Effectiveness and Safety of the Sequential Use of a Second and Third Anti-TNF Agent in Patients With Inflammatory Bowel Disease: Results From the Eneida Registry

María José Casanova, MD, PhD,[*] María Chaparro, MD, PhD,[*] Miguel Mínguez, MD, PhD,[†] Elena Ricart, MD, PhD,[‡] Carlos Taxonera, MD, PhD,[§] Santiago García-López, MD, PhD,[¶] Jordi Guardiola, MD,[‖] Antonio López-San Román, MD, PhD,[**] Eva Iglesias, MD,[††] Belén Beltrán, MD, PhD,[‡‡] Beatriz Sicilia, MD, PhD,[§§] María Isabel Vera, MD, PhD,[¶¶] Joaquín Hinojosa, MD, PhD,[‖‖] Sabino Riestra, MD, PhD,[***] Eugeni Domènech, MD, PhD,[†††] Xavier Calvet, MD, PhD,[†††] José Lázaro Pérez-Calle, MD,[§§§] María Dolores Martín-Arranz, MD, PhD,[¶¶¶] Xavier Aldeguer, MD, PhD,[‖‖‖] Montserrat Rivero, MD, PhD,[****] David Monfort, MD,[††††] Jesús Barrio, MD, PhD,[‡‡‡‡] María Esteve, MD, PhD,[§§§§] Lucía Márquez, MD, PhD,[¶¶¶¶] Rufo Lorente, MD, PhD,[‖‖‖‖] Esther García-Planella, MD,[*****] Luisa de Castro, MD, PhD,[†††††] Fernando Bermejo, MD, PhD,[‡‡‡‡‡] Olga Merino, MD,[§§§§§] Antonio Rodríguez-Pérez, MD,[¶¶¶¶¶] Pilar Martínez-Montiel, MD, PhD,[‖‖‖‖‖] Manuel Van Domselaar, MD,[******] Guillermo Alcaín, MD,[††††††] Manuel Domínguez-Cajal, MD,[‡‡‡‡‡‡] Carmen Muñoz, MD,[§§§§§§] Fernando Gomollón, MD, PhD,[¶¶¶¶¶¶] Luis Fernández-Salazar, MD, PhD,[‖‖‖‖‖‖] Mariana Fe García-Sepulcre, MD, PhD,[*******] Iago Rodríguez-Lago, MD,[†††††††] Ana Gutiérrez, MD, PhD,[‡‡‡‡‡‡‡] Federico Argüelles-Arias, MD, PhD,[§§§§§§§] Cristina Rodriguez, MD, PhD,[¶¶¶¶¶¶¶] Gloria Esther Rodríguez, MD,[‖‖‖‖‖‖‖] Luis Bujanda, MD, PhD,[********] Jordina Llaó, MD, PhD,[††††††††] Pilar Varela, MD,[‡‡‡‡‡‡‡‡] Laura Ramos, MD,[§§§§§§§§] José María Huguet, MD, PhD,[¶¶¶¶¶¶¶¶] Pedro Almela, MD,[‖‖‖‖‖‖‖‖] Patricia Romero, MD,[*********] Mercè Navarro-Llavat, MD,[†††††††††] Águeda Abad, MD,[‡‡‡‡‡‡‡‡‡] Patricia Ramírez-de la Piscina, MD,[§§§§§§§§§] Alfredo J. Lucendo, MD, PhD,[¶¶¶¶¶¶¶¶¶] Eva Sesé, MD,[‖‖‖‖‖‖‖‖‖] Rosa Eva Madrigal, MD,[**********] Mara Charro, MD,[††††††††††] Antonio García-Herola, MD,[‡‡‡‡‡‡‡‡‡‡] Ramón Pajares, MD, PhD,[§§§§§§§§§§] Sam Khorrami, MD,[¶¶¶¶¶¶¶¶¶¶] and Javier P. Gisbert, MD, PhD[*]

