Long-Term Outcomes of Biological Therapy in Crohn's Disease Complicated With Internal Fistulizing Disease: BIOSCOPE Study From GETECCU

Manuel Barreiro-de Acosta, MD, PhD[1], Agnès Fernández-Clotet, MD[2,3], Francisco Mesonero, MD[4], Francisco Javier García-Alonso, MD, PhD[5], María José Casanova, MD, PhD[3,6], Margarita Fernández-de la Varga, MD[7], Fiorella Cañete, MD[3,8], Luisa de Castro, MD, PhD[9], Ana Gutiérrez, MD, PhD[3,10], Beatriz Sicilia, MD, PhD[11], Victoria Cano, MD[12], Olga Merino, MD[13], Ruth de Francisco, MD[14], Irene González-Partida, MD, PhD[15], Gerard Surís, MD[16], Leyanira Torrealba, MD[17], Rocío Ferreiro-Iglesias, MD, PhD[1], Beatriz Castro, MD[18], Lucía Márquez, MD, PhD[19], Ana Sobrino, MD[20], Ainara Elorza, MD[21], Xavier Calvet, MD, PhD[3,22], Pilar Varela, MD[23], Raquel Vicente, MD[24], Luis Bujanda, MD, PhD[3,25], Laura Lario, RN[26], Noemí Manceñido, MD, PhD[27], Mariana F. García-Sepulcre, MD, PhD[28], Eva Iglesias, MD[29], Cristina Rodríguez, MD, PhD[30], Marta Piqueras, MD[31], Juan Ángel Ferrer Rosique, MD[32], Alfredo J. Lucendo, MD, PhD[3,33], Olga Benítez, MD[34], Melody García, MD[35], David Olivares, MD[36], Carlos González-Muñoza, MD[37], Beatriz López-Cauce, PhD[38], Victor Jair Morales Alvarado, MD[39], Katerina Spicakova, MD[40], Alicia Brotons, MD[41], Fernando Bermejo, MD, PhD[42], Pedro Almela, MD, PhD[43], Nahia Ispízua, MD[44], Pau Gilabert, MD[45], Carlos Tardillo, MD[46], Fernando Muñoz, MD[47], Pablo Navarro, MD[48], Rosa Eva Madrigal Domínguez, MD[49], Pau Sendra, MD[50], Esther Hinojosa, RN[51], Empar Sáinz, MD[52], María Dolores Martín-Arranz, MD, PhD[53], Daniel Carpio, MD[54], Elena Ricart, MD, PhD[2,3], Berta Caballol, MD[2,3], Laura Núñez, MD[4], Jesús Barrio, MD[5], Javier P. Gisbert, MD, PhD[3,6], Marisa Iborra, MD, PhD[7], Margalida Calafat, MD, PhD[3,8], Vicent Hernández, MD, PhD[9], Roser Muñoz Pérez, MD[10], José Luis Cabriada, MD[21], Eugeni Domènech, MD, PhD[3,8] and Iago Rodríguez-Lago, MD, PhD[21], on behalf of the BIOSCOPE study group from the ENEIDA registry

INTRODUCTION: **The prevalence of penetrating complications in Crohn's disease (CD) increases progressively over time, but evidence on the medical treatment in this setting is limited. The aim of this study was to evaluate the effectiveness of biologic agents in CD complicated with internal fistulizing disease.**

[1]Department of Gastroenterology, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [2]Department of Gastroenterology, Hospital Clinic and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Department of Gastroenterology, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; [4]Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]Department of Gastroenterology, Hospital Universitario Río Hortega, Valladolid, Spain; [6]Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Madrid, Spain; [7]Department of Gastroenterology, Hospital Universitari i Politecnic la Fe, Valencia, Spain; [8]Department of Gastroenterology, Hospital Universitari German Trias i Pujol, Badalona, Spain; [9]Department of Gastroenterology, Hospital Álvaro Cunqueiro, Vigo, Spain; [10]Department of Gastroenterology, Hospital General Universitario de Alicante, Alicante, Spain; [11]Department of Gastroenterology, Hospital Universitario de Burgos, Burgos, Spain; [12]Department of Gastroenterology, Hospital Universitario de León, León, Spain; [13]Department of Gastroenterology, Hospital Universitario de Cruces, Barakaldo, Spain; [14]Department of Gastroenterology, Hospital Universitario Central de Asturias, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain; [15]Department of Gastroenterology, Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [16]Department of Gastroenterology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [17]Department of Gastroenterology, Hospital Universitari Dr. Josep Trueta, Girona, Spain; [18]Department of Gastroenterology, Hospital Universitario Marqués de Valdecilla, Santander, Spain; [19]Department of Gastroenterology, Hospital del Mar, Barcelona, Spain; [20]Department of Gastroenterology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; [21]Department of Gastroenterology, Hospital Universitario de Galdakao, Biocruces Bizkaia Health Research Institute, Galdakao, Spain; [22]Department of Gastroenterology, Corporació Sanitària Universitària Parc Taulí, Sabadell, Spain; [23]Department of Gastroenterology, Hospital de Cabueñes, Gijón, Spain; [24]Department of Gastroenterology, Hospital Universitario Miguel Servet, Zaragoza, Spain; [25]Department of Gastroenterology, Hospital Universitario Donostia and Instituto Biodonostia, Universidad del País Vasco (UPV/EHU), Donostia, Spain; [26]Department of Gastroenterology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [27]Department of Gastroenterology, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain; [28]Department of Gastroenterology, Hospital General Universitario de Elche, Elche, Spain; [29]Department of Gastroenterology, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain; [30]Department of Gastroenterology, Hospital Universitario de Navarra, Pamplona, Spain; [31]Department of Gastroenterology, Consorci Sanitari de Terrassa, Terrassa, Spain; [32]Department of Gastroenterology, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain; [33]Department of Gastroenterology, Hospital General de Tomelloso and Instituto de Investigación Sanitaria Princesa, Instituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM), Tomelloso, Spain; [34]Department of Gastroenterology, Hospital Universitari Mútua Terrassa, Terrassa, Spain; [35]Department of Gastroenterology, Hospital General San Jorge, Huesca, Spain; [36]Department of Gastroenterology, Hospital Clínico San Carlos, Madrid, Spain; [37]Department of Gastroenterology, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [38]Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [39]Department of Gastroenterology, Hospital General de Granollers, Granollers, Spain; [40]Department of Gastroenterology, Hospital Universitario Araba, Vitoria, Spain; [41]Department of Gastroenterology, Hospital Vega Baja, Alicante, Spain; [42]Department of Gastroenterology, Hospital Universitario de Fuenlabrada, Instituto de Investigación Sanitaria La Paz (IdiPAZ), Fuenlabrada, Spain; [43]Department of Gastroenterology, Hospital General de Castellón, Castellón, Spain; [44]Department of Gastroenterology, Hospital Universitario de Basurto, Bilbao, Spain; [45]Department of Gastroenterology, Hospital de Viladecans, Viladecans, Spain; [46]Department of Gastroenterology, Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; [47]Department of Gastroenterology, Hospital Universitario de Salamanca, Salamanca, Spain; [48]Department of Gastroenterology, Hospital Clínico Universitario de Valencia, Valencia, Spain; [49]Department of Gastroenterology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [50]Department of Gastroenterology, Hospital Son Espases, Palma, Spain; [51]Department of Gastroenterology, Hospital de Manises, Manises, Spain; [52]Department of Gastroenterology, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain; [53]Department of Gastroenterology, Hospital Universitario de la Paz, Madrid, Spain; [54]Department of Gastroenterology, Complexo Hospitalario Universitario de Pontevedra, Pontevedra, Spain. **Correspondence:** Iago Rodríguez-Lago, MD, PhD.
E-mail: iago.r.lago@gmail.com.

