Original Article

Epidemiological profile of 175 patients with Crohn's disease submitted to biological therapy

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ABSTRACT: Introduction: There is currently an increasing use of biological agents in the management of Crohn's disease (CD). There is lack of data regarding the epidemiological profile of patients on infliximab (IFX) and adalimumab (ADA) for CD in Brazil. **Objective:** To identify the epidemiological characteristics of patients with CD who underwent biological therapy. **Method:** Retrospective multicenter study, with CD patients on biological therapy. Analyzed variables: gender, age at treatment initiation, Montreal classification, concomitant perianal disease and smoking status. **Results:** 175 patients without previous exposure to biological agents were included, 93 (53%) were male. The mean age at treatment initiation was 35.5 (2-79) years old an the mean disease duration was 46.9 (0-480) months. Overall, 117 (66.9%) patients used IFX and 58 (33.1%), ADA. Montreal classification: age at diagnosis — A1 (n=21; 12%), A2 (n=102; 58.3%), and A3 (n=52; 29.7%). CD location — L1 (n=42; 24%), L2 (n=51; 29.1%), L3 (n=81; 46.3%), and L4 (n=1, 0.6%). Phenotype —B1 (n=59; 33.7%), B2 (n=46; 26.3%), and B3 (n=70; 40%). Perianal disease was found in 89 (50.9%) patients. **Conclusions:** The epidemiological profile of patients was similar to the literature. There was a high prevalence of patients with fistulizing CD.

Keywords: Crohn's disease; tumor necrosis factor-alpha; epidemiology.

RESUMO: Introdução: Atualmente há uso crescente dos agentes biológicos no manejo da doença de Crohn (DC). Há escassez de dados referentes ao perfil epidemiológico dos usuários de infliximabe (IFX) e adalimumabe (ADA) para DC no Brasil. **Objetivo:** Identificar as características epidemiológicas dos pacientes com DC submetidos à terapia biológica. **Método:** Estudo retrospectivo, multicêntrico, com portadores de DC que utilizaram terapia biológica. Variáveis analisadas: gênero, idade ao início do tratamento, classificação de Montreal, doença perianal concomitante e tabagismo. **Resultados:** Foram incluídos 175 pacientes, sem exposição prévia a biológicos, sendo 93 (53%) homens. A média de idade no início do tratamento biológico foi de 35,5 (2-79) anos. O tempo médio de doença ao início do tratamento foi de 46,9 (0-480) meses. Do total da amostra, 117 (66,9%) utilizaram IFX e 58 (33,1%) ADA. Classificação de Montreal: idade ao diagnóstico — A1 (n=21; 12%), A2 (n=102; 58,3%) e A3 (n=52; 29,7%). Localização da DC — L1 (n=42; 24%), L2 (n=51; 29,1%), L3 (n=81; 46,3%) e L4 (n=1; 0,6%). Forma de apresentação — B1 (n=59; 33,7%), B2 (n=46; 26,3%) e B3 (n=70; 40%). Doença perianal foi encontrada em 89 (50,9%) dos pacientes. **Conclusões:** Os dados epidemiológicos dos pacientes foram compatíveis com os da literatura internacional. Houve uma alta prevalência de pacientes com a forma fistulizante da DC.

Palavras-chave: Doença de Crohn; fator de necrose tumoral alfa; epidemiologia.

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INTRODUCTION

Crohn's Disease (CD) is a chronic transmural inflammatory disease that may affect the whole gastrointestinal tract, and is characterized by alternate episodes of remission and reactivation. Its evolution throughout the years, due to its natural history, can cause complications such as stenosis, fistulas or abscesses[1]. Nowadays, there is a global tendency that the CD incidence will increase, and this is confirmed by important retrospective epidemiological studies from the 1980's[2-4].

The pathogenesis of CD is not well understood, so there is no defined etiology for the disease[5]. Some believe in the existence of complex genetic and environmental interactions that eventually predispose and trigger its pathological manifestations[6]. Its clinical presentation varies according to location, extension and intensity of the inflammation of compromised sites[5].

CD occurs mainly among adolescents and young adults, and represents an important social, psychological and labor impact since it affects this age group of great productivity[7]. Because of this recurring pattern of symptoms and the evolution to the already mentioned complications, which lead more than 70% of patients to surgery and 30% to repeated resections, CD causes a significant impact on the physical and psychological quality of life of patients[7,8].