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From the Gastroenterology Departments at: [*]Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid, and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; [†]Hospital Clínico Valencia, Valencia, Spain; [‡]Hospital Clínic i Provincial, CIBEREHD and IDIBAPS, Barcelona, Spain; [§]Hospital Universitario Clínico San Carlos, Madrid, Spain; [¶]Hospital Universitario Miguel Servet, and CIBEREHD, Zaragoza, Spain; [‖]Hospital Universitario de Bellvitge, Barcelona, Spain; [**]Hospital Universitario Ramón y Cajal, Madrid, Spain; [††]Hospital Universitario Reina Sofía, Córdoba, Spain; [‡‡]Hospital Universitario La Fe, and CIBEREHD, Valencia, Spain; [§§]Hospital Universitario de Burgos, Burgos, Spain; [¶¶]Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [‖‖]Hospital de Manises, Valencia, Spain; [***]Hospital Universitario Central de Asturias, Oviedo, Spain; [†††]Hospital Universitario Germans Trias i Pujol, and CIBEREHD, Badalona, Spain; [†††]Hospital de Sabadell, Corporació Sanitària Universitària Parc Taulí, and CIBEREHD, Sabadell, Spain; [§§§]Hospital Universitario Fundación de Alcorcón, Madrid, Spain; [¶¶¶]Hospital Universitario La Paz, and Instituto de Investigación de La Paz (IdiPaz), Madrid, Spain; [‖‖‖]Hospital Universitari de Girona Dr. Josep Trueta, Girona, Spain; [****]Hospital Universitario Marqués de Valdecilla, and IDIVAL, Santander, Spain; [††††]Consorci Sanitari Terrassa, Terrassa, Spain; [‡‡‡‡]Hospital Universitario Río Hortega, Valladolid, Spain; [§§§§]Hospital Universitario Mútua Terrassa, and CIBEREHD, Terrassa, Spain; [¶¶¶¶]Hospital del Mar, Barcelona, Spain; [‖‖‖‖]Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; [*****]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [†††††]Complejo Hospitalario Universitario de Vigo, Vigo, Spain; [‡‡‡‡‡]Hospital Universitario de Fuenlabrada and Instituto de Investigación de La Paz (IdiPaz), Madrid, Spain; [§§§§§]Hospital Universitario Cruces, Barakaldo, Spain; [¶¶¶¶¶]Hospital Clínico Universitario de Salamanca, Salamanca; [‖‖‖‖‖]Hospital Universitario Doce de Octubre, Madrid, Spain; [******]Hospital de Torrejón, Madrid; [††††††]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [‡‡‡‡‡‡]Hospital General San Jorge, Huesca, Spain; [§§§§§§]Hospital de Basurto, Bilbao, Spain; [¶¶¶¶¶¶]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [‖‖‖‖‖‖]Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [*******]Hospital General Universitario de Elche, Alicante, Spain; [†††††††]Hospital de Galdakao-Usansolo, Galdakao, Spain; [‡‡‡‡‡‡‡]Hospital General Universitario de Alicante, and CIBEREHD, Alicante, Spain; [§§§§§§§]Hospital Universitario Virgen Macarena, Sevilla, Spain; [¶¶¶¶¶¶¶]Complejo Hospitalario de Navarra, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain; [‖‖‖‖‖‖‖]Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; [********]Hospital Universitario de Donostia, Instituto Biodonostia, Universidad del País Vasco (UPV/EHU), and CIBEREHD, Donostia, Spain; [††††††††]ALTHAIA Xarxa Assistencial Universitària de Manresa, Manresa, Spain; [‡‡‡‡‡‡‡‡]Hospital Universitario de Cabueñes, Gijón, Spain; [§§§§§§§§]Hospital Universitario de Canarias, La Laguna, Spain; [¶¶¶¶¶¶¶¶]Consorcio Hospital General Universitario de Valencia, Valencia, Spain; [‖‖‖‖‖‖‖‖]Hospital General Universitario de Castellón, Castellón, Spain; [*********]Hospital General Universitario de Santa Lucía, Murcia, Spain; [†††††††††]Hospital de Sant Joan Despí Moisès Broggi, Sant Joan Despí, Spain; [‡‡‡‡‡‡‡‡‡]Hospital de Viladecans, Barcelona, Spain; [§§§§§§§§§]Hospital Universitario de Álava, Vitoria, Spain; [¶¶¶¶¶¶¶¶¶]Hospital General de Tomelloso, Ciudad Real, Spain; [‖‖‖‖‖‖‖‖‖]Hospital Universitario Arnau de Vilanova, Lleida, Spain; [**********]Complejo Asistencial Universitario de Palencia, Palencia, Spain; [††††††††††]Hospital Royo Villanova, Zaragoza, Spain; [‡‡‡‡‡‡‡‡‡‡]Hospital Marina Baixa, Alicante, Spain; [§§§§§§§§§§]Hospital Universitario Infanta Sofía, Madrid, Spain; [¶¶¶¶¶¶¶¶¶¶]Hospital Universitario Son Espases, Palma de Mallorca, Spain

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Address correspondence to: Javier P. Gisbert, MD, Gastroenterology Unit, Hospital Universitario de La Princesa, Diego de León, 62. 28006 Madrid, Spain (javier.p.gisbert@gmail.com).

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Background: The effectiveness of the switch to another anti–tumor necrosis factor (anti-TNF) agent is not known. The aim of this study was to analyze the effectiveness and safety of treatment with a second and third anti-TNF drug after intolerance to or failure of a previous anti-TNF agent in inflammatory bowel disease (IBD) patients.

Methods: We included patients diagnosed with IBD from the ENEIDA registry who received another anti-TNF after intolerance to or failure of a prior anti-TNF agent.

Results: A total of 1122 patients were included. In the short term, remission was achieved in 55% of the patients with the second anti-TNF. The incidence of loss of response was 19% per patient-year with the second anti-TNF. Combination therapy (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.8–3; $P < 0.0001$) and ulcerative colitis vs Crohn's disease (HR, 1.6; 95% CI, 1.1–2.1; $P = 0.005$) were associated with a higher probability of loss of response. Fifteen percent of the patients had adverse events, and 10% had to discontinue the second anti-TNF. Of the 71 patients who received a third anti-TNF, 55% achieved remission. The incidence of loss of response was 22% per patient-year with a third anti-TNF. Adverse events occurred in 7 patients (11%), but only 1 stopped the drug.

Conclusions: Approximately half of the patients who received a second anti-TNF achieved remission; nevertheless, a significant proportion of them subsequently lost response. Combination therapy and type of IBD were associated with loss of response. Remission was achieved in almost 50% of patients who received a third anti-TNF; nevertheless, a significant proportion of them subsequently lost response.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, anti-TNF, switch

INTRODUCTION

Anti–tumor necrosis factor (anti-TNF) drugs are certainly effective in patients diagnosed with inflammatory bowel disease (IBD). Nevertheless, approximately 30% of IBD patients treated with anti-TNF agents are nonresponders to the therapy, and a significant proportion of those who respond experience intolerance or loss of response over time.[1] The use of a second anti-TNF is a common practice when a first has failed.[2] In this context, a significant number of patients will be treated with a second anti-TNF. Nevertheless, the clinical management of patients who experience loss of response to a first anti-TNF agent is done empirically. A recent meta-analysis found that the efficacy of a second anti-TNF drug in patients diagnosed with Crohn's disease (CD) was clearly dependent on the reason for switching treatment.[2] On the other hand, only few studies have evaluated the efficacy of a second anti-TNF in ulcerative colitis (UC) patients, and the remission rates reported are highly variable.[3–9] Moreover, a significant number of patients who have an initial response to a second anti-TNF finally lose the response or become intolerant to the drug.[10] Furthermore, the use of a third anti-TNF agent when the second has failed is not unusual; however, available data are scarce. In the last few years, new molecules have been incorporated into the therapeutic armamentarium for IBD patients. However, these treatments are not

effective in all patients. For this reason, it is important to get the most out of anti-TNF drugs.

The aims of our study were to evaluate the effectiveness and safety of the sequential use of a second and a third anti-TNF agent after intolerance to or failure of a previous anti-TNF drug, to identify the predictors of remission with a second anti-TNF, and to investigate which variables are associated with the risk of loss of response to a second anti-TNF.

