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CLINICAL AND ECONOMIC IMPACT OF TERAPEUTIC DRUG MONITORING IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE PATIENTS ON MAINTENANCE THERAPY WITH ANTI-TNF.

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ABSTRACT

Goals: To valorate whether therapeutic drug monitoring (TDM) of anti-TNFα drugs may improve clinical control of patients with inflammatory bowel disease (IBD) in a treat to target approach and its economic impact on direct costs. **Study**: Prospective single center cohort study based on algorithm decision-making in IBD patients on maintenance therapy with anti-TNFα. Remission/active IBD status was defined based on a combination of clinical, laboratory and image techniques data. Anti-TNFα trough levels (TL) and anti-drug antibodies (ADA) levels in baseline and 6 months apart taking algorithm-based therapeutic decisions in a treat to target approach with a subsequent follow-up. The economic impact on direct costs of this approach was also calculated. **Results**: We included 67 patients. Mean follow-up was 15.3 months. Adequacy to decisions recommended by algorithm was 91% and 86,7% after first and second TDM. At baseline therapeutic TL were seen in 79,1% of patients, with ADA being positive in 3% of patients. At 6 months and at the end of follow-up, 97,4% and 89,5% of those in remission at baseline continued in remission, and most of them with the same scheme of therapy, 5 de-escalated, 5 stopped biologics and 1 escalated dose. Of those with active-IBD at baseline, 44,8% and 48,3% of them achieved remission at 6 months and at the end of follow-up (dose escalation in 13 patients, switch to another anti-TNFα and surgery in 3 patient each). Globally, while 56,7% of patients were in remission at baseline, they accounted 74,6% at 6 months (p:0,002) and 71,6% at the end of protocol (p:0,031). Direct cost of anti-TNF was reduced in 15,7%. **Conclusion**: TDM allows an efficient decision-making and associates a reduction in direct costs of anti-TNFα.

KEYWORDS: Therapeutic drug monitoring (IBD). Anti-TNF. IBD.Crohn´s disease. Ulcerative colitis. Treat to target. Direct costs.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is defined by a persistent and disproportionate inflammation in the digestive tract resulting from the interaction of a genetic predisposition and environmental factors not yet well known. Abdominal pain, diarrhea, digestive bleeding and complications such as intestinal obstruction, intra-abdominal abscesses or perianal fistulas impact on the quality of life of these patients. Alpha Tumor Necrosis Factor blocking agents (anti-TNFα) are used in patients with moderate-to-severe luminal and / or perianal IBD who are refractory to or intolerant of inmunomodulators (INM). Anti-TNFα drugs improve response and remission rates as well as quality of life, reducing hospital stays and surgeries but with an increase in direct drug costs (1). However, 20-40% of those who initiate anti-TNFα do not obtain clinical response (primary failure-PF), and 30-40% of those who reach clinical response lose it after one year (secondary failure or loss of response-LOR). Faced with an anti-TNFα failure, we try to rescue LOR with intensification of treatment (shortened interval between doses, increased doses per administration or both simultaneously) (2) or we shift into a second anti-TNFα (3), which potentially implies for adverse effects and increased cost. In the PF it is believed that the target of the treatment is not TNFα. In the LOR, low bioavailability of the drug or immunological blockade by anti-TNFα antibodies (Anti-Drug-Antibodies: ADA) seem to be the causes (4). Therefore, pharmacokinetic (plasma levels of anti-TNFα) and immunogenic information (absence or presence of antibodies against the drug) may help to assess more precisely what happens in a patient with anti-TNFα

failure (5). This would allow optimization of anti-TNF posology or changing the thetrapeutic strategy to reach an inactive inflammatory disease (6), which may result in lower treatment costs and fewer adverse effects. Most of the published papers use therapeutic drug monitoring (TDM) of anti-TNFα when LOR happens (21-26). Our protocol included not only patients with LOR but also those in remission, a group in which literature available data are scarce.

PATIENTS AND METHOD

Aim

The aim of this study is to assess whether the pharmacokinetic and immunologic information may allow to optimize the clinical control of patients with IBD in maintenance treatment with anti-TNFα in secuential treat to target approach, as well as to determine the economic impact of this strategy.

Patients

We included patients with IBD (ulcerative colitis-UC and Crohn´s disease-CD) on anti-TNFα maintenance treatment in clinical remission or with active disease. Inclusion Criteria: Patients with UC or CD in maintenance treatment with infliximab or adalimumab for more than 12 weeks. Exclusion Criteria: Refusal to participate in the study or to the signing of the informed consents. Age younger than 18 years-old or over 80 years-old. Refusal or impossibility to carry out the necessary studies to assess disease activity. Scope of the study: Costa del Sol Hospital (Marbella) and Virgen de la Victoria Hospital (Málaga).

Clinical management

Taking as a frame of reference the European and Spanish clinical guidelines in the management of IBD (ECCO and GETECCU Guidelines) we elaborated a decision-making algorithm integrating the clinical information, TL of TNFα and the presence or absence of ADA. Once algorithm-guided decision was taken a minimum follow-up of 3 months was established. Patients on follow-up were assessed with the periodicity that the treating physician considered adequate, according to common clinical practice.