Received July 11, 2022; accepted November 14, 2022; published online December 14, 2022

METHODS: **Adult patients with CD-related fistulae who received at least 1 biologic agent for this condition from the prospectively maintained ENEIDA registry were included. Exclusion criteria involved those receiving biologics for perianal disease, enterocutaneous, rectovaginal, anastomotic, or peristomal fistulae. The primary end point was fistula-related surgery. Predictive factors associated with surgery and fistula closure were evaluated by multivariate logistic regression and survival analyses.**

RESULTS: **A total of 760 patients from 53 hospitals (673 receiving anti–tumor necrosis factors, 69 ustekinumab, and 18 vedolizumab) were included. After a median follow-up of 56 months (interquartile range, 26–102 months), 240 patients required surgery, with surgery rates of 32%, 41%, and 24% among those under anti–tumor necrosis factor, vedolizumab, or ustekinumab, respectively. Fistula closure was observed in 24% of patients. Older patients, ileocolonic disease, entero-urinary fistulae, or an intestinal stricture distal to the origin of the fistula were associated with a higher risk of surgery, whereas nonsmokers and combination therapy with an immunomodulator reduced this risk.**

DISCUSSION: **Biologic therapy is beneficial in approximately three-quarters of patients with fistulizing CD, achieving fistula closure in 24%. However, around one-third still undergo surgery due to refractory disease. Some patient- and lesion-related factors can identify patients who will obtain more benefit from these drugs.**

KEYWORDS: Crohn's disease; fistula; biologic therapy; surgery

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C842 and http://links.lww.com/AJG/C843

Am J Gastroenterol 2023;118:1036–1046. https://doi.org/10.14309/ajg.0000000000002152

INTRODUCTION

Crohn's disease (CD) is a chronic disorder of the gastrointestinal tract, characterized by an uncontrolled inflammatory process that usually involves the terminal ileum and right colon (1). Most patients have an inflammatory behavior at diagnosis according to the Montreal classification (2), but up to 8% already demonstrate intra-abdominal penetrating complications (fistulas or abscesses) (3). The prevalence of these disease-related complications increases progressively over time, and they can be found in up to 53% of patients, although the highest rates were reported during the prebiological era (4,5). These lesions are often associated with internal septic complications that often require percutaneous drainage or even surgery.

The primary goal of medical treatment in these patients is to halt the uncontrolled inflammatory process that leads to symptoms and infectious complications. The availability of biologic agents, and especially tumor necrosis factor (TNF)-α inhibitors, has led to overall better disease control. However, evidence on their efficacy in penetrating CD is still limited (6). Anti–TNF-α are possibly the most effective drugs in this scenario, but data supporting its use are still insufficient (7). Previous reports have usually included a limited number of patients, in which the reported proportion of patients undergoing intestinal resection was 40%–50% (8–11). Data from a recent retrospective study from France observed that almost half of patients with CD with internal fistulizing disease treated with anti-TNF-α remained free of intestinal resection after 5 years of treatment (11). Therefore, our aim was to evaluate the effectiveness of biologic agents in patients with CD complicated with internal fistulizing disease within the ENEIDA registry.

METHODS

Study design

Patients with an established diagnosis of CD according to the ECCO guidelines (1) and a penetrating behavior based on the Montreal classification (B3) (2) who received treatment with at least 1 biologic agent (infliximab, adalimumab, vedolizumab, and/or ustekinumab) for internal abdominal fistulizing disease were identified from the ENEIDA registry. Only those patients with fistulous tracts confirmed by cross-sectional imaging at the time of starting the treatment were included in the study. Patients were excluded if the treatment had been prescribed for perianal disease, stricturing complications, or anastomotic, rectovaginal, enterocutaneous, or peristomal fistulae. Patients with concomitant perianal disease were eligible to be included only if they had inactive disease at this level and the internal fistulizing complications were the main condition leading to the prescription of biologic treatment.

Data were obtained from the ENEIDA registry, a prospectively maintained database supported by the Spanish Working Group on Crohn's disease and Ulcerative Colitis (GETECCU) (12). The database contained information from over 65,000 patients from 88 sites at the time of data extraction. Demographic, CD, and fistula-related characteristics and information about medical therapies were prospectively registered, including data on surgery at baseline or during follow-up. However, detailed information about the number of fistulae, concomitant abscess, and the probability of fistula closure was retrospectively compiled. Investigators at each center reviewed the medical records of all patients to ensure that they fulfilled all the inclusion and none of the exclusion criteria. This study was approved by the Research Board of GETECCU and the local Ethics Committees of each participating center. Written informed consent to participate in the ENEIDA registry was obtained from all patients before their inclusion in the database.

Outcomes and definitions

A fistula was defined as a disruption of the intestinal wall with an abnormal communication between 2 epithelial surfaces. The

primary end point of the study was the performance of surgical procedures due to intra-abdominal penetrating complications during follow-up. Secondary outcomes included the rate of abdominal abscess, the need for percutaneous drainage, the change in the number of fistulous tracts, and the proportion of patients with fistula healing along with the safety profile. All surgical procedures related to the fistula tracts were compiled, including the date, indication, type of surgery, the need for an ostomy, and any postoperative complications. Fistula closure was defined as the evidence of the closure of the fistulous tract by cross-sectional imaging.

Data collection

All disease and demographic-related variables were obtained from the ENEIDA registry. Additional information related to the time of starting each biologic agent (baseline) and data about the primary and secondary outcomes of the study were compiled. At baseline, we also compiled information about concomitant therapy—antibiotics or steroids—and combination with thiopurines or methotrexate. Baseline biomarkers including C-reactive protein, hemoglobin, albumin, and total white blood cell count were recorded. Information obtained from cross-sectional imaging at baseline included the number of fistulae, their type, and the presence of intestinal strictures distal to the fistulous tracts.

All data were collected and managed using electronic data capture tools at the Spanish Platform for Collaborative Research in Gastroenterology (AEG-REDCap) hosted by Asociación Española de Gastroenterología (www.aegastro.es) (13). REDCap is a secure, web-based application designed to support data capture for research studies, providing (i) an intuitive interface for validated data entry; (ii) audit trails for tracking data manipulation and export procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for importing data from external sources.

Statistical analysis

The demographic and clinical characteristics of the patients were analyzed by descriptive statistics, using medians with interquartile range (IQR) or mean with SD and its 95% confidence intervals (CIs), as needed. Categorical variables are expressed as proportions and compared by means of the χ^2 test, whereas quantitative variables were compared with the Wilcoxon test. Kaplan-Meier survival and cumulative hazard analyses were also performed to evaluate the cumulative rate of surgery and fistula closure during follow-up. Log-rank and Cox regression models were applied to the main outcome. Factors associated with surgery and fistula closure in the univariate analysis ($P < 0.2$) and those considered clinically relevant were included in the multivariate model. All analyses were performed using R software (RStudio 2022.07.01; http://www.R-project.org). P values <0.05 were considered statistically significant.

RESULTS

Patient and fistulae characteristics

From 65,380 patients included in the ENEIDA registry as of July 2020, we identified 2,689 who were eligible for inclusion. After a review from each investigator, a total of 760 biologic treatments at 53 inflammatory bowel disease units fulfilled the previously described selection criteria and were included in the final analysis (Figure 1). The main clinical characteristics of the cohort are summarized in Table 1.