METHODS

Study Population

The study included patients who had been diagnosed with CD or UC from the ENEIDA registry who received another anti-TNF after intolerance to or failure of a prior anti-TNF drug to achieve clinical remission. ENEIDA is a prospectively maintained registry of the Spanish Working Group in Crohn's disease and Ulcerative Colitis (GETECCU), which includes patients with IBD. The database prospectively records clinical characteristics of the patients and the use, effectiveness, and adverse events of immunomodulators and biologic therapy. Physicians from IBD centers that are registered in ENEIDA can voluntarily include the data of their patients in ENEIDA. At the time of data extraction, the registry contained 11,866 patients who were exposed to anti-TNF therapy. The ENEIDA registry was approved by research ethics committees in all participating centers. All co-authors had access to the study data and have reviewed and approved the final manuscript.

Patients were excluded from the study if the anti-TNF agent was initiated for treatment of extraintestinal manifestations of IBD or as a preventive therapy of postoperative recurrence in CD patients, if the time between the end of the previous anti-TNF and the onset of the second or third anti-TNF was longer than 6 months, and if the previous anti-TNF was stopped for other reasons than failure or intolerance (eg, elective decision, pregnancy, etc.).

Data Collection

The data collected included demographic data, age at diagnosis, smoking habit, duration of IBD, location, disease extent, disease behavior, perianal disease, extraintestinal manifestations, history of abdominal surgery due to IBD, concomitant therapy with immunomodulators, type of anti-TNF agent, indications for anti-TNF therapy, reasons for discontinuation of the anti-TNF, response to anti-TNF and the need for dose escalation, and the occurrence of adverse events.

Definitions of Study Variables

Primary failure

It was considered that the patient had a primary failure if she/he did not achieve remission after having received the induction doses of the anti-TNF (nonresponders and partial responders).

Secondary failure

It was considered that a patient had a secondary failure if she/he achieved remission with the anti-TNF agent and then lost effectiveness over time.

Intolerance to treatment

The patient was considered intolerant to the anti-TNF treatment if he/she had adverse events that led to withdrawal of the drug.

Sequential use of anti-TNF drugs

If the period of time between the end of the first or second anti-TNF drug (due to intolerance, primary failure, or secondary failure) and the onset of the next anti-TNF was less than 6 months.

Loss of efficacy

If the patient achieved remission with the anti-TNF agent and then had symptoms compatible with clinical activity together with radiographic, endoscopic, and/or biochemical evidence of disease activity that led to a dose escalation or to a switch to another anti-TNF.

Dose escalation

If the patient was treated with adalimumab (ADA), a reduction in the interval of administration was defined as a dose escalation. A decrease in the administration interval, an increase in the dose, or both was considered dose escalation in patients treated with infliximab (IFX).

Concomitant immunomodulators

Immunosuppressive treatment was considered concomitant with anti-TNF if the patient had been on immunomodulators (IMMs; eg, azathioprine, mercaptopurine, or methotrexate) after starting the anti-TNF therapy for a period of ≥6 months.

Smoking

Patients were categorized as having smoked or as never having smoked.

Clinical remission

A Harvey-Bradshaw index score ≤4 points was considered remission for luminal CD.[11] A partial Mayo score ≤2 points was considered remission for UC patients.[12]

Short-term effectiveness

It was defined as remission at week 12 (after induction doses).

Long-term effectiveness

It was defined as the proportion of patients who maintained clinical remission with the anti-TNF over time.

Statistical Analysis

In the descriptive analysis, we used the mean and standard deviation for quantitative variables if they were normally distributed. If they were not, we used the median and interquartile range (IQR). Ninety-five percent confidence intervals (95% CIs) and the percentage were provided for the categorical variables. The *t* test for independent samples was used to perform comparisons between means. The χ^2 test and the Fisher exact test were used to compare categorical variables if they were normally distributed. If they were not, the Wilcoxon rank-sum test was used. A P value <0.05 was considered statistically significant.

In the case of the second anti-TNF agent, the factors associated with short-term efficacy were studied with multivariate analyses (logistic regression). The variables that were statistically significant after performing a univariate analysis were included in the multivariate analysis. Moreover, those variables that could be relevant even if they were not statistically significant were also included.

In the patients who achieved remission in the short term with a second and or third anti-TNF agent, Kaplan-Meier curves were used to estimate the long-term maintenance of remission. The log-rank test was used to evaluate the impact of some variables on long-term remission. In the group of patients who achieved remission with the second anti-TNF therapy, predictive factors for loss of efficacy were identified using a Cox regression model. All the variables that reached statistical significance in the univariate analysis and those that were considered clinically relevant were included in the multivariate analysis. The dependent variable was the loss of efficacy to a given anti-TNF.

Ethical Considerations

The study was approved by the respective institutional ethics review boards and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

RESULTS

Study Population

We included 1122 IBD (CD or UC) patients who switched to a second anti-TNF after failure (primary or secondary failure) of or intolerance to a first anti-TNF drug and met the inclusion criteria. The main characteristics of the study population are summarized in Table 1.

The median duration of the first anti-TNF therapy before switching to a second anti-TNF (IQR) was 12 (4–26) months.