Disease activity assessment

Remission or active disease status was assessed in all patients by the integration of the following:

Clinical indices: We calculated the CDAI (Crohn's Disease Activity Index) for CD patients and UCDAI (Ulcerative Colitis Disease Activity Index) for CU patients. In UC patients with no endoscopic information available we used pUCDAI (partial Ulcerative Colitis Disease Activity Index).

Laboratory data: We included serum C-Reactive Protein (CRP) and fecal Calprotectin.

Ultrasonographic studies: Abdominal ultrasound was performed at inclusion and at every follow-up visit using both convex and linear probes for a more accurate valoration of gut wall.

Endoscopic studies: Endoscopic exams were performed when indicated by the treating physician, and always in case of doubts about the IBD remission/active disease status. Biopsies were taken to assess histological disease activity and to rule out Cytomegalovirus (CMV) infection.

We considered that IBD was in remission when the patient showed normal levels of clinical indexes (CDAI<150, UCDAI=0), normal levels of CRP (less than 5 mg/dl) and fecal calprotectin (≤150 ug/g) and imaging studies without evidence for active disease. We considered active disease when patients had abnormal clinical indexes (CDAI> 150, DAI greater than or equal to 1) and/or high levels of fecal calprotectin (>150 ug/g) and confirmed with image technique (abdominal and gut ultrasound with/without colonoscopy), once potentially confusing factors (intestinal infection, bile salt diarrhea, bacterial overgrowth, food intolerances, etc) were excluded.

Serum Infliximab and adalimumab trough levels and serum Anti-Drug-Antibodies (ADA).

A peripheral blood sample was obtained in all patients the same day that infliximab or adalimumab were going to be administered in order to obtain anti-TNFα trough levels and to assess ADA status. Once the blood sample was obtained and the clot formed, the plasma was separated and stored frozen at -80ºC until analysis. This analysis was carried out by enzyme-linked immunosorbent assay (ELISA) in the Clinical Analysis laboratory of the Costa del Sol Hospital by using the Promonitor Kit (Proteomika, Bizkaia, Spain). The collection, storage and analysis of blood samples were authorized by patients through the corresponding informed consent and following the guidelines of the Autonomous Community of Andalucia (Biobanco).

Decisions by algorithm

Once clinical, laboratory and imaging techniques information were available we stablished the patient´s disease status. We correlated this IBD remission/active disease status with TL of anti-TNFα and ADA presence or absence to take an attitude according to the algorithm of decisions. (table 1).

Economic impact

The Pharmacy Department of the participating centers provided information on the cost of anti-TNFα drugs at the start date of the study in February 2012 (505.58 euros/100 mg of infliximab and 480.45 euros/pen of 40 mg of adalimumab). We collected information on the dose and frequency of administration of these drugs in the 12 months prior to being included in the study, calculating the cost per patient/year. During follow-up the same calculation was made to determine the individual cost for anti-TNFα in the first 12 months

following second TDM. Therefore we could calculate the difference in anti-TNFα direct costs before and after decisions taken.

Statistical analysis

The quantitative variables were assessed to confirm normal distribution using the Kolmogorov-Smirnov test. A descriptive analysis was made with measures of central tendency and dispersion for these quantitative variables as well as a study of frequency distribution for the qualitative variables. Patients´ variables were assessed between the baseline assessment, six months after decision making and at the end of follow-up. For the quantitative variables, the T-Sudent test for paired samples was used, or in case of non-normal distribution, the Wilcoxon rank test. To assess paired differences between clinical results between two periods of study in dichotomous qualitative variables, the McNemar test or the U-Mann-Whitney test was used as appropriate. The level of statistical significance was established at $p < 0.05$.

Ethical aspects

This study respects the Organic Law of Protection of Personal Data in force in the legislation of the Spanish state. It has been approved by the Ethics Committees of the Costa del Sol Hospital and by the Andalusian Committee of Clinical Trials. All patients have provided their written informed consent.

RESULTS

This study was carried out from February-2012 to November-2014. Sixty seven patients were included (36 men and 31 women) with a mean age of 39.7 years (range 18-72), 74.6% of whom with CD (n = 50) and 25.4% with UC (n = 17). Mean time from IBD diagnosis to inclusion in the study was 147.4 (24-348) months. All patients were in maintenance treatment with infliximab or adalimumab for at least 3 months. Concomitant medications included: mesalazine (46.3%), budesonide (28.4%), prednisone (4.5%), azathioprine (22.4%) and methotrexate (1.5%). In 11 patients (16.42%) another anti-TNFα (infliximab in all cases) had been used prior to the one currently in use.