The characteristics of intra-abdominal fistulae are summarized in Table 2. The most common types of fistula were entero-enteric (51%), followed by entero-colic (30%). Patients had a median of 1 (IQR, 1–2; range 1–6) fistulous tract at baseline, and a concomitant abscess was observed in 147 cases (19%). These patients received antibiotic therapy for a median of 20 days (IQR, 15–50 days), 53% received concomitant oral or intravenous steroid therapy, and 59% received immunomodulators. Around one-fourth of the abscesses (23%) were drained percutaneously before starting biologic therapy.

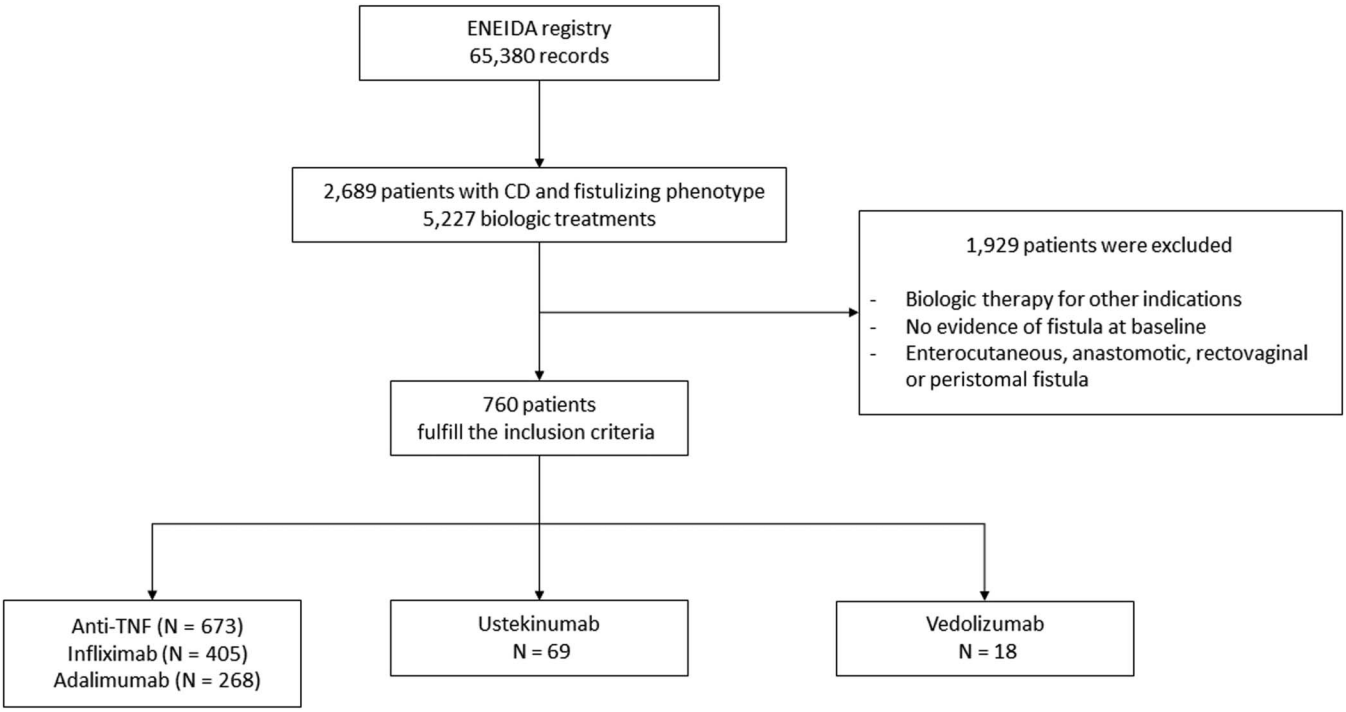

Figure 1. Flowchart of patients included in the study. CD, Crohn's disease; TNF, tumor necrosis factor.

Table 1. Patient characteristics

	Anti-TNF (N = 673)	Infliximab (N = 405)	Adalimumab (N = 268)	Ustekinumab (N = 69)	Vedolizumab (N = 18)
Age, yr, median (IQR)	40 (32–50)	40 (34–50)	39 (30–48)	47 (31–55)	47 (38–52)
Sex, male, n (%)	416 (62)	246 (61)	170 (63)	39 (57)	12 (67)
Disease duration, mo, median (IQR)	81 (8–177)	75 (8–160)	88 (21–184)	113 (65–225)	300 (255–310)
Crohn's disease extent, Montreal classification, n (%)					
Ileal	282 (42)	162 (40)	120 (45)	32 (47)	5 (28)
Colonic	21 (3)	18 (4)	3 (1)	1 (2)	1 (6)
Ileocolonic	366 (55)	223 (55)	143 (54)	35 (52)	12 (67)
Exclusive upper tract disease	3 (0.4)	2 (0.5)	1 (0.4)	—	—
Upper tract disease	154 (22)	101 (25)	50 (19)	16 (23)	5 (28)
Perianal disease, n (%)	165 (25)	108 (27)	57 (21)	26 (38)	7 (39)
Extraintestinal manifestations, n (%)	235 (35)	155 (39)	80 (30)	24 (35)	5 (28)
Active smokers, n (%)	282 (41)	169 (45)	111 (46)	13 (37)	6 (43)
Previous treatments, n (%)					
Thiopurines	368 (56)	211 (53)	157 (60)	29 (42)	8 (50)
Methotrexate	31 (5)	17 (4)	14 (5)	7 (10)	2 (13)
At least 1 anti-TNF	64 (10)	24 (6)	40 (15)	29 (42)	8 (50)
≥2 anti-TNF	11 (2)	3 (1)	8 (3)	15 (22)	3 (19)
Vedolizumab	0	0	0	3 (4)	—
Ustekinumab	1 (0.1)	0	1 (1)	—	2 (12)
Surgery	209 (32)	133 (34)	71 (25)	3 (4)	7 (37)
Baseline laboratory, median (IQR)					
C-reactive protein, mg/dL	2.0 (0.5–6.8)	2.6 (0.6–7.6)	1.6 (0.5–5.6)	1.6 (0.8–4.9)	5.02 (1.6–8.8)
Hemoglobin, g/dL	12.9 (11.5–14.1)	12.8 (11.1–13.9)	13.0 (11.7–14.3)	13.2 (11.8–14.4)	13.2 (10.8–15.6)
Albumin, g/dL	3.9 (3.5–4.2)	3.9 (3.4–4.2)	4.0 (3.5–4.3)	4.1 (3.7–4.3)	3.9 (3.6–4.1)
Leukocytes, mm^3	8,070 (6,270–10,060)	8,120 (6,700–10,175)	8,000 (5,870–9,920)	7,810 (6,200–9,480)	7,795 (5,495–9,970)
Concomitant therapy, n (%)					
Antibiotics	213 (32)	150 (37)	63 (24)	14 (20)	6 (33)
Thiopurines	398 (59)	253 (62)	145 (54)	14 (20)	3 (16)
Methotrexate	27 (4)	16 (4)	11 (4)	5 (7)	2 (11)
Oral steroids	212 (32)	130 (32)	82 (31)	17 (25)	8 (44)
Intravenous steroids	51 (8)	40 (10)	11 (4)	1 (1)	1 (6)

IQR, interquartile range; TNF, tumor necrosis factor.

Thirty-two patients had an abscess greater than 40 mm, but in 16 cases (50%), they were not accessible to percutaneous drainage before starting biological therapy. Patients with an abscess received antibiotics more frequently (70% vs 51%, $P = 0.011$), but there were no differences in the use of concomitant steroids or immunomodulators.