TABLE 1. Baseline Characteristics of the Patients

Variables	Total
Type of disease, No. (%)	1122 (100)
Crohn's disease	822 (73.3)
Ulcerative colitis	300 (26.7)
Male, No. (%)	563 (50.2)
Mean age at diagnosis (range), y	30 (5–79)
Median time from diagnosis to the start of anti-TNF therapy (IQR), mo	
First anti-TNF	44 (12–120)
Second anti-TNF	65 (28–141)
Third anti-TNF	76 (48–134)
Extra-intestinal manifestations, No. (%)	417 (37.2)
Smoking history, No. (%)	383 (34.1)
History of abdominal surgery, No. (%)	341 (56.9)
Type of first anti-TNF therapy, No. (%)	
Infliximab	752 (67)
Adalimumab	348 (31)
Certolizumab	1 (0.1)
Golimumab	21 (1.9)
Type of second anti-TNF therapy, No. (%)	
Infliximab	354 (31.6)
Adalimumab	728 (64.9)
Certolizumab	14 (1.2)
Golimumab	26 (2.3)
Type of third anti-TNF therapy, No. (%)	
Infliximab	3 (4.2)
Adalimumab	8 (11.3)
Certolizumab	36 (50.7)
Golimumab	24 (33.8)
Concomitant IMMs, No. (%)	
First anti-TNF	694 (62)
Second anti-TNF	370 (33)
Third anti-TNF	16 (22.5)
Reasons for the first anti-TNF discontinuation, No. (%)	
Nonresponse	124 (11.1)
Partial response	117 (10.4)
Loss of efficacy	573 (51.1)
Adverse events	308 (27.5)
Montreal location at Crohn's disease diagnosis, No. (%)	
L1 (ileal)	281 (34.2)
L2 (colonic)	155 (18.9)
L3 (ileocolonic)	385 (46.8)
L4 (upper gastrointestinal tract)	1 (0.1)
Montreal behavior at Crohn's disease diagnosis, No. (%)	
B1 (inflammatory)	441 (53.6)
B2 (stricturing)	199 (24.2)
B3 (penetrating)	182 (22.1)
Perianal disease, No. (%)	358 (43.7)
Ulcerative colitis extension, No. (%)	
Proctitis	15 (5)
Left-sided colitis	109 (36.3)
Extensive colitis	175 (58.3)
Unknown	1 (0.3)

Most of the patients (67%) had received IFX as a first anti-TNF agent. Most of the patients (65%) received ADA as a second anti-TNF. Approximately half of the patients (51%) who switched to a third anti-TNF received certolizumab.

Sixty-two percent of the patients received IMMs with the first anti-TNF, 33% of them continued this therapy after switching to a second anti-TNF drug, and 23% continued this therapy after switching to a third anti-TNF. The reasons for discontinuation of the first anti-TNF were secondary failure (51%), intolerance (27%), and primary failure (nonresponders and partial responders, 22%). In a subanalysis, the mean time from the IBD diagnosis until the start of the second anti-TNF was shorter in patients on combo therapy with the second anti-TNF than in those on anti-TNF monotherapy (85 months vs 102 months, $P = 0.003$). Similarly, the mean duration of disease until the start of the first anti-TNF was shorter in patients on combo therapy with the second anti-TNF (68 months vs 82 months, $P = 0.009$).

Second Anti-TNF: Short-term Effectiveness

After the start of the second anti-TNF drug, the median time of follow-up (IQR) was 14 (5–32) months. In the short term, 45% (500) of the patients achieved remission with the second anti-TNF agent. Patients who switched to a second anti-TNF due to intolerance to the first drug had higher remission rates than those who switched due to secondary failure (52% vs 42%, $P = 0.003$) or primary failure (52% vs 39%, $P = 0.003$). We did not find a difference between patients who switched due to primary failure vs secondary failure (39% vs 42%, $P = 0.5$). The remission rate in the short term was similar in CD patients (46%) in comparison with UC patients (41%, $P = 0.06$). Remission rates were similar among the sequences of the anti-TNF administration: adalimumab-infliximab or infliximab-adalimumab (48% vs 42%, $P = 0.07$).

In the multivariate analyses (Table 2), combo therapy (odds ratio [OR], 0.5; 95% CI, 0.4–0.8), withdrawal of the first anti-TNF due to primary failure (vs intolerance; OR, 0.6; 95% CI, 0.4–0.9), and withdrawal of the first anti-TNF due to secondary failure (vs intolerance; OR, 0.6; 95% CI, 0.5–0.9) were associated with a lower probability of achieving remission with the second anti-TNF. Sex, age at diagnosis, smoking history, type of IBD, extraintestinal manifestations, and duration of disease were not associated with the effectiveness of a second anti-TNF.

In a subanalysis to evaluate the variables associated with short-term remission in CD patients who switched to a second anti-TNF, none of these factors (plus the localization and phenotype of the disease, the presence of perianal disease, and previous surgery owing to IBD) was statistically significant.

Second Anti-TNF: Long-term Effectiveness

In the patients who achieved remission with the second anti-TNF, the median time of follow-up (IQR) was 19 (8–40) months. After achieving remission with the second anti-TNF, the cumulative incidence of loss of efficacy was 45% (95% CI, 41%–49%): 23% at 1 year, 38% at 2 years, 66% at 3 years, and 62% at 5 years after switching. The proportion of patients who remained in remission during follow-up is shown in Figure 1. The incidence of loss of efficacy in patients in remission with the second anti-TNF was 19% (95% CI, 17%–22%) per patient-year.

The univariate analyses showed that combo therapy (74% combo therapy vs 36% anti-TNF in monotherapy, $P < 0.0001$) and type of IBD (45% CD vs 57% UC, $P = 0.009$) were the only variables associated with the loss of efficacy to a second anti-TNF (Figs. 2 and 3). In the multivariate analysis, type of IBD (UC vs CD; hazard ratio [HR], 1.6; 95% CI, 1.1–2.1; $P = 0.005$) and combo therapy (HR, 2.4; 95% CI, 1.8–3; $P < 0.0001$) were associated with a higher probability of loss of efficacy. Sex, smoking history, age at diagnosis, duration of disease, extraintestinal manifestations, and reasons to withdraw the first anti-TNF were not associated with the loss of efficacy.

In CD patients, none of these variables (plus the presence of perianal disease, the localization and phenotype of disease, and previous abdominal surgery owing to IBD) had an impact on the loss of efficacy to a second anti-TNF agent.

