

Influence of first-line anti-TNF therapy on the effectiveness of adalimumab in ulcerative colitis: long-term clinical practice data

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SUMMARY

Objective: Tumour necrosis factor (TNF) is a relevant therapeutic target in the treatment of inflammatory diseases. The objective was to determine the influence of the effect of a first-line anti-TNF regimen on the effectiveness of adalimumab, as well as to obtain real long-term data.

Methods: Retrospective descriptive study was conducted between January 2013 and July 2021. Patients diagnosed with ulcerative colitis treated with adalimumab who previously received at least one anti-TNF agent were included.

Mayo Clinic Score up to 72 months was measured as effectiveness endpoint.

Results: Thirty-one patients were included. More than a third of patients treated with adalimumab as second-line anti-TNF had primary non-response. More than half of the patients treated with adalimumab presented clinical remission or response at 6 months of treatment, decreasing to one-tenth at 72 months.

Conclusion: The use of two anti-TNF therapy could be a strategy with acceptable effectiveness and favorable efficiency.

Key words: Ulcerative colitis, tumour necrosis factor inhibitors, adalimumab, treatment failure, long term effect.

Influencia de la terapia anti-TNF de primera línea en la efectividad de adalimumab en colitis ulcerosa: resultados de práctica clínica a largo plazo

RESUMEN

Objetivo: El factor de necrosis tumoral (TNF) es una diana terapéutica relevante en el tratamiento de enfermedades inflamatorias. El objetivo fue determinar la influencia del efecto de una terapia anti-TNF de primera línea sobre la eficacia de adalimumab, así como obtener datos reales a largo plazo.

Métodos: Estudio descriptivo retrospectivo realizado entre enero de 2013 y julio de 2021. Se incluyeron pacientes diagnosticados de colitis ulcerosa tratados con adalimumab que recibieron previamente al menos un agente anti-TNF. Como criterio para la valoración de la eficacia se usó Mayo Clinic Score hasta 72 meses.

Resultados: Treinta y un pacientes fueron incluidos. Más de un tercio de los pacientes tratados con adalimumab como anti-TNF de segunda línea tuvieron un fallo primario. Más de la mitad de los pacientes tratados con adalimumab presentaron remisión clínica o respuesta a los 6 meses de tratamiento, descendiendo a una décima parte a los 72 meses.

Conclusiones: El uso de dos terapias anti-TNF podría ser una estrategia con una efectividad aceptable y una eficiencia favorable.

Palabras clave: Colitis ulcerosa, inhibidor del factor de necrosis tumoral, adalimumab, fallo terapéutico, efecto a largo plazo.

INTRODUCTION

Ulcerative colitis is a chronic disease characterized by inflammation and ulceration of colon and rectum. Some symptoms are diarrhoea and abdominal pain. The incidence and prevalence in the Western countries increased in recent years, reaching 8/100,000 inhabitants in Spain¹. Tumour necrosis factor (TNF) is a proinflammatory cytokine involved in the pathogenesis of the disease. TNF inhibitors (anti-TNF) –such as infliximab and adalimumab– prevent the binding of TNF with its receptor, avoiding the triggering of the inflammatory process^{2,3}. The use of these drugs in ulcerative colitis controls the disease progression in many patients. However, no clinical improvement is obtained in other patients. This treatment failure can occur at the start of the anti-TNF regimen (primary non-response) or after having achieved a primary response (secondary non-response). A common strategy for treating ulcerative colitis is the sequential use of a second anti-TNF agent when the first drug fails. However, previous studies have suggested an insufficient response of the second anti-TNF regimen after failed therapy with the first anti-TNF scheme⁴. It is important to generate evidence on the relationship between different types of therapeutic failures of anti-TNF drugs in their sequential use. The objective was to evaluate the influence of the effect of a first-line anti-TNF regimen on adalimumab, in addition to obtaining real long-term effectiveness data.

