which allows for the quantification of the costs associated to refractory CPF in EC in Spain. The study includes the direct costs of the different therapeutic approaches, costs incurred as a result of the primary side effects associated to each of the treatment options, and the costs associated to work absenteeism as a consequence of the different treatments as well as of the perianal disease itself.

The resulting direct costs is estimated to be of at least 15,241 €/patient. This is a significantly higher result than that obtained by a previous study carried out in Spain in 2013 [11]. In that earlier study, the average direct cost was estimated to be of 8,289€/ patient. This difference may result from fact that, whilst our study uses unitary costs per intervention updated and published in 2017 by the Spanish Ministry of Health, Consumer Affairs and Social Welfare (MSCBS), the 2013 study used unitary costs from the year 2000 published by INSALUD in 2001. Moreover, our study exclusively estimates the costs of CPF refractory to prior treatments, whereas the 2013 study also included cases of CPF not treated previously. As a consequence, our study presumably takes into account more complex and expensive surgical approaches as well as a greater number of anti-TNF intensifications. In fact, in our study, treatment with biological drugs accounts for a 79.8% of the total annual direct costs for the treatment of refractory CPF in CD. Meanwhile, in the 2013 study, the costs of biological drugs accounted for a 61.4% of the total annual direct costs.

In our study, costs have been estimated for a timeframe 52 weeks. However, as indicated by the bibliography, the average duration of the fistulas is 42.8 months (3.6 years) [17] with, usually, a complex circle of recurrences and retreatments. Therefore, the total costs of a complete treatment per patient should be higher than the one shown in the article.

Moreover, the traditional therapeutic approach does not guarantee a complete remission, nor does it prevent disease recurrence, and frequently it results in significant side effects and complications such as perianal abscess formation, extension of the fistula, extrusion of the seton and faecal incontinence in the case of surgery [38], and abscesses in the case of treatment with anti-TNF drugs. These side effects require further treatment, thereby increasing the total cost of treatment, and, above all, further deteriorating patient's quality of life.

In addition to high costs, it is thus necessary to highlight the great personal burden that this disease causes in patients and the extra burden and secondary costs due to the invasive surgical nature of traditional management, greatly impacting their quality of life as well as their social relationships, and the subsequent work absenteeism that the disease entails. 73% of CPF patients felt depressed and 33% felt not worth living [39], with quality of life equivalent or worse than conditions such as advanced cancer or multiple sclerosis based on published utility values [40].

It is important to remark that these results are based on hospital costs published in Spain. Respective costs in other European countries could be significantly higher. Based on data published by the World Health Organization, average cost by inpatient bed day in Germany is 24.7% higher than in Spain, in Austria 42.0% higher and in the UK 16,8% higher)[36].

Conclusions

The management of CPF in CD requires a high consumption of healthcare resources, with anti-TNF biologic drugs accounting for nearly 80% of these resources. Being a chronic disease, the annual estimated costs of the disease will frequently extend over several years. Thus, the actual costs associated with the definite remission of CPF would be significantly greater than those calculated in this study.

There is a need for new treatment approaches that could reduce the necessity of surgical interventions and the use of anti-TNF drugs, thereby reducing the costs associated with the treatment, as well as side-effects, complications and sequels derived from the current medical or surgical procedures.

The authors of this study suggest that this study be subject to a future review including new treatment options that may arise and that could reduce the need for invasive surgical procedures or anti-TNF drugs [32]. Furthermore, all this could contribute to a total cost reduction in the treatment of these types of patients.

Limitations of the Study

This study has been carried out using information from bibliographical sources as well as the opinion of experts Hospital Universitario La Paz, Madrid. No primary patient data have been collected.

The extrapolation of the results of this study to other countries must take into account that the data used for costs analysis are those published in Spain.

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Contributorship Statement

MD Martín-Arranz, I Pascual Migueláñez and JL Marijuán planned, conducted and reported this work.

Conflict of Interest

MD Martín-Arranz has served as speaker, consultant, advisory board member or has received research funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Shire Pharmaceuticals, Tillotts Pharma and Faes Farma. I Pascual Migueláñez has received financial support from Takeda for attending symposia in 2019. JL Marijuán has no potential conflict of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, MD Martín-Arranz, upon reasonable request.

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