TABLE 2. Multivariate Analysis of Factors Associated With the Probability of Achieving Remission With the Second Anti-TNF

Factors	OR	95% CI	*P* Value
Concomitant IMMs	0.5	0.4–0.7	<0.0001
To withdraw the first anti-TNF due to a primary failure (vs intolerance)	0.6	0.4–0.9	0.007
To withdraw the first anti-TNF due to secondary failure (vs intolerance)	0.6	0.5–0.9	0.003
Sex	0.84	0.7–1.1	0.1
Age at diagnosis	0.9	0.9–1	0.1
Smoking history	1.1	0.9–1.5	0.4
Type of IBD (UC vs CD)	0.9	0.7–1.3	0.5
Extraintestinal manifestations	0.9	0.7–1.2	0.5
Duration of disease	1	0.99–1.001	0.9

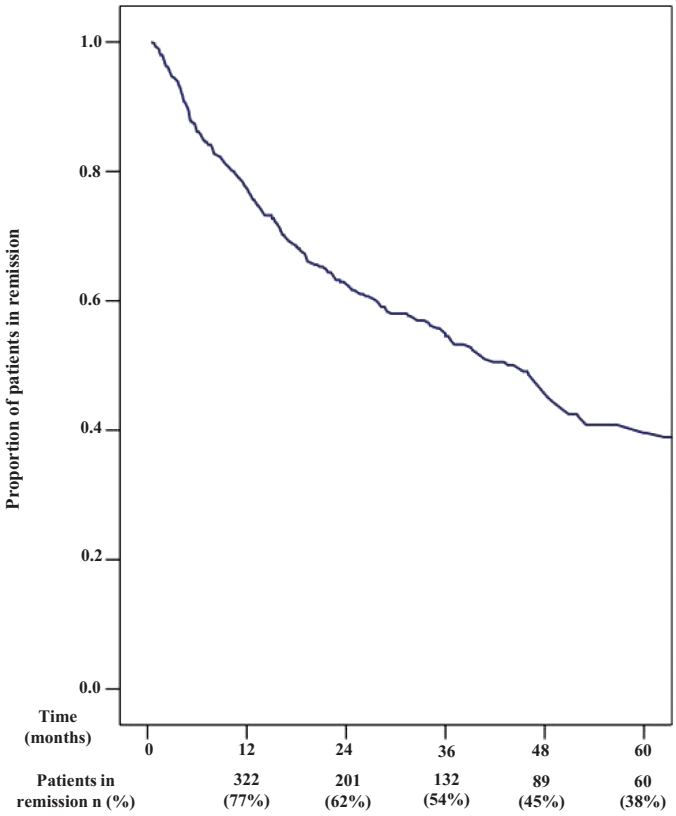

FIGURE 1. Kaplan-Meier curve of long-term remission after treatment with a second anti-TNF.

Second Anti-TNF: Dose Escalation

Of the 1122 patients who were treated with a second anti-TNF agent, 21% (230 patients) needed dose escalation of the drug. Of these, 42% achieved remission. The reasons for dose escalation were secondary failure (84%), partial response (14%), and nonresponse (2%). The rates of remission were, according to the reason for dose escalation, 40% for secondary failure, 57% for partial response, and 0% for nonresponders. Only 22% of the patients who achieved remission with the second anti-TNF needed to increase the anti-TNF dose during follow-up. The median time to dose escalation (IQR) was 15 (5–37) months. The median follow-up time after dose escalation (IQR) was 13 (6–26) months. After escalating the anti-TNF dose, 70% of the patients achieved remission again. At 1 year, the vast majority of these patients (89%) remained in remission.

Second Anti-TNF: Safety

Fifteen percent (95% CI, 13%–17%) of the patients had adverse events. Of these, 66% (95% CI, 59%–74%) required discontinuation of the drug. Therefore, 10% of all the patients treated with a second anti-TNF discontinued the drug because of adverse events. Infusion reactions and infections were the most frequent adverse events, as is shown in Table 3.

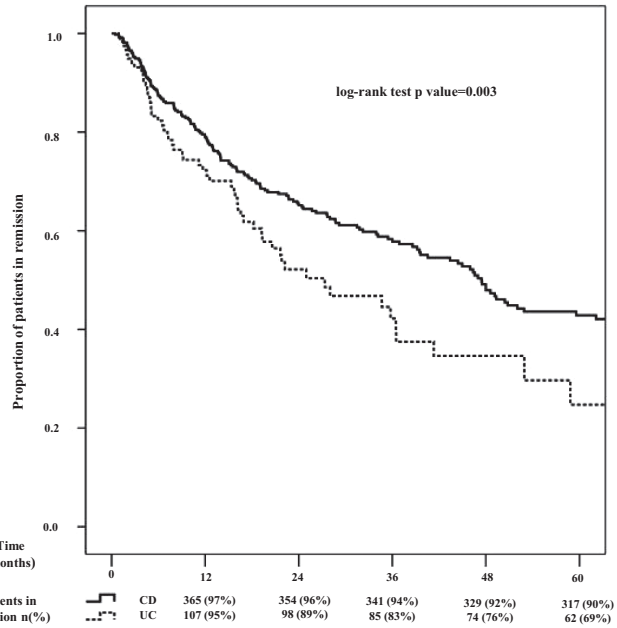

FIGURE 2. Kaplan-Meier analysis of long-term remission after treatment with a second anti-TNF in Crohn's disease vs ulcerative colitis patients.

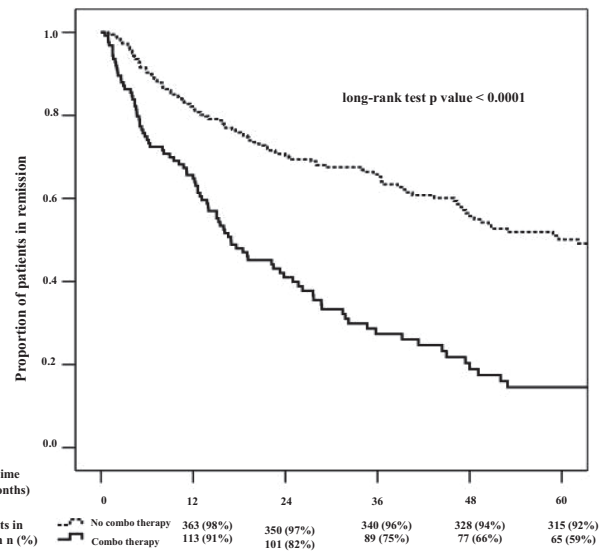

FIGURE 3. Kaplan-Meier analysis of long-term remission after treatment with a second anti-TNF in patients treated with immunomodulators vs untreated patients.

Third Anti-TNF

A third anti-TNF was started in 71 patients. Of these, 45% discontinued the second anti-TNF due to primary failure, 30% due to secondary failure, and 16% due to intolerance. Table 4 summarizes the characteristics of the patients. Most of the patients (51%) received certolizumab as a third anti-TNF. Twenty-three percent of patients (16) had received combo therapy.