METHODS

Retrospective descriptive study included patients diagnosed with ulcerative colitis pre-treated with a prior anti-TNF agent from January 2013 to July 2021. The standard dose of adalimumab used was 80 mg at week 0, followed by 40 mg at week 2, and 40 mg every two weeks subsequently. The adalimumab dosage of 160 mg at week 0, followed by 80 mg at week 2, and 40 mg every two weeks subsequently was used in patients in need of achieving a faster response. The Dominion Farmatools[®] software and digital medical records were used to collect patient data.

The effectiveness of adalimumab was assessed using the Mayo Clinic Score (MCS) at 6, 12, 24, 36, 48, 60, and 72 months of treatment. This index assesses stool frequency, rectal bleeding, mucosa appearance at endoscopy,

and general patient evaluation. The score ranges from 0 to 12⁵. Clinical remission (R) was defined as an MCS value ≤ 2 . The clinical response (CR) was considered as a decrease of ≥ 3 points in MCS with respect to baseline value. The lack of clinical response (LOR) was defined as the absence of any of the above situations. Those patients with LOR and treatment suspension in a certain week were categorized as LOR patients in subsequent weeks. The influence of the effect of the first anti-TNF drug was estimated by the association between the primary and secondary non-responses of the first and second anti-TNF agents. Primary non-response to anti-TNF therapy was considered as LOR in the induction period (before week 10 for infliximab and before week 4 for adalimumab). Secondary non-response to anti-TNF treatment was defined as LOR after the induction period. The results obtained were reviewed by two pharmacists, discussing the possible discrepancies found and reaching a consensus.

RESULTS

Thirty-one patients were included. With respect to gender, 55% were women and 45% men. The median age was 43 (21-86) years. The most frequently administered anti-TNF agents in the first line of biological treatment –previously to adalimumab– were infliximab (77,4%) and golimumab (3,2%). The median duration of treatment with adalimumab was 18 (1-91) months. The baseline MCS value of patients presented a median of 8 (2-12). Table 1 shows the effectiveness data of adalimumab according to MSC score at 6, 12, 24, 36, 48, 60 and 72 months of therapy. The number of patients with R decreased progressively over time, from 32,2% of patients in R at 6 months to 6,5% of cases at 72 months. At 6 months, 51,6% of the patients achieved R or CR. This effectiveness progressively decreased up to 72 months, when we found 9,7% of patients with R or CR.

Regarding the dosage regimen used in the induction phase, 90,3% of the patients received 160 mg of adalimumab in week 0, followed by 80 mg in week 2, and subsequently 40 mg every two weeks. In the maintenance phase, 9,7% of the patients required intensification of the drug, administering 40 mg weekly instead of every 14 days.

Table 1. Adalimumab effectiveness data based on Mayo Clinic Scores

	R	CR	LOR
6 months (n° patients, % patients)	10 (32.2%)	6 (19.4%)	15 (48.4%)
12 months (n° patients, % patients)	9 (29.0%)	5 (16.2%)	17 (54.8%)
24 months (n° patients, % patients)	9 (29.0%)	3 (9.7%)	19 (61.3%)
36 months (n° patients, % patients)	8 (25.9%)	1 (3.2%)	22 (70.9%)
48 months (n° patients, % patients)	7 (22.6%)	0 (0%)	24 (77.4%)
60 months (n° patients, % patients)	3 (9.7%)	1 (3.2%)	27 (87.1%)
72 months (n° patients, % patients)	2 (6.5%)	1 (3.2%)	28 (90.3%)

R: clinical remission; CR: clinical response; LOR: lack of clinical response.

