Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

REVIEW
Bilingual edition English/Spanish

Proactive therapeutic drug monitoring and pharmacogenetic analysis in inflammatory bowel disease: A systematic review

Monitorización farmacocinética proactiva y análisis farmacogenético en la enfermedad inflamatoria intestinal: Revisión sistemática

Octavio Ballesta-López[1,2], María Centelles-Oria[1], María Remedios Marqués-Miñana[1], Juan Eduardo Megías-Vericat[1], José Luis Poveda-Andrés[1]

[1]Department of Pharmacy, Medicines Unit, Hospital Universitari i Politècnic La Fe, Valencia. Spain. [2]Instituto de Investigación Sanitaria La Fe, Valencia. Spain.

Author of correspondence
María Remedios Marqués-Miñana
Servicio de Farmacia,
Área del Medicamento
Hospital Universitari i Politècnic La Fe
Avda. Fernando Abril Martorell, 106
46026 Valencia. Spain.

Email:
marques_mre@gva.es

Received 30 June 2021;
Accepted 26 July 2021.
DOI: 10.7399/fh.11780

How to cite this paper
Ballesta-López O, Centelles-Oria M, Marqués-Miñana MR, Megías-Vericat JE, Poveda-Andrés JL. Proactive therapeutic drug monitoring and pharmacogenetic analysis in inflammatory bowel disease: A systematic review. Farm Hosp. 2021;45(Suppl 1):S56-63

Abstract

Objective: The rise in the development of monoclonal antibodies has brought about a revolution in the pharmacotherapy of inflammatory bowel disease (Crohn's disease and ulcerative colitis). Systematic plasma concentrations monitoring of these biological drugs in anticipation of potential clinical failures of treatment is known as proactive therapeutic drug monitoring. New pharmacogenetic analysis techniques have recently been developed that can predict response to these treatments even before they are administered. The goal of this systematic review is to analyze the potential benefits of proactive therapeutic drug monitoring and of the pharmacogenetic analysis of biological drugs in inflammatory bowel disease patients in terms of clinical remission.

Method: A systematic search was performed in the MEDLINE/Pubmed, Embase and Cochrane Library databases using the descriptors *proactive drug monitoring*, *biological drugs*, *inflammatory bowel disease* and *pharmacogenetics*. Only randomized clinical trials published between January 2015 and May 2021 were included; all articles whose main topic was not related to the topic were excluded by hand. The quality of the articles

Resumen

Objetivo: El auge del desarrollo de los anticuerpos monoclonales supuso una revolución en la farmacoterapia de la enfermedad inflamatoria intestinal, principalmente enfermedad de Crohn y colitis ulcerosa. La monitorización de niveles plasmáticos de estos fármacos biológicos de forma programada y anticipada a un posible fracaso clínico del tratamiento se conoce como monitorización farmacocinética proactiva. Además, recientemente se han puesto a punto nuevas técnicas para el análisis farmacogenético que pueden predecir la respuesta a estos tratamientos, incluso antes de ser administrados. El objetivo de esta revisión sistemática es analizar los posibles beneficios de la monitorización proactiva y del análisis farmacogenético de fármacos biológicos en pacientes con enfermedad inflamatoria intestinal en términos de remisión clínica.

Método: Se buscó en las bases de datos Medline/PubMed, Embase y Cochrane Library con los descriptores *"Proactive drug monitoring"*, *"biological drugs"*, *"inflammatory bowel disease"* y *"pharmacogenetics"*. Se incluyeron únicamente ensayos clínicos aleatorizados publicados entre enero de 2015 y mayo de 2021, y se excluyeron las publicaciones cuyo

KEYWORDS
Inflammatory bowel disease; Therapeutic drug monitoring; Pharmacogenetic testing; Proactive control; Monoclonal antibodies; TNF inhibitors.

PALABRAS CLAVE
Enfermedad inflamatoria intestinal; Monitorización farmacocinética; Análisis farmacogenético; Monitorización proactiva; Anticuerpos monoclonales; Inhibidores anti-TNF.

was assessed using the Jadad scale and risk of bias was assessed using the Cochrane Collaboration tool.