Third Anti-TNF: Effectiveness

In the short term, 55% (95% CI, 43%–67%) of the patients achieved remission with the third anti-TNF. Of these, 16% were switched to the third agent due to intolerance of the second drug, 39% due to secondary failure, and 45% due to primary failure. The median follow-up time after switching to a third agent (IQR) was 9 (4–16) months. The incidence of loss of response was 22% (95% CI, 13%–34%) per patient-year. The cumulative incidence of loss of response was 38% (95% CI, 23%–55%): 18% at 1 year and 37% at 2 years of follow-up (Fig. 4). In the univariate analysis, none of the variables studied were associated with the probability of loss of efficacy (sex, age at diagnosis, type of IBD, reasons to withdraw the second anti-TNF, combo therapy, smoking history, and extraintestinal manifestations). The multivariate analysis could not be performed due to the small sample size (39 patients). A flowchart of the patients who switched to a second and a third anti-TNF is showed in Figure 5.

Seven patients (11%) had adverse events. Of these, 3 patients had infection (1 herpes, 1 bronchitis, and 1 perianal abscesses), 2 patients had psoriasis, 1 paresthesias in the lower limbs, and 1 delayed hypersensitivity reaction. Only 1 patient (the patient with perianal abscesses) discontinued the therapy due to the adverse event.

TABLE 3. Adverse Events With the Second Anti-TNF Drug

Adverse Event	No. (%)
Infusion reaction	45 (26.4)
Infections	45 (26.4)
Delayed hypersensitivity reaction	26 (15.3)
Toxicodermia	17 (10)
Drug-induced psoriasis	15 (8.8)
Drug-induced lupus	8 (4.7)
Headache	5 (3)
Malignancy	4 (2.4)
Thrombocytopenia	3 (1.8)
Anaphylaxis	1 (0.6)
Myelitis	1 (0.6)

TABLE 4. Baseline Characteristics of the Patients who Switched to a Third Anti-TNF

Variables	Total
Type of disease, No. (%)	71 (100)
Crohn's disease	45 (63.4)
Ulcerative colitis	26 (36.6)
Male, No. (%)	39 (54.9)
Mean age at diagnosis (range), y	32 (11–75)
Extra-intestinal manifestations, No. (%)	29 (40.8)
Smoking history, No. (%)	22 (34.9)
History of abdominal surgery, No. (%)	20 (28.2)
Reasons for the second anti-TNF discontinuation, No. (%)	
Primary failure	32 (45.1)
Secondary failure	28 (39.4)
Adverse events	11 (15.5)
Montreal location at Crohn's disease diagnosis, No. (%)	
L1 (ileal)	14 (31.1)
L2 (colonic)	9 (20)
L3 (ileocolonic)	22 (48.9)
Montreal behavior at Crohn's disease diagnosis, No. (%)	
B1 (inflammatory)	20 (44.4)
B2 (stricturing)	15 (33.3)
B3 (penetrating)	10 (22.2)
Perianal disease, No. (%)	19 (42.2)
Ulcerative colitis extension, No. (%)	
Proctitis	0
Left-sided colitis	14 (53.8)
Extensive colitis	12 (46.2)

DISCUSSION

To the best of our knowledge, this is the largest cohort of IBD patients (1122 patients) in whom the strategy of switching to a second anti-TNF after intolerance, primary failure, or secondary failure to the first has been evaluated. Moreover, the present study is one of the few studies to assess the sequential administration of a third anti-TNF after failure of the second.

In IBD patients, anti-TNF agents are efficacious in inducing and maintaining disease remission. Nevertheless, some patients have no response or have only a partial response

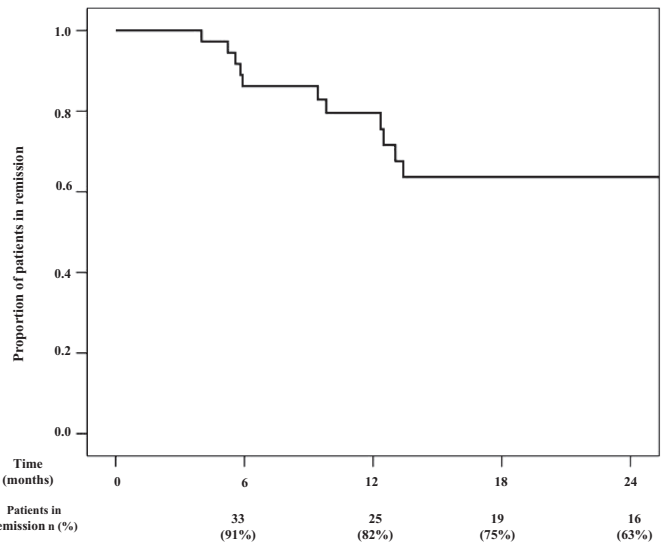

FIGURE 4. Kaplan-Meier curve of long-term remission after treatment with a third anti-TNF.