The proper treatment for CD is yet significantly limited, since there is no type of clinical or surgical intervention that can cure the disease[5]. Therefore, there is a constant search for new forms of treatment. In the past few years, the management of CD has evolved, especially due to the increasing use of biological agents all over the world[1].

Until the end of the 1990s, when the first biological drug was approved for CD, the conventional therapeutic arsenal was composed of corticosteroids, antibiotics, aminosalicylates and immunomodulators (azathioprine, 6-mercaptopurine and methotrexate)[5,8].

Nowadays, the objectives of CD treatment include the fast induction to clinical remission, with the efficient maintenance of remission without the use of corticosteroids, as well as mucosal healing, closure of fistulas, prevention and reduction of the number of hospital admissions and surgeries, besides the improvement in the quality of life of patients. As an additional objective, the ability to prevent long term complications has been more and more discussed[5]. The drugs that are most likely to meet these objectives are the anti-TNF antibodies, infliximab (IFX), adalimumab (ADA) and certolizumab pegol (CER), which are the only biological agents available in Brazil to handle the disease. Today, a great proportion of the patients with CD in outpatient clinics, doctors offices or reference centers, use these drugs. Due to the recent approval of CER in Brazil to manage CD, the number of patients being treated with this third agent is still small, but it should increase in the next years.

Currently, the incidence of CD in the United States is approximately 15 to 20 cases per 10 thousand inhabitants[2]. It is difficult to measure this number in countries of Africa or Latin America, like Brazil, since the epidemiological data of the disease are only available in few publications. Therefore, there is no national prevalence or incidence rate that is officially acknowledged.

Even with data from isolated regions, it is possible to observe the increasing number of CD cases diagnosed in the past few decades in South America and Brazil[2]. Studies performed in the 1980s and 1990s in some states of Brazil showed dozens of new diagnosed cases, with much higher numbers in comparison to previous decades[2].

In the international literature, many papers analyze isolated factors such as ethnicity, age, gender, medication, association with smoking and other variables. However, none of them have designed an epidemiological profile, including only patients with CD on anti-TNF therapy. In Brazil, both epidemiological data of patients with CD and on biological therapy are lacking.

With this scenario of limited data, this study aimed to identify the epidemiological characteristics of Brazilian patients with CD submitted to biological therapy, based on baseline characteristics and the Montreal classification. Morover, it aims to determine which is the most frequent phenotype of the disease in this sample of patients and to compare this information with data from the international literature.

METHOD

This study was carried out after the approval by the Research Ethics Committee of *Pontifícia*

Universidade Católica do Paraná (PUC-PR), protocol number 0005580/11.

This was a retrospective, transversal multicenter study with patients with CD who were on biological therapy from May 2000 to May 2012, coming from five different reference centers of inflammatory bowel disease (IBD) from the South and Southeast of Brazil.

The study included: patients with CD, users of IFX, ADA or CER as the first anti-TNF agent, who had not previously been on biological therapy, at any age. The study excluded: patients with ulcerative colitis or indeterminate IBD, and those who were using a second biological drug in the treatment (patients with previous exposure to a first biological agent).

The study sample was not calculated, but performed by means of a convenience sample, including the actual number of patients coming from the mentioned reference centers. A data review was conducted with information from medical files and posterior completion of a specific protocol, with previously chosen variables to be analyzed. When necessary, the patient received a phone call in case there was conflicted or missing information, to clear any doubts or to request any additional information. After the revision of medical files and data collection, 175 patients met the criteria and were included in this study.

All reference centers of IBD that offered their patients data manage CD according to the guidelines by the European Crohn's and Colitis Organization (ECCO), which standardizes specially the indication to biological treatment in the included subjects[9].

The analyzed variables were gender, age at biological therapy initiation, time of diagnosis, associated perianal disease, concomitant medications, smoking, type of anti-TNF agent anti-TNF (IFX, ADA or CER) and Montreal classification (age at diagnosis of CD, location of disease and phenotype). The Montreal classification is detailed in Table 1. Protocols were fulfilled based on the compiled data concerning the beginning of biological treatment, and not the time of diagnosis of CD.

Literature review was based on searches in the following databases: PubMed, MEDLINE and SciELO. The searched terms were: "infliximab", "adalimumab", "certolizumab pegol", "anti-TNF", "biologics" and "epidemiology", always combined with "Crohn's disease". All relevant articles published until July 2012 were reviewed, and those with similar epidemiological data to the analyzed ones were selected for further comparison.