Type of biologic therapy

Patients received treatment with anti–TNF-α agents (n = 673), ustekinumab (n = 69), or vedolizumab (n = 18). Notably, in 90% of patients receiving anti-TNFs, 58% of those receiving ustekinumab, and 50% of those receiving vedolizumab, these biologicals were prescribed as first-line therapy. Conversely, 22% and 19% of ustekinumab- and vedolizumab-treated patients had already received at least 2 biologic agents before, respectively. In addition, 63% of patients received combination therapy either with a thiopurine or methotrexate (59% and 4%, respectively). Patients in the anti-TNF group were more frequently on combination therapy with an immunomodulator compared with those treated with vedolizumab and ustekinumab (64%, 28%, and 28%, respectively).

Surgery rate during follow-up

After a median follow-up of 56 months (IQR, 26–102 months), 240 patients (32%; 95% CI, 38%–35%) required surgery due to intra-abdominal fistulizing complications after a median of 8

Table 2. Characteristics of internal fistula at baseline

	Anti-TNF (N = 673)	Infliximab (N = 405)	Adalimumab (N = 268)	Ustekinumab (N = 69)	Vedolizumab (N = 18)
No. of fistulae					
Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–3)	1 (1–1.3)
≥2 fistulous tracts, n (%)	77 (11)	47 (12)	30 (11)	7 (10)	1 (6)
Type of fistula tracts, n (%)					
Entero-enteric	354 (53)	201 (50)	153 (57)	31 (45)	6 (33)
Entero-colic	202 (30)	119 (29)	83 (31)	15 (22)	7 (39)
Sinus	109 (16)	75 (19)	34 (13)	13 (19)	2 (11)
Entero-urinary	90 (13)	61 (15)	29 (11)	2 (3)	—
Colo-colic	15 (2)	10 (3)	5 (2)	3 (4)	3 (16)
Entero-uterine	10 (1.5)	7 (2)	3 (1)	—	—
Entero-duodenal	2 (0.3)	1 (0.2)	1 (0.4)	1 (1.4)	—
Abscess at baseline, n (%)	133 (20)	92 (23)	41 (15)	11 (16)	3 (17)
Size, mm, median (IQR)	30 (20–50)	30 (20–50)	30 (20–50)	28 (14–36)	18 (18–19)
Drained abscess at baseline,[a] n (%)	32 (24)	23 (25)	9 (22)	1 (10)	1 (33)
Stricture distal to the fistula, n (%)	260 (39)	150 (37)	110 (41)	31 (45)	7 (39)

IQR, interquartile range; TNF, tumor necrosis factor.
[a]Among patients with abscess at baseline.

months (IQR, 3–23 months). The most common indication for surgery was the penetrating complication itself (218 patients, 91%), followed by obstructive symptoms (17 patients, 7%) and intestinal perforation (4 patients, 2%).

Among those patients receiving anti-TNF agents, 223 patients (32% [95% CI, 29%–36%]; 34% infliximab and 30% adalimumab, respectively; $P = 0.28$) underwent surgery, whereas the corresponding figures for those receiving vedolizumab or ustekinumab were 41% (95% CI, 14%–64%) and 24% (95% CI, 13%–33%; log-rank [vs anti-TNF], $P = 0.79$ and $P = 0.33$), respectively (Figure 2). The cumulative probability of remaining free of surgery was 81%, 72%, and 67% for anti-TNF, 82%, 70%, and 70% for ustekinumab, and 73%, 64%, and 64% for vedolizumab at 1, 3, and 5 years of follow-up, respectively. There were no differences in the risk of surgery over time between the different drugs (median of 13, 7, 6, and 5 months in the adalimumab, infliximab, vedolizumab, and ustekinumab groups; hazard ratio [HR] 1.13 [95% CI, 0.14–9.29], $P = 0.91$; and HR 1.06 [95% CI, 0.43–2.61], $P = 0.89$; for vedolizumab and ustekinumab, respectively). The most frequent surgical procedure was ileocecal resection (184 patients, 77%), followed by small bowel resection (33 patients, 14%).

In the Cox regression analysis, age (HR 1.03; 95% CI, 1.02–1.05; $P = 0.001$), ileocolonic disease (HR 2.72; 95% CI, 1.12–6.59; $P = 0.03$), entero-urinary fistulae (HR 2.22; 95% CI, 1.13–4.37; $P = 0.02$), or an intestinal stricture distal to the origin of the fistula (HR 1.92; 95% CI, 1.25–2.96; $P = 0.003$) showed a higher risk of undergoing a surgical intervention (Table 3); however, the type of biological agent did not influence this outcome (Figure 2a). Meanwhile, a lower probability of surgery was observed in nonsmokers (HR 0.49; 95% CI, 0.31–0.79; $P = 0.003$) and in those patients receiving combination therapy with an immunomodulator, irrespectively of the type of biologic (HR 0.65; 95% CI, 0.45–0.93; $P = 0.02$).

In the analyses by drug type, we observed that under anti-TNF therapy, ileocolonic disease (HR 2.80; 95% 1.15–6.81; $P = 0.02$) and age (HR 1.03; 95% CI, 1.02–1.05; $P = 0.001$) were associated with the risk of surgery, whereas baseline immunomodulators (HR 0.68, 95% CI, 0.47–0.99; $P = 0.045$) and being a nonsmoker (HR 0.47; 95% CI, 0.29–0.77; $P = 0.003$) reduced this risk (Figures 2b and 3 and see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C843). Regarding vedolizumab, patients with ileocolonic disease and exposed to α2 at least 2 previous biologics also showed an increased risk of surgery. There were no factors associated with the risk of surgery in those patients receiving ustekinumab, probably due to the small number of patients and their characteristics.

Long-term clinical effectiveness

The clinical effectiveness of each drug on the penetrating complication is summarized in Table 3. For this purpose, we included data from 603 patients (79%), with data available from cross-sectional imaging follow-up examinations. A reduction in the number of fistulous tracts or fistula closure was observed in 234 patients (31%), whereas 11% of cases demonstrated new fistula tracts or worsening of those already present at baseline. In 24% of patients (n = 182), the fistulous tracts were closed after a median of 15 months (IQR, 7–25 months) of biologic therapy, with no differences between the different drugs (log-rank, $P = 0.54$ and $P = 0.58$, for anti-TNF vs vedolizumab or ustekinumab, respectively) (Figure 4).

In the multivariable analysis on the whole cohort, the probability of achieving fistula closure was higher in those with a lower number of fistulous tracts (HR 1.72; 95% CI, 1.09–2.7; $P = 0.02$), abscess at baseline (HR 1.79; 95% CI, 1.05–3.05; $P = 0.03$), older (HR 1.02; 95% CI, 1.01–10.4; $P = 0.004$), and nonsmokers (HR 2.09; 95% CI, 1.14–3.86; $P = 0.02$), whereas it was lower in female patients (HR 0.56; 95%, 0.35–0.91; $P = 0.02$) and in colonic disease (HR 0.51; 95% CI, 0.33–0.80; $P = 0.003$). In anti-TNF treated patients, the same figures were observed regarding abscesses, disease extension, age, sex, and smoking habits.