Table 2. Results of primary and secondary non-response to adalimumab

	Primary non-response to adalimumab (total patients with primary non-response in denominator, % patients)	Secondary non-response to adalimumab (total patients with secondary non-response in denominator, % patients)
Primary non-response to first anti-TNF drug (patients in numerator, % patients)	2/10 (20%)	0/18 (0%)
Secondary non-response to first anti-TNF drug (patients in numerator, % patients)	8/10 (80%)	18/18 (100%)

Table 2 shows the results of primary and secondary non-response to adalimumab at 72 months, with respect to the type of failure presented to the first anti-TNF agent. Ten patients (32,3%) showed primary non-response to adalimumab, of which 2 cases presented primary non-response to the previous anti-TNF drug and 8 had secondary non-response to the first anti-TNF agent. On the other hand, 18 (58,1%) patients with prior secondary non-response to anti-TNF therapy showed secondary non-response to adalimumab.

DISCUSSION

The sequential use of two anti-TNF agents is a widely used strategy. There is literature indicating the loss of efficacy of an anti-TNF drug in 20-50% of patients during the first 12 months and recommending switching to another agent of the same group⁶. Systematic reviews with meta-analyses report a mean R rate of 45% of patients at 24 months after switching to a second anti-TNF drug⁷. Less effectiveness was found in our population, since 29% of cases reached R at 24 months. The effectiveness of second anti-TNF agent could be related to the reason for the switch in treatment. The 20% of our patients with primary non-response to the first anti-TNF therapy subsequently had primary non-response to adalimumab. Likewise, no patients with secondary non-response to adalimumab had presented primary non-response to the first anti-TNF regimen. Considering our limited sample size, it could also be thought that there is a greater proportion of patients with primary non-response to adalimumab who had secondary non-response to the first line of anti-TNF therapy because there are simply fewer patients with primary non-response at the first anti-TNF agent in the global population.

Almost 50% of our patients demonstrated R or CR in the first 12 months of treatment with adalimumab after a prior anti-TNF agent. As indicated in some reviews based on clinical practice, some patients previously exposed to a first anti-TNF therapy required an increase in dose of adalimumab both during induction and maintenance periods in contrast to naïve patients^{8,9}. This finding may be due to a phenomenon of immunogenicity¹⁰. Other studies pointed to short-term re-induction of the drug to regain treatment response as an intensification practice¹¹. In our study, 90,3% of patients started with 160 mg at week 0, followed

by 80 mg at week 2, and then 40 mg every two weeks. It is important to generate evidence to decrease the probability of two sequential primary non-responses. Perhaps intensifying the treatment regimen could decrease this probability. Furthermore, the response to a second anti-TNF agent could occur later, such that a 4-week interval may be short to assess possible primary failures¹¹.

There are few studies involving patients routinely found in this clinical practice context and with an extensive follow-up period like our work. On the other hand, our data review was conducted by two pharmacists. This could reduce subjectivity in the interpretation of the extracted data. The main limitations of this study are the small sample size and the study design. The lack of randomization and a control group does not allow us to reliably confirm whether results observed may be due to the disease evolution itself or to a sequencing strategy of two anti-TNFs agents. Consequently, the data should be interpreted with caution and considering the available information in clinical trials.

In the current context, adalimumab biosimilars have extensive experience of use in real clinical practice and clinical trials found adequate efficacy and safety^{12,13}. Biosimilar drugs are subject to control standards that guarantee quality, safety and efficacy comparable to reference drugs. Its introduction in the market (after patents expiry) and consequent reduction in prices have allowed a very favorable impact on pharmaceutical spending for public administrations¹⁴. Therefore, the use of two biosimilar anti-TNF agents sequentially could be an efficient strategy that favors the sustainability of national health systems.

CONCLUSION

In conclusion, the use of adalimumab as second anti-TNF drug administered sequentially reported more than one third of cases with primary drug non-response. About 90% of our patients required dose intensification of adalimumab as second anti-TNF therapy. Patients treated with adalimumab in R or CR were more than half at 6 months of treatment, progressively decreasing to one-tenth at 72 months.

Conflict of interest: Gil-Sierra MD participated in an advisory board of Janssen Pharmaceutica. The rest of the authors have no conflicts of interest.

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