The clinical pattern of CD was inflammatory in 66% of patients (33/59), fistulizing in 28% of them (14/50) and inflammatory-stricturing in 8% (4/50), with ileocolonic involment in 40% and just ileal in 26% of them. Perianal disease was present in 42%. Fifty six percent of CD patients were treated with infliximab while 44% of them used adalimumab, being the accumulated time of use of 65.4 (17-164) and 48.5 (19-99) months respectively. At baseline 44% of CD patients had an active disease with a median CDAI higher than in those CD patients in remission (39.IQR-118 vs 25. IQR-36.8, *p: 0.005*). Of those CD patients with active disease 45.5% were using infliximab and 54.6% adalimumab.

In UC patients the extent of the colitis was extensive in 47.1% (8/17), left-sided in 35.3% (6/17) and limited to the rectum in 17.6% (3/17). The mayority of UC patients were on infliximab (76.5%), with an accumulated time of use of 48.8 months (20-96) for infliximab and 22.3 (18-25) for adalimumab. At baseline 41.2% of UC patients showed active disease, with a median partial UCDAI significantly higher than that of those who were in remission (4-IQR 3 vs 0-IQR-0, *P: 0.001*).

C Reactive Protein and fecal calprotectine

At baseline medians of CRP and fecal calprotectin were significantly higher in patients with active IBD than in those in remission (CRP: 0.3 mg/dl-IQR 1.4 versus 0.1 mg/dl-IQR 0.28 *p: 0.001*. Fecal Calprotectin: 289 ug/g-IQR 556 versus 77 ug/g-IQR 166, *p: 0.003*). After the decisions taken, we observed a significant decrease in CRP in patients with active CD and in fecal calprotectin in patients with active UC (Figure 1).

Use of corticosteroids and immunomodulators (INM)

Nineteen out of 22 patients taking corticosteroids at baseline (32.8% of all IBD patients) had Crohn´s disease. Half of them had an active disease, 85.4% using low bioavailability corticosteroids. At the end of the study 26.9% of patients were still using steroids (*p: 0.388*). On the other hand only 23.9% of patients used INM at baseline (93.7% of them using thiopurines). This percentage did not vary throughout the study.

Anti-TNF trough levels (TL) and Anti-drug-antibodies (ADA)

We adopted as therapeutic TL those recommended by the comercial kit used (≥1.5 ug/ml for infliximab and ≥1.4 ug/ml for adalimumab). With this threshold, 79.1% of our patients had therapeutic TL at baseline. When IBD inflammatory status was considered, therapeutic TL were more frecuently found in patients in remission (86.8%) than in those with active disease (62.1%). Moreover, median TL of anti-TNFα were significantly lower in patients with active-IBD (Infliximab: 1.33 - IQR 3.08 vs 4.09-IQR 3.48 ug/ml, *p: 0.015*. Adalimumab: 6.71-IQR 10.39 vs 12.00-IQR 0.0 ug/ml, *p: 0.006*). At the second TDM performed (30 out of the 67 patients monitored, CD-19, UC-11) adalimumab TL were lower in those with active disease (3.61-IQR 8.63 versus 12.0-1.06 ug / ml; *p: 0.037*), not similarly for infliximab (3.10-IQR 14.32 versus 2, 81-IQR 2.74 ug/ml; *p: 0.930*). Interestingly, patients with sustained remission and all time under biological treatment showed mean infliximab TL of 5.39 ± 3,07 ug/ml and mean adalimumab TL of 11.33±2.0 ug/ml, all cases within therapeutic range (infliximab ≥1,42 ug/ml and adalimumab ≥6 ug/ml). In a multivariate analysis anti-TNF TL were not influenced by sex, age, type of IBD, biological behavior (inflammatory, penetrating, stricturing or mixed) or location of CD, extension of UC, use of other drugs (5-ASA, budesonide, prednisone or immunomodulators), dose or interval of administration of anti-TNFα (Table 2).

ADA were detected in just 3 patients (4.5%), all three with active-IBD, two of them using adalimumab and the remaining one with infliximab. All showed subtherapeutic TL (0.024 and 0.017 ug/ml respectively for adalimumab and 0.035 ug/ml for infliximab).

Disease inflammatory activity troughout study protocol

At baseline 56.7% of the patients were in remission. After six months on follow-up the percentage of patients in remission reached 74.6% (*p: 0.002*), being 71.6% at the end of follow-up (*p: 0.031*). When type of IBD was considered remission rates were 56%, 70% and 66% in CD patients and 58.8%, 88.2% and 88.2% for UC patients in baseline, at six months and at the end of follow-up respectively (Figure 2). Of those who had therapeutic anti-TNFα TL at baseline, up to 44.8% were able to maintain the same treatment regime and 9% could de-escalate doses before the second TDM was carried out. On the other hand, only 3% of those with a baseline low subtherapeutic TL maintained the same treatment regime. At the second TDM, 54.8% of those with therapeutic TL maintain the same anti-TNFα regime but none of those with subtherapeutic TL.

Decissions taken according to protocol algorithm (figure 3 and table 3)

Patients in remission: Twenty eight out of 38 patients maintained the same treatment regime (in one of them it was scalated), 5 patients de-escaleted doses due to very high TL and in another 5 patients the anti-TNFα was stopped due to suspicion of remission not dependent on anti-TNFα (of them, just 1 patient had to resume the treatment due to a relapse during the study follow-up). As a consequence, 37 out of 38 patients in remission at baseline maintained remission at 6 months (97.4%) being 34 out of 38 (89.5%) at the end of follow-up.