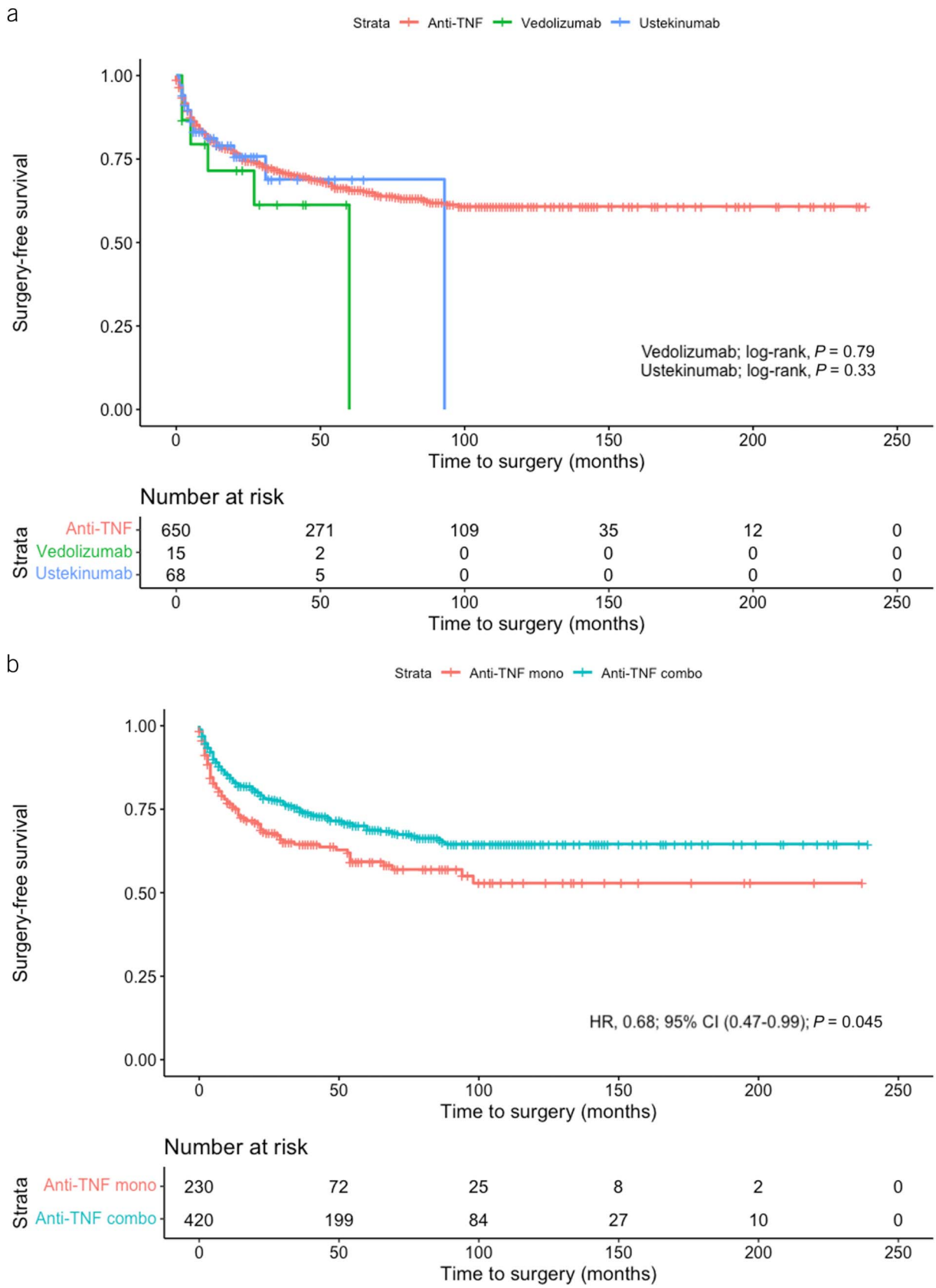

Figure 2. Kaplan-Meier survival curves of surgery-free survival according to the type of biologic agent (**a**) and combination therapy in anti–TNF-treated patients (**b**). TNF, tumor necrosis factor.

Table 3. Main outcomes observed during follow-up in each treatment group

Outcome	All (N = 760)	Anti-TNF (N = 673)	Infliximab (N = 405)	Adalimumab (N = 268)	Ustekinumab (N = 69)	Vedolizumab (N = 18)
Follow-up, mo, median (IQR)	56 (26–102)	65 (32–108)	69 (36–112)	62 (26–103)	18 (8–28)	39 (16–46)
Surgery, n (%)	240 (32)	217 (32)	137 (34)	80 (30)	16 (23)	7 (39)
Secondary aims, n (%)						
Increased no. of fistulous tracts	82 (11)	77 (11)	41 (10)	33 (12)	6 (9)	2 (11)
Reduction in the no. of fistulous tracts	234 (31)	214 (32)	127 (31)	87 (32)	16 (23)	4 (22)
Fistula closure	182 (24)	168 (25)	95 (23)	73 (27)	12 (17)	2 (11)
New abscess	92 (12)	81 (12)	49 (12)	32 (12)	8 (12)	3 (17)
Percutaneous drainage[a]	37 (40)	34 (42)	19 (39)	15 (47)	2 (25)	1 (33)

IQR, interquartile range; TNF, tumor necrosis factor.
[a]Among patients with abscess.

Regarding drug persistence, treatment with anti-TNF was maintained for a median of 15 months (IQR, 4–36 months), whereas vedolizumab and ustekinumab were used for a median of 11.5 months (IQR, 2–27 months) and 3 months (IQR, 2.5–6.3 months), respectively (HR 1.99; 95% CI, 0.82–4.83; $P = 0.13$, and HR 1.83; 95% CI, 1.07–3.13; $P = 0.03$, for vedolizumab and ustekinumab, respectively; Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C842). Following drug withdrawal, patients under anti-TNF (excluding those undergoing surgery) required subsequent therapy with another anti-TNF agent (80%), and in a lower proportion ustekinumab (15%) or vedolizumab (5%). Among those receiving ustekinumab or vedolizumab who required a new line of biological therapy, all of them received anti-TNF.

A new intra-abdominal abscess developed in 92 patients after a median of 5 months (IQR, 2–26 months), and 29% required percutaneous drainage. In most patients (88%), this was the first reported abscess, whereas 12% occurred in patients with an abscess already at baseline. Patients with an abscess at baseline showed a higher risk of recurrent abscess during follow-up (HR 2.04; 95% CI, 1.12–3.71; $P = 0.03$). The rate of developing new abscess during follow-up according to the type of biological therapy was 12% for anti-TNF and vedolizumab and 18% among ustekinumab-treated patients (Cox regression, $P = 0.89$ and $P = 0.96$ for ustekinumab and vedolizumab compared with anti-TNF, respectively).

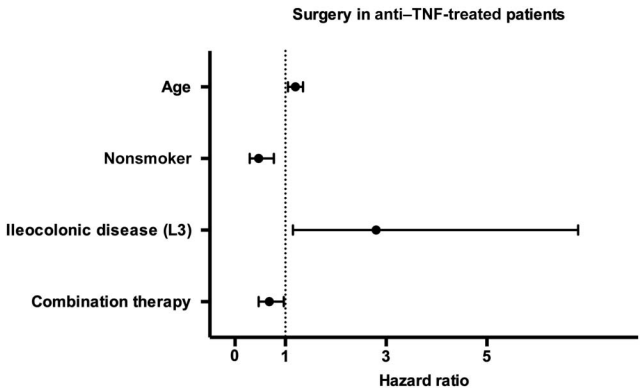

Figure 3. Forest plot of the predictive factors associated with the risk of surgery in anti–TNF-treated patients. TNF, tumor necrosis factor.