Table 1. *Detailed Montreal Classification, adapted from Silverberg et al[10].*

Montreal Classification		
Age at diagnosis (A)	A1	≤16 years old
	A2	17–40 years old
	A3	≥40 years old
Disease location (L)	L1	Terminal ileum
	L2	Colon
	L3	Ileum-colon
	L4	Upper gastrointestinal tract
Behavior (B)	B1	Nonstenotic /non-penetrating
	B2	Stenotic
	B3	Penetrating

With complete protocols and literature review, data were compiled and organized in frequency tables. The obtained results from this sample were expressed by means, medians, minimum values, maximum values and standard deviation (quantitative variables) or by frequencies and percentages (qualitative variables). Each variable was individually analyzed with the objective to compare them with data found in literature.

RESULTS

The study included 175 patients, 93 (53%) were male and 82 (47%) female. In relation to age at the beginning of biological treatment, a mean of 35.5 years old (2–79; SD=13.9) was found. The mean time of duration of CD at the beginning of treatment was 46.9 months (0–480; SD=69.6). However, it was observed that most cases (55.4%) started biological treatment less than 24 months after the onset of the disease.

One hundred and forty-six patients (83.4%) were on concomitant use of azathioprine (AZA), using the strategy of combo therapy, more recently described[1]. Corticosteroids were used at the beginning of biological treatment in 102 patients (58.3%). No patient used methotrexate. There were only 11 smoking patients, which corresponded to 6.3% of the total sample. Perianal disease was found in 89 patients (50.9%). The biological therapies used were IFX in 117 (66.9%) patients and ADA in 58 (33.1%). No patient was on CER. Table 2 summarizes the baseline characteristics of the analyzed patients.

According to the Montreal classification, the following results were obtained for each of the variables: age at diagnosis A1 (n=21; 12%), A2 (n=102; 58.3%) and A3 (n=52, 29.7%). CD location: L1 (n=42; 24%), L2 (n=51, 29.1%), L3 (n=81, 46.3%), and L4 (n=1, 0.6%). So, there was a higher prevalence of patients diagnosed with CD between 17 and 40 years old (A2), patients with ileocolic location (L3) and with fistulizing disease (B3). Figure 1 illustrates these data.

DISCUSSION

The determination of epidemiological characteristics in patients with CD is very difficult, in Brazil and in other developing countries, due to the deficient registration systems. It is more difficult to characterize patients with CD on biological therapy, because even in developed countries these data are controversial, and analyzed in different manners by the studies that are available in literature[2]. Some assess only isolated users of biological therapy, most of the time analyzing its efficacy, safety or loss of response[11-16,18]. Therefore, this study aimed to assess data from subjects coming from five reference centers of IBD from the South and Southeast of Brazil in order to present a general epidemiological profile of these patients, which is more adequate to our reality, and compare them with other studies conducted in Brazil and in other parts of the world.

The findings in this study demonstrated the greater prevalence of CD in young patients – A2 in the Montreal classification, and mean age of 35.5 years old – in accordance with national and international literature[2,11-18]. This fact reveals the great importance of diagnosis and adequate management of these patients, since it's a period of major activity and productivity of subjects. Since the disease is considerably debilitating, both physically and emotionally, and because the treatment is long, these years in the patient's life end up being compromised[11,13].

The higher prevalence of male (53 *versus* 47%) was a bit different than findings from literature, which presents 45 to 61.8% of female patients and 32.8 to 55% of male patients[2,11-18]. According to Cosnes et al.[17], in countries with low incidence of CD, in Europe and North America, the prevalence of the disease has increased among men, being similar or even superior to women.

Table 2. *Baseline characteristics of the 175 analyzed patients.*

	n (%)
Gender	
Male	93 (53)
Female	82 (47)
Used biological drug	
ADA	58 (33.1)
IFX	117 (66.9)
Time of diagnosis (months)	
<24	97 (55.4)
24 to 60	36 (20.6)
>60	42 (24.0)
Mean±SD	46.9±69.6
Median (range)	12.0 (0.0~480.0)
Age at treatment initiation (years)	
Mean±SD	35.5±13.9
Median (range)	34.0 (2.0~79.0)
Azathioprine	
Yes	146 (83.4)
No	29 (16.6)
Corticosteroids	
Yes	102 (58.3)
No	73 (41.7)
Smoking	
Yes	11 (6.3)
No	164 (93.7)
Perianal CD	
Yes	89 (50.9)
No	86 (49.1)

SD: Standard deviation; CD: Crohn's Disease; ADA: adalimumab; IFX: infliximab.