Patients with active disease: We tried to find out the reason for LOR to anti-TNFα treatment. Baseline TDM showed 30.02% of pharmacokinetic failure (subtherapeutic anti-TNFα-TL with negative ADA), and 7.39% in the second TDM. A pharmacodynamic failure (therapeutic anti-TNFα-TL and ADA negative) was detected in 62.12% of patients at baseline TDM and 52.19% in the second TDM. An immunogenic failure (low or no anti-TNFα-TL detected and positivity to ADA) was evidenced in 6.93% and 7.39% of patients at baseline and second TDM respectively. Consecuently we initialy decided to scalate anti-TNFα treatment in 11 out of 29 patients (37.9%) with pharmacokinetic failure, elective surgery in 3 patients (10.3%) with a pharmacodynamic failure and a shift to a second anti-TNFα in 2 patients with an immunogenic failure (6.9%). After the second TDM we scalated doses of anti-TNFα in 3 patients (25%), maintained the therapeutic regime in another 3 patients (25%), de-escalated doses of biologics in 2 patients (16.7%) while a second anti-TNFα was indicated in 1 patient (8.3%) and surgery in another patient (8.3%). As a consecuence, six months after the second TDM we achieved remission in 44,8% (13 out of 29) of those patients with active disease at baseline, being 48.3% of them at the end of follow-up (14 out of 29). The adequacy of the decisions taken to the proposed algorithm was 91% and 82.7% in the first and second TDM respectively. Inadequacy of decisions was due to the absence of an alternative medical option, rejection of the patient to or no adecuate surgical option (84.6%).

Changes in anti-TNFα therapy during the study protocol

Thirty nine out of 41 (92.7%) patients on infliximab at the begining of the protocol kept the same anti-TNFα at 6 months on follow-up, 2.4% shifted to adalimumab and 4.9% stopped the biologics. Of those initially on adalimumab, 80.8% (22 out of 26) kept the same drug, while 3.8% shifted to infliximab and 15.4% stopped biologics. At the end of the follow-up 56 out of 67 patients continued with anti-TNF therapy.

Direct costs of anti-TNF

In our cohort of 67 patients direct cost of anti-TNFα reached 14,898.80 euros/patient in the 12 months before starting the protocol. In the 12 months following decisions guided by TDM the cost of anti-TNF use accounted for 12,564.16 euros/patient, leading to an average reduction in anti-TNFα direct costs of 15.7%, corresponding to 2,334.64 euros/patient/year saved.

Table 1: Algorithm of decissions.

IBD inflammatory status	Anti-TNF Trough Level	Anti-Drug Antibodies (ADA)	Interpretation	Proposed Action
Remission	Normal/High	Negative	Normal kynetics	Same therapeutic scheme
Remission	Normal/High	Positive	Non-neutralizing or low-afinity antibodies?	Repeat tests (Anti-TNF trough levels and ADA)
Remission	Low/Null	Negative	Pharmacokinetic problems	Repeat tests. If same results valorate anti-TNF withdrawal
Remission	Low/Null	Positive	Immunologic blockade of anti-TNF	Anti-TNF withdrawal
Active disease	Normal/High	Negative	Pharmacodynamic failure	1.Rule out local complication or infection 2. Switch to a non-anti-TNF drug
Active disease	Normal/High	Positive	Non-neutralizing or low-afinity antibodies? Pharmacodynamic failure?	1.Repeat tests 2.Rule out local complication or infection 3. Switch to a non-anti-TNF drug
Active disease	Low/Null	Negative	Pharmacokinetic failure	Scalate dose of the anti-TNF
Active disease	Low/Null	Positive	Immunogenic failure	Switch to another anti-TNF