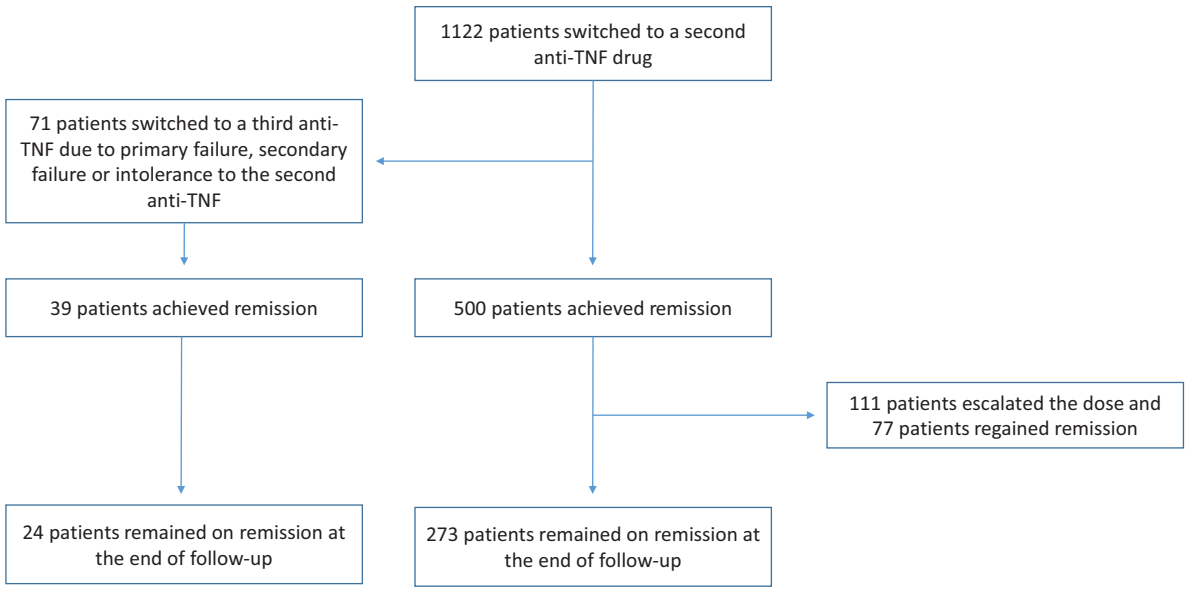

FIGURE 5. Flowchart of the patients who switched to a second and a third anti-TNF.

to these agents. Furthermore, patients who initially respond may lose efficacy over time or develop intolerance, which sometimes leads to stopping treatment. In these possible scenarios, switching from 1 anti-TNF agent to another could represent an option.[13]

In our study, 45% of the patients achieved remission with the second anti-TNF in the short term. These results are in agreement with other studies.[2, 14–18] We also found that nearly half of patients diagnosed with CD achieved remission with the second anti-TNF. In CD patients, several studies have proven that a second anti-TNF therapy is efficacious in patients who are intolerant or lose response to the prior anti-TNF drug.[13, 16, 18–21] However, only a few studies with small sample sizes have analyzed the effectiveness of the strategy of the sequential use of a second anti-TNF if the reason for withdrawal of the first drug was primary failure.[14–16, 21–27] The rates of remission in these studies were highly variable, ranging from 11% to 60% at 1 year.

On the other hand, in UC patients, only a few studies with a small number of patients and heterogeneous designs have evaluated the effectiveness of a second anti-TNF drug, with reported rates of remission from 0% to 50%.[3, 7–9] We found that, in the short term, UC patients had an overall remission rate of 41%. Moreover, the remission rate in CD patients was similar to that in UC patients in the short term; however, in the long term, patients with UC had a higher probability of losing efficacy than CD patients. Sandborn et al. assessed the efficacy of ADA after IFX in 98 UC patients. At 1 year, the rate of remission with the second anti-TNF was 10%. However, the reason for withdrawal of the first anti-TNF in these patients was not reported.[8] Nonetheless, in UC patients, the remission rate to a second anti-TNF seems to be lower than the remission rate in CD patients. Therefore, further studies are needed in UC patients to investigate the efficacy of a second anti-TNF drug in those patients with intolerance, primary failure, or secondary failure to the first drug.

In the present study, the probability of achieving remission in the short term was associated with the reason for discontinuing the first anti-TNF. In fact, patients who discontinued the first anti-TNF due to primary or secondary failure had a lower probability of achieving remission than those whose reason for switching was intolerance. According to our results, a very recent study evaluated the efficacy of ADA and vedolizumab in 161 UC patients who were previously treated with IFX. The authors reported that the efficacy of ADA was similar to that of vedolizumab in patients who were intolerant of IFX. However, vedolizumab was more effective than ADA in IFX secondary failures.[28] These results are similar to those reported in a recent meta-analysis, in which the remission rate in the short term was higher when the reason for switching was intolerance (50%) in comparison with primary (18%) or secondary failure (41%).[2]

According to our results, of patients who switched to a second anti-TNF due to primary failure of the first anti-TNF, approximately 40% achieved remission. This remission rate after primary failure was slightly lower than in other studies.[14, 18, 25] This finding could be explained by the small sample sizes of the previous studies. As primary failure is considered a class effect phenomenon, the similar structure and function shared by the anti-TNF drugs might lead to the assumption that if a patient was a nonresponder to the first anti-TNF, they will not respond to the second.[29, 30] However, our results indicate that remission may still be achieved with a second anti-TNF in approximately 50% of the patients after primary nonresponse to a prior drug. In accordance with our results, switching to another

anti-TNF after primary failure may still be a valid therapeutic option in IBD, especially considering that the therapeutic armamentarium of IBD is still limited.

We found that in patients in remission with the second anti-TNF, the incidence of loss of response was relatively high: 19% per patient-year, with a cumulative incidence of loss of response of 45% in 19 months (IQR, 8–40 months) of follow-up. These results are similar to other smaller studies.[14, 31–33]

In the multivariate analysis, we found that in patients who switched to a second anti-TNF, the long-term effectiveness was associated with the reason for switching the first drug. In fact, the probability of remission of the patients treated with a second anti-TNF was lower in those patients who switched due to primary or secondary failure to the first, in comparison with those patients who switched due to intolerance. These results are consistent with a recent meta-analysis by our group that included 35 studies and evaluated the efficacy of a second anti-TNF when the previous has failed. In this study, the patients who discontinued the first anti-TNF due to intolerance had higher rates of remission (61%) than those who switched to a second anti-TNF due to primary (30%) or secondary failure (45%).[2] Only 1 randomized trial has specifically evaluated the efficacy of a second-line anti-TNF agent in patients diagnosed with CD who were intolerant of or lost response to a first anti-TNF drug (IFX).[19] In this study, ADA proved to be superior to placebo for inducing remission and response. The reason for discontinuing IFX (intolerance vs secondary failure) had no impact on clinical improvement; however, the primary end point of this study was remission in week 4 (short term).