Safety

A total of 74 patients reported at least 1 adverse event (9.3%). The most frequent adverse events were infusion reactions (n = 30, 4%), followed by infections (n = 14, 2%) and psoriasiform skin lesions (n = 10, 1.3%). The rate of adverse events was higher with infliximab compared with adalimumab, vedolizumab, and ustekinumab (13%, 8%, 0%, and 0%, respectively; $P = 0.001$). Most of these events led to the discontinuation of the treatment (81%). One patient with entero-colic fistula receiving adalimumab treatment in combination with thiopurines was diagnosed of gastric adenocarcinoma with peritoneal carcinomatosis after 37 months of treatment. There was no additional diagnosis of fistula-related dysplasia or cancer during follow-up.

DISCUSSION

In this nationwide and multicentric cohort based on the ENEIDA registry, the largest to date, we observed that TNF antagonists, vedolizumab, and ustekinumab are effective therapies in a significant proportion of patients with CD complicated with internal fistulae. In this context, the surgery rate is 32% after a median follow-up of almost 5 years. We did not observe differences in the main outcomes between drug classes, but larger studies with the more recently available biologics should confirm our data. Relevant predictive factors associated with worse outcomes were age, ileocolonic disease, entero-urinary fistulas, and distal intestinal strictures. In addition, combination therapy with immunomodulators showed a beneficial effect in reducing the risk of surgery, and patients with a lower number of fistulous tracts also had a higher probability of resolution of these complications.

Although the natural history of CD shows that the rate of development of stricturing and penetrating disease-related complications increases every year since the moment of diagnosis (3,14), the role of medical therapy with immunomodulators or biologics on the natural history of the disease is still uncertain (15). Combination therapy with immunomodulators and biologics has demonstrated some clear benefits in patients with uncomplicated (purely inflammatory) disease behavior. This might be expected through an increase on through levels of the biologic or by a synergistic effect, that would lead to a better control of the disease (16). Whether these results might be obtained in penetrating disease is still to be demonstrated, and the chronic and potentially irreversible nature of these lesions could play against it (7,17). Nevertheless, no

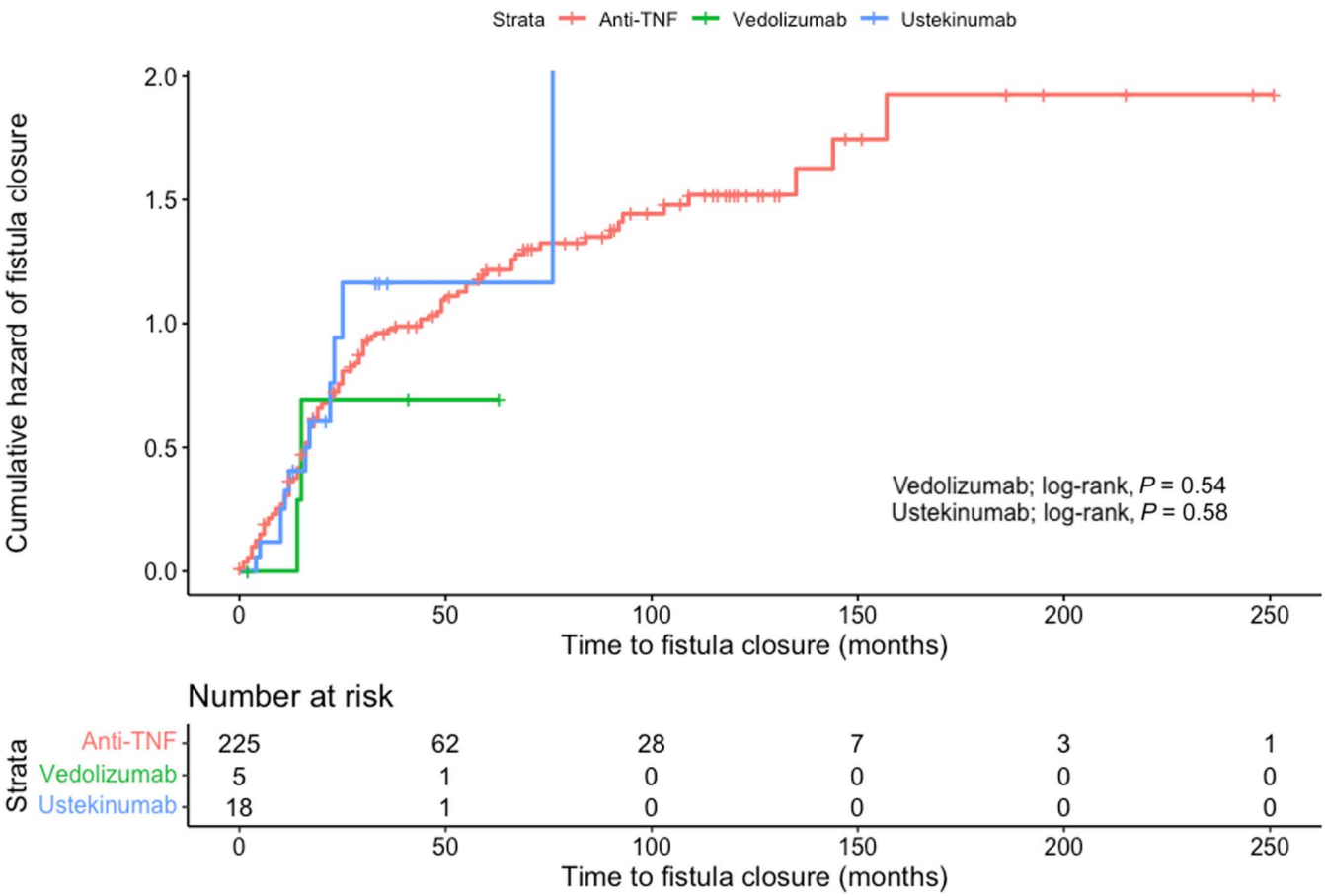

Figure 4. Kaplan-Meier survival curves showing the cumulative hazard of fistula closure according to the type of biologic agent. TNF, tumor necrosis factor.

randomized placebo-controlled trial has directly evaluated the efficacy of biologic agents when stricturing or penetrating disease has already developed (6). In addition, surgical management should be also discussed with these patients, including aspects such as the risk of postoperative recurrence, the need for prophylactic therapy, and even further surgical interventions (18).

Previous studies evaluating different types of fistulas and outcomes showed that anti-TNF agents may be effective in this setting (6,18), although this has been mostly in small case series and only in the short term (8,19–23). In a cohort of 93 patients with penetrating disease (77% entero-enteric or entero-colonic, 17% entero-vesical, and 5% entero-vaginal), 27% of patients achieved fistula closure after 5 years of follow-up, and 47% required surgery (10). Notably, 11% developed abdominal abscesses during treatment, requiring surgery in most of them. The efficacy of medical treatment in entero-urinary fistulas has been recently evaluated (9). Among 33 cases who were treated with anti-TNF agents, 45% achieved remission, defined as the absence of symptoms and radiological confirmation of the closure of the fistula. A recent retrospective and observational study conducted in France evaluated the efficacy of anti-TNF agents in 156 patients with internal penetrating disease (11). After 1, 2, and 5 years of follow-up, 83%, 64%, and 51% of patients remained free of surgery. Moreover, these authors observed that the proportion of patients achieving fistula closure increased progressively during treatment (15%, 32%, and 44%, respectively). In our cohort, we observed that 31% of the fistula tracts improved during anti-TNF treatment and, interestingly, that the closure of the fistula could be demonstrated in up to one-fourth of the patients. However, it must be stressed that in our results, fistula closure was more frequently observed during the first 2 years of therapy. This finding suggests that patients under these conditions may avoid surgery in the long term, but healing of the fistula is rarely observed after 2 years of treatment.