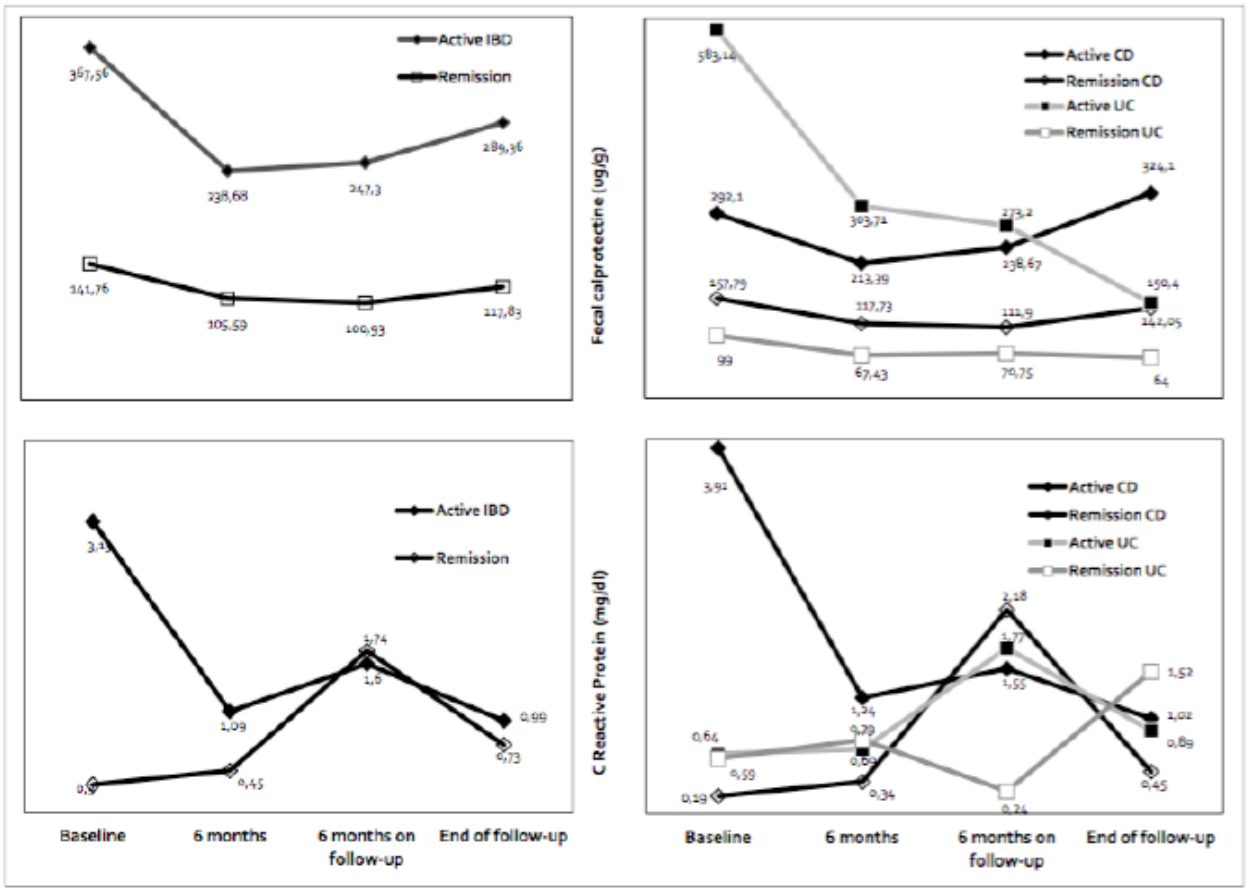


Figure 1: Fecal calprotectine and C Reactive Protein (CRP) throughout the study.

Table 2: Influence of clinical, pharmacologic and therapeutic variables in anti-TNFα trough levels (w:week. eow: every other week. Ns: non-significative value).

	Infliximab trough level (ug/ml)	n	Adalimumab trough leve (ug/ml)	N	P
Sex	2.25-3.34 (males)	22	12.0-3.46 (males)	14	Ns
	2.70-3.54 (females)	19	7.07-7.79 (females)	12	Ns
IBD subtype	2.25-3.24 (CD)	28	11.50-8.04 (CD)	22	Ns
	4.09-8.56 (UC)	13	11.02-4.46 (UC)	4	
Montreal-A	0.0-0.0 (A1)	0	6.7-0.0 (A1)	1	Ns
	1.88-3.14 (A2)	20	12.0-3.68 (A2)	14	
	2.92-2.73 (A3)	9	5.04-8.0 (A3)	8	
Montreal-B	2.11-3.03 (B1)	17	10.01-8.27 (B1)	16	Ns
	2.58-4.72 (B2)	2	9.72-4.57 (B2)	2	
	2.21-3.39 (B3)	10	12.0-7.79 (B3)	4	
Montreal-L	2.04-2.33 (L1)	5	9.03-8.39 (L1)	11	Ns
	4.33-11.98 (L2)	4	6.0-0.0 (L2)	1	
	2.66-3.1 (L3)	19	12.0-0.0 (L3)	7	
	1.42-0.0 (L4)	1	4.08-3.5 (L4)	3	
Montreal-E	1.48-13.41 (E1)	3		0	Ns
	5.79-10.23 (E2)	4	11.02-1.70 (E2)	2	
	3.27-5.23 (E3)	6	9.35-5.29 (E3)	2'	
5-ASA	4.09-3.81 (yes)	25	9.0-11.19 (yes)	6	Ns
	2,04-3.45 (no)	16	11.5-5.67 (no)	20	
INM	4.09-4.51 (yes)	9	10.01-11.98 (yes)	6	Ns
	2.41-3.45 (no)	32	12.0-5.95 (no)	20	
Budesonide	1.90-3.06 (yes)	10	11.00-10.66 (yes)	9	
	2.66-4.05 (no)	31	12.00-5.90 (no)	17	
Prednisone		0	10.03-8.39 (yes)	3	Ns
	2.44-3.54 (no)	41	11.50-5.95 (no)	23	
Extraintestinal symptoms	1.74-4.96 (yes)	4	6.80-10.39 (yes)	2	Ns
	2.66-3.50 (no)	37	9.20±5.19 (no)	24	
Perianal disease	2.04-3.74 (yes)	14	12.0-5.79 (yes)	7	Ns
	2.66-3.46 (no)	27	11.0-7.92 (no)	19	
Anti-TNF scheme of treatment	2.68-3.21 (5 mg/kg/8 w)	30	8.23-9.77 (40 mg eow)	16	Ns
	8.04-13.01 (5 mg/kg/6 w)	4	12.0-1.48 (40 mg/w)	8	
	2.66-4.55 (5 mg/kg/4 w)	2	7.81-8.39 (80 mg eow)	2	
	4.69-5.22 (7.5 mg/kg/8 w)	2			
	1.37-1.83 (5 mg/kg/10 w)	3			