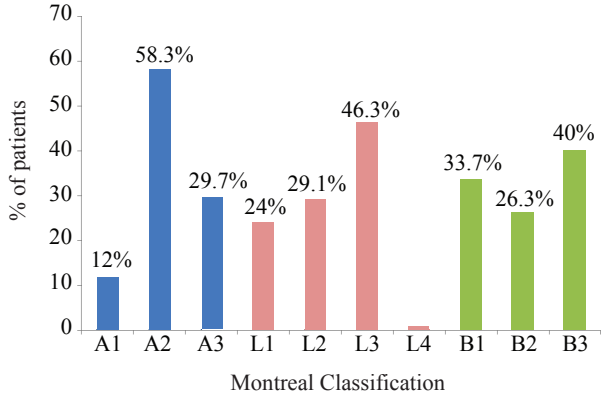

Figure 1. *Montreal Classification of the 175 patients submitted to biological therapy.*

The other two analyzed variables that presented different numbers than those found in literature were the presence of perianal disease and smoking. Since the study was performed in specialized IBD centers, especially coloproctology units, more than half of the patients (50.9%) had associated perianal disease. This percentage was significantly different when compared to other papers in literature, which showed 13.1–42% patients affected by perianal disease[2,11-13,16,17]. However, it is important to notice the increase of severe and complicated forms of CD, such as perianal compromise or other conditions[2]. The presence of fistulae is especially emphasized, since they have a significant impact on the quality of life of patients and make the treatment for CD even more challenging[13,15].

Regarding smoking, the difference was even greater. In this study, only 6.3% of patients smoked, while in literature this habit was present in 19 to 47.8% of the cases[2,12,13,15-17]. Maybe this fact is justified by the greater announcement of the relation between smoking and the worse evolution of the disease, especially in patients' associations and reference services.

In relation to immunosuppressive drugs, distinct values were found in comparison to the literature when analyzing only the use of AZA: 83.4% in this study and percentages between 25 and 49.7% in the international literature. However, in relation to the use of concomitant drugs, such as methotrexate, 6-mercaptopurine and aminosalicylates, which are common in Europe and in the United States, if added to the use of AZA, the percentage is close to 70%[2,11-16]. These values suggest that even with adverse effects and slow action onset, there are benefits to the combined treatment with anti-TNF that overcome its disadvantages[1,14]. The results presented by Colombel et al.[1], in the SONIC study, demonstrated that the combined therapy of IFX and AZA presented better clinical remission rates for CD as well as mucosal healing, in comparison to monotherapy with IFX or AZA.

By analyzing the use of corticosteroids at the beginning of biological treatment, 58.3% of the patients in this study used them. In the national and international literature, these values ranged from 26 to 77% of the cases, which demonstrates one of the great indications to use biological drugs for the treatment of CD, the corticosteroid dependency[2,11-18]. Brazilian studies that also reported the analysis of this variable, demonstrated that 67 to 77% of the patients were on the medication. These data may seem to reflect the tendency of the great use of corticosteroids in Brazil in relation to the other countries[2,19,20].

It is very difficult to define which biological agent is more used nowadays. The most relevant international studies on the subject aim to assess the safety and efficacy of each isolated drug[2,11-16]. National studies and other case series do not present these data comparatively[2,19,20]. Even though, a significantly higher prevalence of IFX is still observed, maybe for its longer presence in the market or because of its availability in some centers. It could also be due to the experience of professionals who prescribe it and handle it. However, ADA is being more and more used, so this difference is being reduced as observed in publications throughout the years[1,2,15]. It is certain that within a few years there will be a greater number of patients on CER, which was recently approved in Brazil to treat CD patients. The results in this study demonstrated 66.85% of patients on IFX and 43.15% on ADA, with a clear progression on the use of ADA each year during the analyzed period. No patient was on CER. The main epidemiological data found in this study in comparison to data from literature are described on Table 3.