Evidence on the best treatment strategy for fistulizing CD is limited, and therefore, data on predictive factors of response are lacking (6). Serum albumin and C-reactive protein concentrations, presence of an abscess, or bowel strictures have been associated with subsequent need for surgery (11). We were able to identify additional predictors of failure to biologic treatment, including age, ileocolonic disease, entero-urinary fistulas, and distal strictures. Although we observed that age, sex, disease extension, smoking habits, the number of fistulous tracts, and the presence of an abscess were associated with closure, Bouguen et al (11) found that sex, concomitant bowel strictures, hemoglobin, and albumin concentrations improved the likelihood of healing intra-abdominal fistulas. Kobayashi et al (10) described that patients with higher clinical activity (as measured by the Crohn's Disease Activity Index) and in whom more time had elapsed from diagnosis to initiation of treatment had an increased risk of surgery, whereas the number of fistulas was the only one associated with the closure of fistulas. Therefore, it seems that patients with less extensive disease, a lower number of fistulas, and a reduced inflammatory burden lead to improved outcomes. In contrast, patients with more complicated lesions including an increased number of fistulous tracts or additional complications like abscess or distal strictures have a higher probability of undergoing surgery.

Additional factors like age and sex seem to have an important role in this context. Notably, our results show that age is associated with both fistula closure and surgery, and this might be due to the different disease characteristics and management across different age groups (24). It is possible that elderly patients with complicated CD can benefit from biological therapies, but the threshold for undergoing surgery might be lower than other age subgroups once they have an inadequate response to medical therapy.

Evidence with vedolizumab or ustekinumab for internal fistulizing disease is also limited (6). In the pivotal trials of ustekinumab UNITI-1 and -2, 14% and 10% of patients had a history of an abdominal abscess, respectively (25). In the GEMINI 2 trial that assessed the efficacy of vedolizumab in CD, 37% of patients had a fistulizing disease behavior (26). However, no clear data on the efficacy of any of both drugs in these patients are available, and, in addition, it is not stated whether penetrating complications were still present at the time of patient enrollment. A recent retrospective analysis compared the efficacy of vedolizumab and ustekinumab in 239 patients with CD in France (27). Among other predictive factors, the authors observed that after anti-TNF failure, ustekinumab showed a higher efficacy in fistulizing disease compared with vedolizumab. We did not find statistically significant differences in the rates of surgery or fistula closure across the different biologic agents, especially with anti-TNF, but the number of patients included in the ustekinumab and vedolizumab cohorts requires a more detailed evaluation in larger studies. Furthermore, concomitant therapy with immunomodulators was associated with a beneficial effect in terms of reducing probability of surgery, irrespectively of the biological agent. Whether this is due to an improve on through levels still remains unclear. Nevertheless, this finding suggests that immunosuppressants may add a synergistic effect even in patients with significant bowel damage, and they could benefit from a more aggressive medical treatment, although the optimal strategy remains to be completely elucidated.

Our study has some limitations that should be considered. The heterogeneous follow-up may have included some bias in our findings, especially regarding the evaluation of the course of the fistula tracts. This is expected to be more pronounced in the evaluation of fistula improvement or healing, as patients with a more favorable course would probably undergo cross-sectional examinations less frequently compared with those with persistent symptoms. We also lack comparable evaluations of disease activity scores in our cohort, which also limits our capacity of evaluating treatment response apart from fistula-related outcomes. Another limitation is the lack of data about dose or interval adjustments of the biologic, and this also includes detailed information about trough levels and therapeutic drug monitoring in this setting. Although it should not affect our findings and it reflects the real-world experience in this setting, providing detailed data on dosing and, particularly, through levels or additional biomarkers (e.g., fecal calprotectin) would bring interesting information about the best treatment strategies. Though, the nationwide and multicentric assessment from a prospectively maintained database including a large number of patients, using robust end points like surgery should be considered as the main strengths of the current study.

In conclusion, data from this large prospectively maintained cohort have shown that biologic therapy is beneficial in a significant proportion of patients with CD complicated with intestinal penetrating lesions. Around one-third of them can demonstrate an improvement of the fistula tracts, showing fistula closure in one-fourth of patients. However, one-third of these patients have refractory disease, and they will be candidates for surgical treatment. Thus, our results support the efficacy of biologics in this setting in patients with complicated CD, where a significant proportion of them can achieve long-term disease control.

CONFLICTS OF INTEREST

Guarantor of the article: Iago Rodríguez-Lago, MD, PhD.

Specific author contributions: I.R.-L. and M.B.-d.A.: conceived the study and its design, analyzed and interpreted the data, and drafted the manuscript. All authors: compiled the clinical information. J.L.C., E.D., and M.B.-d.A.: revised the manuscript for important intellectual content. All authors have significantly contributed and accepted the final version of the manuscript.

Financial support: The ENEIDA registry is supported by Biogen, Pfizer, and Takeda. None of them were involved in the study design, data analysis, interpretation of the results, or drafting the manuscript. I.R.-L. is supported by a research grant from Gobierno Vasco—Eusko Jaurlaritza (Grant No. 2020222004).

Potential competing interests: M.B.-d.A. has received financial support for traveling and educational activities from or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern, Janssen, Fresenius Kabi, Biogen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma, Adacyte, and Tillotts Pharma. A.F.-C. has served as a speaker or has received education funding from Dr. Falk Pharma, Janssen, Takeda, Chiesi, and Pfizer. F.M. has served as a speaker or has received research or education funding from MSD, AbbVie, Takeda, Janssen, Ferring, Pfizer, Chiesi, Galapagos, Faes Pharma, Kern Pharma, and Dr. Falk Pharma. R.F.-I. has served as a speaker for or has received research funding from Takeda, MSD, AbbVie, Janssen, Palex, Shire Pharmaceuticals, Tillotts Pharma, Dr. Falk Pharma, Chiesi, Otsuka Pharmaceutical, and Casen Recordati. R.d.F. has served as a speaker or has received research funding from MSD, AbbVie, Takeda, Janssen, and Kern Pharma. I.G.-P. has received speaker fees from Tillots Pharma, Amgen, Pfizer, and Kern Pharma. E.I. has received financial support for educational activities and research and scientific support from AbbVie, MSD, Pfizer, Takeda, Janssen, Ferring, and Dr. Falk Pharma. M.J.C. has received research or education funding from Pfizer, Takeda, Janssen, MSD, Ferring, AbbVie, Biogen, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, and Norgine. X.C. has received grants for research from Abbott, MSD, and Vifor; fees for advisory boards from Abbott, MSD, Takeda, Pfizer, Janssen, and Vifor; and lectures fees from Abbott, MSD, Janssen, Pfizer, Takeda, Shire Pharmaceuticals, and Allergan. R.V.L. has served as a scientific advisor or received support for research and/or training activities from AbbVie, Janssen, MSD, Pfizer, Faes Farma, Ferring, Shire, and Takeda. N.M. has received support for attending meetings and speaker fees and consulting fees from AbbVie, Janssen, Takeda, Ferring, Chiesi, Dr. Falk Pharma, and Tillotts Pharma. M.F.G.-S. has received research grants from AbbVie, Janssen, and Takeda and has received speaker fees from MSD, Takeda, and Janssen. C.R. has served as a speaker or has received research or education funding or advisory fees from AbbVie, Janssen, MSD, Pfizer, Galápagos, Takeda, and Tillotts Pharma. M.P. has served as a speaker or has received research or education funding from Takeda, AbbVie, and Janssen. P.A. has served as a speaker, consultant, or advisory member for or has received research funding from MSD, AbbVie, Takeda, Janssen, Gebro Pharma, and Tillotts Pharma. D.C. has received research grants from AbbVie, Janssen, and MSD; has served on the advisory board of AbbVie, Amgen, Celltrion, Janssen,