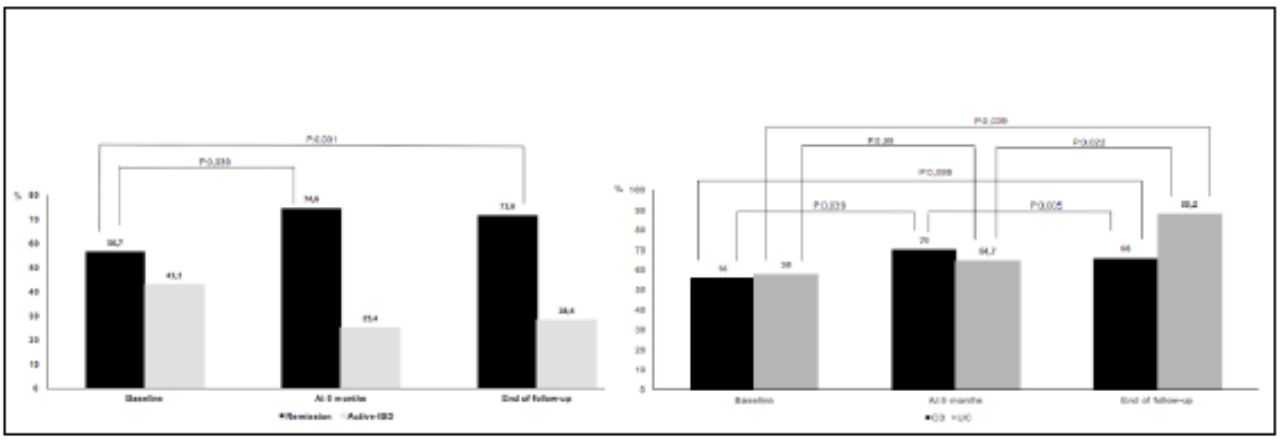


Figure 2: Patients´ remission rates at baseline, at six months and at the end of follow-up. In the chart on the left absolute remission rates are considered (CD and UC are expressed together). The chart on the right considers remission rates for CD and UC separately.