Concerning the Montreal classification, many studies were analyzed; however, those that described the samples with this system were not only studies with patients on biological treatment, but with CD in general. Some analyses that assessed only patients on ADA or IFX did not use this classification, since their objectives were not related to epidemiological variables. So, the values found in this study were comparable to those of Brazilian analyses reflecting a reality closer to ours, besides an international study that aimed to expose the evolution of the incidence and prevalence of IBD, CD and ulcerative colitis, separately, throughout the years, which consistently demonstrated the prevalence of each one of the classifications[2,17,19-21].

Group A2 in the Montreal classification (age at diagnosis between 17 and 40 years) was the most prevalent in this study, accounting for 58.3% of the patients. This number was similar to that of papers in literature analyzed in this comparison (between 59 and 73%), which shows the great prevalence of CD and the biological treatment in this age group[17,19-21].

The disease location was also shown in this study, and the percentages were in accordance with literature.

The most prevalent type was L3 (ileocolic CD), in 46.3% of the cases. In the literature, this was also the most common form observed in most of the reviewed studies, with percentages ranging from 34.5 and 47%[2,17,19-21].

Regarding the behavior of CD, differences between the findings in this sample were found in comparison to literature. The B3 type (penetrating CD) was described as being the most frequent one, representing 40% of the cases. In most studies, the B1 type was more prevalent (luminal CD), ranging between 29.2 and 71%. This fact can be explained by the conduction of studies in colorectal surgery units, instead of gastroenterology clinics, where the reference and indications for patients with fistulizing perianal CD is more prevalent[2,17,19,20]. The comparative data in the present sample in relation to the Montreal classification and other studies in literature are detailed in Table 4.

CONCLUSIONS

Patients with CD on biological treatment, who had not been previously on anti-TNF therapy, had mean age of 35.5 years old, and most of them were male (53%). The subtype A2, from the Montreal classification, was the most found one (68.3%), and ileocolic segment (L3) as the most frequent compromised location in 46.3% of the cases. Most patients were on treatment with AZA or corticosteroids together with the biological treatment. These data characterize an epidemiological profile compatible with that found in international literature.

The presence of perianal disease was shown in 50.9% of the cases, and the subtype B3 from the Montreal classification was present in 40% of the cases, with higher prevalence comparing to the literature.

Table 3. *Clinical and epidemiological basal characteristics of patients in comparison to papers from the national and international literature.*

Author	Gender (%)		Mean age	Perianal Disease (%)	Smoking (%)	Concomitant AZA (%)	Concomitant corticosteroid (%)
	Male	Female					
Panaccione et al.[11]	43.1	56.9	37	22.4	–	46.4	47.4
Colombel et al.[12]	38.2	61.8	37.1	15.2	35.5	32.2	44.0
Lichtiger et al.[13]	40.9	59.1	40.8	13.1	23.5	41.2	42.3
Hanauer et al.[14]	42.0	58.0	35	–	–	25.0	51.0
Sands et al.[15]	55.0	45.0	37	–	45.0	30.0	26.0
Schnitzler et al.[16]	39.0	61.0	33.9	28.0	47.8	49.7	32.2
Cosnes et al.[17]	54.0	46.0	33	31.0	19.0	–	–
Souza et al.[2]	44.0	56.0	32	42.0	–	48.8	77.0
Kotze et al.[8]	46.3	53.7	36.7	50.0	–	–	55.5
This study	53.0	47.0	35.5	50.9	6.3	83.4	58.3

AZA: azathioprine.

Table 4: *Montreal classification: data found in this study compared with data from national and international literature.*

Author	Montreal									
	A1	A2	A3	L1	L2	L3	L4	B1	B2	B3
Teixeira et al.[21]	10.0%	72.0%	18.0%	34.5%	31.0%	34.5%	0.0%	-	-	-
Souza et al.[20]	-	-	-	22.0%	29.0%	47.0%	2.0%	58.0%	19.0%	23.0%
Poli et al.[19]	8.0%	73.0%	19.0%	34.0%	15.0%	45.0%	1.0%	38.0%	26.0%	36.0%
Souza et al.[2]	8.0%	59.0%	33.0%	46.0%	10.0%	43.0%	1.0%	71.0%	8.0%	21.0%
Cosnes et al.[17]	11.0%	72.0%	17.0%	25.3%	27.2%	34.6%	13.1%	29.2%	33.6%	37.2%
This study	12.0%	58.3%	29.7%	24.0%	29.1%	46.3%	0.6%	33.7%	26.3%	40.0%

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