Surprisingly, in patients who switched to a second anti-TNF and were on combination therapy with immunomodulators, the probability of remission was lower. An explanation for this fact could be that patients who were on combo therapy probably had more aggressive disease than those on monotherapy. In fact, we found that in patients on combo therapy, the duration of the disease until the start of both the first and second anti-TNF was shorter than in patients on monotherapy, which suggests that these patients probably had a more aggressive disease. Nonetheless, in accordance with the results of a recent meta-analysis, combo therapy after starting anti-TNF therapy is no more effective than anti-TNF in monotherapy (IFX or ADA) in inducing or maintaining remission in patients who have been previously exposed to anti-TNF.[34]

One year after switching, 77% out of 45% IBD patients who achieved remission with the second anti-TNF maintained remission. This finding is similar to another study that included 118 patients diagnosed with CD who switched to a second anti-TNF after failure of the previous anti-TNF.[14] Therefore, a considerable number of patients who switch to a second anti-TNF will be in remission in the first year; however, a high proportion of these patients will lose efficacy over time. Accordingly, the sequential use of a second anti-TNF is an option that should be considered, especially in those patients for whom the reason for switching was intolerance.

In the present study, we found a higher risk of loss of efficacy in UC patients than in CD patients. This finding was reported by a meta-analysis that included 6 studies in UC patients who had primary or secondary failure to the first anti-TNF and switched to a second drug. The overall remission rates in these studies were lower than those reported in CD patients.[2] Nevertheless, more prospective studies are needed to investigate the effectiveness of a second anti-TNF agent in UC patients in whom the first drug has failed.

In IBD patients, dose escalation of the anti-TNF drug is a common and effective strategy in those patients who lose their response to anti-TNF drugs.[1] According to our results, approximately 20% of the patients who achieved remission with the second anti-TNF escalated the dose due to loss of response. Of these, 70% regained remission. This elevated rate of remission could be explained by the fact that all the patients escalated the dose due to secondary failure. Almost half of the cohort of patients who switched to a second anti-TNF agent and who escalated the dose of the drug achieved remission. Of these, almost two-thirds of the patients who escalated the dose due to partial response and half of the patients who did it due to secondary failure regained remission. However, none of the patients who escalated the dose due to nonresponse regained remission. These results are similar to those of another study.[14] Our findings suggest that the escalation of the dose of the anti-TNF drug in patients who lose response to a second anti-TNF may also be considered a valid therapeutic strategy. Moreover, according to our results, an important number of patients with partial response to a second anti-TNF could benefit from dose escalation. None of the nonresponder patients who escalated the dose of the second anti-TNF achieved remission. Nevertheless, the number of these patients was small. For this reason, there are not enough data to recommend the escalation of the dose of the anti-TNF in patients who do not respond to the second anti-TNF.

The sequential use of anti-TNF drugs is potentially risky, as the second agent may worsen the immunosuppression induced by the first agent.[35] Of all patients who switched to a second drug, 15% had adverse events. Two-thirds of them (10% of the total cohort) discontinued the drug due to adverse events. In a systematic review of the use of ADA after IFX failure in CD patients, adverse events were reported in 13% to 69% of the patients, and the severity of the majority these effects was mild to moderate, with a rate of discontinuation ranging from 0% to 14%.[32]

In clinical practice, the switch to a third anti-TNF drug is not exceptional; however, data are limited.[35] In our study, we report the largest cohort of patients who switched to a third anti-TNF after intolerance to or failure of the second one. In the short term, of the 71 patients who were included, approximately 50% achieved remission, whereas two-thirds of them were in remission at 24 months. Two studies have assessed the remission rate of a third anti-TNF. Allez et al. studied 67 patients diagnosed with CD who were treated with a third anti-TNF due to

intolerance to or failure of the second drug. At week 6, 61% of the patients had clinical response, whereas 51% of the patients had clinical response at week 20.[36] Silva et al. studied 63 IBD patients who received a third anti-TNF after intolerance or loss of response. Remission was achieved in 36% of these patients, and >50% of the patients who achieved remission remained on the third anti-TNF after 1 year.[37] In our study, the probability of maintaining remission after the third anti-TNF was higher than in the Silva et al. study. However, the long-term benefit of a third anti-TNF agent is still unknown.

We found that 11% of patients had adverse events, although only in 1 patient did the drug have to be withdrawn. However, the use of a third anti-TNF raises additional safety concerns. Allez et al. reported that 14 patients had to discontinue the third anti-TNF due to severe adverse events. Also, 2 deaths were reported by the authors.[36] Nonetheless, there were no deaths reported in the study of Silva et al. during the follow-up period.[37] Although the efficacy of switching to a third anti-TNF seems to be relatively favorable, this strategy cannot be generally recommended because of the risk of severe adverse events, especially with the availability of other recently approved medical options (eg, vedolizumab, ustekinumab) that are effective and safe for the treatment of IBD.

The present study has several limitations. First, information about anti-TNF trough levels, antidrug antibodies, and endoscopic activity was not available. Nonetheless, because this is a retrospective study, the investigators made an effort to obtain information on all components of clinical indices. Second, as this was a real-life study, the treating physicians decided to discontinue 1 anti-TNF and switch to another based on their criteria. Third, the number of patients who switched to a third anti-TNF was small, and the follow-up period of these patients was relatively short. However, the number of patients in which this strategy was evaluated is one of the largest that has been published.

One of the main strengths of this study is that it reflects real-life clinical practice. Moreover, this is the largest cohort of IBD patients in whom the strategy of switching to a second anti-TNF after intolerance, primary failure, or secondary failure to the first has been evaluated. In addition, this is the largest study in which the strategy of the sequential use of a third anti-TNF has been evaluated.

In conclusion, our results suggest that the sequential use of a second anti-TNF is efficacious in IBD patients after intolerance, primary failure, or secondary failure of a first anti-TNF. In any case, a high proportion of the patients who achieve remission with a second anti-TNF lose response afterward. Combination therapy with immunomodulators and type of IBD are predictors of loss of response to a second anti-TNF. Of the patients treated with a third anti-TNF, two-thirds achieved remission with the drug; nonetheless, a significant number of these patients experienced loss of efficacy over time. Finally, the sequential use of a second anti-TNF is safe; although switching to a third anti-TNF seems to be relatively safe, this last strategy cannot be generally recommended in clinical practice.

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