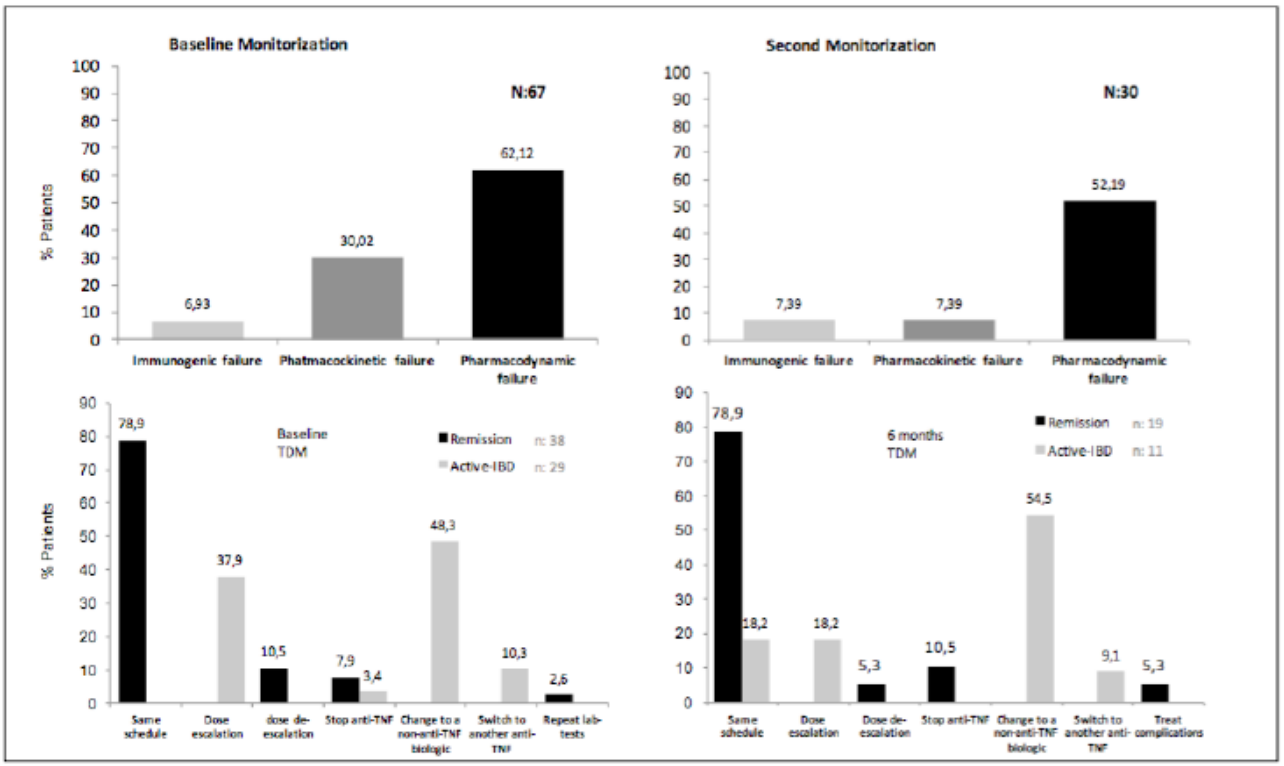
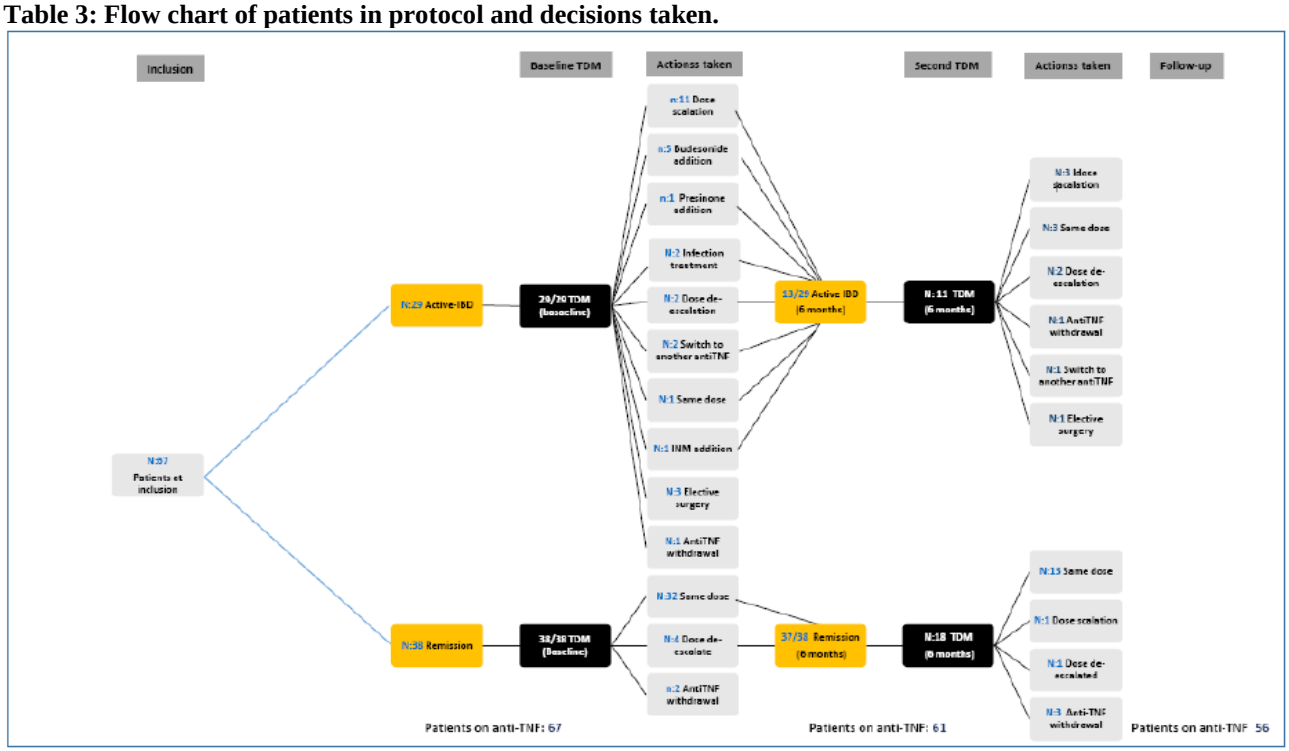


Figure 3: Above left: types of anti-TNFα failures in the first monitoring (n: 67). Above right: types of anti-TNFα failures in the second monitoring (n: 30). Lower charts show the decisions proposed by the algorithm after baseline monitoring (bottom left).

Table 3: Flow chart of patients in protocol and decisions taken.



DISCUSSION

In clinical practice we need to define when anti-TNFα treatment should be used, which are adecuate doses, when treatment should be maintained, when to scalate or de-escalate doses, when to shift to another drug and when to stop therapy without losing disease control. Pharmacokinetic and immunogenic information may help a more accurate decision making.

It is essential to reliably define the inflammatory activity or remission status of IBD. Several papers suggest that

only the assessment by clinical indexes may be insufficient (7). Hence in our study we also included analytical parameters (such as CRP and fecal calprotectin) and imaging studies for a more accurate definition of active disease or remission. CRP correlates well with the presence of inflammation but lacks of the necessary specificity and does not correlate well with endoscopic activity, aspects for which fecal calprotectin has been shown to be highly effective in both CD and UC (8-10).