MSD, Pfizer, and Takeda; and has served as a speaker for AbbVie, Dr. Falk, Janssen, MSD, Pfizer, and Takeda. F.M. has served on the advisory board of Janssen, AbbVie, and Takeda and has received educational grants from Janssen, Takeda, AbbVie, Tillotts Pharma, Pfizer, and Dr. Falk. REMD has received educational grants from Tillotts Pharma and Janssen. E.R. has served as a speaker, consultant, or advisory member for or has received research funding from MSD, AbbVie, Takeda, Janssen, Galapagos, Fresenius Kabi, Pfizer, Amgen, Kern Pharma, and Ferring. C.G.-M. has received financial support for educational activities from AbbVie, MSD, Pfizer, Takeda, Janssen, Ferring, Norgine, and Kern Pharma. F.B. has served as a speaker, consultant, or advisory member for or has received research funding from MSD, AbbVie, Takeda, Janssen, Pfizer, Biogen, Amgen, Galápagos, Ferring, Faes Farma, Tillotts Pharma, Chiesi, and Vifor Pharma. J.P.G. has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine, and Vifor Pharma. M.I. has received financial support for traveling and educational activities from or has served as an advisory board member for MSD, Takeda, Janssen, Chiesi, Otsuka Pharmaceutical, and Adacyte. E.D. has served as a speaker or has received research or education funding or advisory fees from AbbVie, Adacyte Therapeutics, Gilead, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Shire Pharmaceuticals, Takeda, Tillotts Pharma, and Thermofisher. I.R.-L. has received financial support for traveling and educational activities from or has served as an advisory board member for MSD, Pfizer, AbbVie, Takeda, Janssen, Tillotts Pharma, Roche, Celltrion, Shire Pharmaceuticals, Galapagos, Ferring, Dr. Falk Pharma, Otsuka Pharmaceutical, and Adacyte. The remaining authors declare no conflicts of interest related to this manuscript.

Study Highlights

WHAT IS KNOWN

- ✓ Up to 8% of patients with Crohn's disease demonstrate intra-abdominal penetrating complications at diagnosis, and this proportion progressively increases over time.
- ✓ Patients with this type of penetrating phenotype are at higher risk of internal septic complications that often require percutaneous drainage or even surgery.
- ✓ Despite the availability of biologics agents and immunosuppressive therapies, the evidence on their effectiveness in this context is still limited.

WHAT IS NEW HERE

- ✓ Up to 68% of patients receiving biological therapy are surgery-free after a median follow-up of almost 5 years, and no differences are observed between drugs.
- ✓ Older patients, ileocolonic disease, entero-urinary fistulas, and distal intestinal strictures are associated with a higher risk of surgery, whereas combination therapy with immunomodulators and not smoking showed a beneficial effect in reducing this risk.
- ✓ Approximately one-third (31%) of patients show a decrease in the number of fistulous tracts or even fistula closure.

REFERENCES

1. Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. J Crohns Colitis 2017;11(1):3–25.
2. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut 2006;55(6):749–53.
3. Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: An Epi-IBD study. Gut 2019;68(3):423–33.
4. Schwartz DA, Loftus EV Jr., Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122(4):875–80.
5. Thia KT, Sandborn WJ, Harmsen WS, et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology 2010;139(4):1147–55.
6. Tjandra D, Garg M, Behrenbruch C, et al. Review article: Investigation and management of internal fistulae in Crohn's disease. Aliment Pharmacol Ther 2021;53(10):1064–79.
7. Hirten RP, Shah S, Sachar DB, et al. The management of intestinal penetrating Crohn's disease. Inflamm Bowel Dis 2018;24(4):752–65.
8. Poritz LS, Rowe WA, Koltun WA. Remicade does not abolish the need for surgery in fistulizing Crohn's disease. Dis Colon Rectum 2002;45(6):771–5.
9. Taxonera C, Barreiro-de-Acosta M, Bastida G, et al. Outcomes of medical and surgical therapy for entero-urinary fistulas in Crohn's disease. J Crohns Colitis 2016;10(6):657–62.
10. Kobayashi T, Hishida A, Tanaka H, et al. Real-world experience of anti-tumor necrosis factor therapy for internal fistulas in Crohn's disease: A retrospective multicenter cohort study. Inflamm Bowel Dis 2017;23(12):2245–51.
11. Bouguen G, Huguet A, Amiot A, et al. Efficacy and safety of tumor necrosis factor antagonists in treatment of internal fistulizing Crohn's disease. Clin Gastroenterol Hepatol 2020;18(3):628–36.
12. Zabana Y, Panes J, Nos P, et al. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: Design, monitoring and functions. Gastroenterol Hepatol 2020;43(9):551–8.
13. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
14. El Ouali S, Click B, Holubar SD, et al. Natural history, diagnosis and treatment approach to fibrostenosing Crohn's disease. United European Gastroenterol J 2020;8(3):263–70.
15. Rodriguez-Lago I, Gisbert JP. The role of immunomodulators and biologics in the medical management of stricturing Crohn's disease. J Crohns Colitis 2020;14(4):557–66.
16. Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: A post hoc analysis. Clin Gastroenterol Hepatol 2019;17(8):1525–32 e1.
17. Ananthakrishnan AN, Sakuraba A, Barnes EL, et al. The benefit of combination therapy depends on disease phenotype and duration in Crohn's disease. Aliment Pharmacol Ther 2017;46(2):162–8.
18. Vuyyuru SK, Desai D, Kedia S, et al. Long-term outcomes of anti-tumor necrosis factor therapy and surgery in nonperianal fistulizing Crohn's disease. JGH Open 2021;5(4):420–7.
19. Miehsler W, Reinisch W, Kazemi-Shirazi L, et al. Infliximab: Lack of efficacy on perforating complications in Crohn's disease. Inflamm Bowel Dis 2004;10(1):36–40.
20. Ricart E, Panaccione R, Loftus EV, et al. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: The first 100 patients. Am J Gastroenterol 2001;96(3):722–9.
21. Ardizzone S, Maconi G, Colombo E, et al. Perianal fistulae following infliximab treatment: Clinical and endosonographic outcome. Inflamm Bowel Dis 2004;10(2):91–6.
22. Schroder O, Blumenstein I, Schulte-Bockholt A, et al. Combining infliximab and methotrexate in fistulizing Crohn's disease resistant or intolerant to azathioprine. Aliment Pharmacol Ther 2004;19(3):295–301.
23. Miheller P, Lakatos PL, Horvath G, et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe–a Hungarian nationwide observational study. BMC Gastroenterol 2009;9(1):66.

24. Mañosa M, Calafat M, de Francisco R, et al. Phenotype and natural history of elderly onset inflammatory bowel disease: A multicentre, case-control study. Aliment Pharmacol Ther 2018;47(5):605–14.
25. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2016;375(20): 1946–60.
26. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369(8):711–21.
27. Alric H, Amiot A, Kirchgesner J, et al. The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor. Aliment Pharmacol Ther 2020; 51(10):948–57.