To increase the specificity in the definition of remission/active disease status, we incorporated imaging studies to confirm the suspicion suggested by clinical and laboratory tests. (11-13). Therefore we considered IBD as active when patients showed a high clinical index and/or CRP> 5 mg/L of fecal calprotectin ≥150 ug/g with demonstration of inflammation in image techniques (intestinal wall thickness> 3.5 mm. with intestinal wall vascular enhancement by Doppler ultrasound exams and/or mucosal inflammation/ulceration without histological signs of infection in endoscopic exams). With this definition 43.3% of patients in our cohort in maintenance treatment with anti-TNFα showed active disease at baseline (44% -CD and 41.2% -UC), with no significant differences regarding the type of anti-TNFα used (45.5 vs 54.6% for active CD and 57 vs 43% for active UC with infliximab and adalimumab respectively).

We also observed that patients in remission showed higher anti-TNFα TL than those with active disease, not influenced by the use of concomitant INM as other studies suggest (14), possibly due to the small percentage of patients with INM in our series (23.9%). Moreover, in those patients that maintained infliximab treatment throughout the study with sustained remission (n: 19), infliximab TL were ≥ 1.42 ug/ml, quite similar to the therapeutic threshold provided by the ELISA kit used, while for those patients on adalimumab (n: 9) TL were ≥6 ug/ml. Defining a therapeutic threshold is important as it was suggested in the TAXIT trial for infliximab (3-7 ug/ml) or by Vaughn B.P. et al. (> 5 ug/ml) that described higher percentages of remission and longer duration of anti-TNFα treatment (15-16).

Besides, our results are consistent with published studies that define worse disease outcome in patients with positive ADA (17-20), in our series 3 patients ADA (+) had an active disease requiring a second anti-TNFα or surgery. As the type of anti-TNFα failure in active-IBD patients determined therapeutic decisions, around half of these patients were recommended to change the therapeutic target (48.3 and 54.5% after fisrt and second TDM respectively), scalate doses of anti-TNFα (37.9% and 18.2%) or switching to a second anti-TNFα (10.3% and 9.1%), as shown in Table 3. In some instances decisions proposed by algorithm could not be applied due to the unavailability of vedolizumab or ustekinumab at the time this study was carried out. In spite of this, our study is in agreement with several publications that suggest that management of patients with secondary LOR to anti-TNFα can be optimized through TDM. A retrospective study of the Mayo Clinic including 155 patients with CD, UC and IC (21) with loss of response (49%), partial response (22%) or hypersensitivity reaction (10%) to anti-TNFα demonstrated that when ADA are positive switching to a second anti-TNFα is better than dose scalation (92% vs 17%, p <0.004) while in those with negative ADA and low trough levels dose scalation is better than switching to another anti-TNFα (86% vs. 33%, p <0.016), whereas with negative ADA and therapeutic TL it is better to move on to another drug with a different therapeutic target. Roblin X., et al come to similar conclusions in patients with LOR to adalimumab (22). Moreover, Vande Casteele N., et al observed that in case of persistent anti-infliximab antibodies the risk of anti-TNFα withdrawal due to sustained disease activity or infusional reactions was 5 times higher than in patients with transient anti-infliximab antibodies (2. 3).

With regard to the economic impact, Steenholdt C. et al. demonstrated a clear economic benefit in patients with CD and loss of response to infliximab by TDM with similar rates of disease control than by just dose scalation (24 -25). Similar results were also provided by pooled observational studies comparing TDM versus empirical biological intensification in CD with LOR, highlighting the significant cost reduction (26). In our series we included UC and CD patients in maintenance therapy with anti-TNFα, some of them with active disease but others in remission. The use of an adequate integration of clinical, pharmacokinetic and immunogenic data in these patients also shows a clear economic benefit, with a 15.7% reduction in the direct cost of anti-TNFα (savings of 2334.64 euros/patient/year) in our series. It seems therefore advisable to use TDM in patients with active IBD to gain control of the disease , but also in the better management of those in remission by allowing de-escalation of doses in case of very high TL, or anti-TNFα withdrawal in case of repeatedly undetectable or subtherapeutic TL in the setting of sustained disease remission as disease remission may no longer depend on the biological drug, as recent publications suggest (27-32) and under evaluation in an ongoing clinical trial (ClinicalTrial.gov: NTC01817426).

As limitations of our study we must mention the absence of serial monitoring beyond those carried out at inclusion and 6 months apart, and the fact that the second TDM included only 30 out of our 67 patients. As vedolizumab and ustekinumab were not available when the study was carried out, several patients potentialy candidates for these drugs had to undergo surgery. Finally, the economic analysis included in our study refers to a period of time before the advent of biosimilars in the Spanish market. These less costly medications would had probably changed the economic impact of TDM.

CONFLICT OF INTEREST

The authors of this original paper declare no conflict of interest.

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