Results: After applying inclusion and exclusion criteria, seven of the 228 retrieved articles were selected for review. Almost all the studies measured the same clinical variables (Harvey-Bradshaw index for Crohn's disease and Mayo score for ulcerative colitis). Only in two of the included studies was proactive therapeutic drug monitoring superior to reactive monitoring- or no level-guided dose adjustments. No pharmacogenetic analyses were found that met the criteria defined.

Conclusions: This review shows that the data supporting the use of proactive therapeutic drug monitoring in inflammatory bowel disease is limited and of low quality. Although pharmacogenetic analysis can be a useful tool for personalizing treatment, further and better designed randomized clinical trials are needed to determine the role of proactive drug monitoring strategies in clinical practice.

tema principal no era el de la búsqueda. La calidad de los artículos se evaluó mediante la escala de Jadad y además se evaluaron los riesgos de sesgo por la herramienta de la Colaboración Cochrane.

Resultados: Tras aplicar los criterios de inclusión y exclusión, se seleccionaron para la revisión 7 de las 228 referencias recuperadas. Casi todos los estudios coincidían en las variables clínicas medidas (índice de Harvey-Bradshaw en enfermedad de Crohn e índice de Mayo en colitis ulcerosa). Sólo en dos de los estudios incluidos la monitorización proactiva era superior a la reactiva o al no realizar ajustes de dosis guiados por niveles. No se encontraron ensayos clínicos con los criterios de búsqueda definidos acerca del análisis farmacogenético.

Conclusiones: Esta revisión muestra que los datos que apoyan el uso de la monitorización farmacocinética proactiva en enfermedad inflamatoria intestinal son limitados y de baja calidad. El análisis farmacogenético puede ser una herramienta útil para ofrecer a los pacientes el tratamiento más personalizado, pero son necesarios más ensayos clínicos aleatorizados con mejor diseño para determinar el lugar de estas estrategias en la práctica clínica.

Introduction

The treatment of inflammatory bowel disease (IBD) experienced a radical change nearly two decades ago with the advent of monoclonal antibodies, particularly tumor necrosis factor antagonists (antiTNFs) such as infliximab (IFX), adalimumab, golimumab and certolizumab pegol. These drugs have allowed more effective control of the disease, a reduction in the number of hospitalizations and surgical procedures, and an improvement in the patients' quality of life[1,2]. Despite these benefits, many patients fail to respond to the treatment during the induction phase (primary therapeutic failure), while in others the lack of response occurs during the maintenance phase (secondary therapeutic failure)[3,4]. Although the reasons behind this failure to respond are not wholly understood, it seems that they may be related of individual pharmacokinetic or pharmacodynamic changes or to the immunogenicity of the medication[3,5,6].

The development of antiTNF agents has been accompanied by the design of a series of tools intended to measure the concentration of the drugs in plasma as well as anti-drug antibodies (ADAs) concentrations. AntiTNF therapeutic drug monitoring (TDM) in IBD has gained significant ground in the last decade. Numerous studies have sought to determine the most desirable concentrations for achieving clinical remission (CR) or mucosal healing as a function of: a) the antiTNF agent used; b) the condition diagnosed; and c) the point in the therapeutic process the patient is at[7].

Two kinds of TDMare used in clinical practice: reactive[8] and proactive[9]. The former, which has been used for longer, requires that drug and ADAs concentrations only be obtained in the presence of signs that the treatment has failed or that symptoms have worsened; the goal is to explain whether a given relapse is due to low antiTNF concentrations. The latter provides for a regular determination of antiTNF plasma concentrations during quiescent phases of the disease to ensure optimal dosing, maintain drug concentrations within the therapeutic range, predict potential flare-ups of the disease, and prevent therapeutic failure. This may be particularly useful in patients at risk of treatment failure (e.g., those with more severe disease and/or with a history of antiTNF treatment) or to prepare for a change of approach following the loss of response (e.g., indicating a surgical procedure).

In the last few years, several new pharmacogenetic platforms have been developed, based on automated analyses, microarrays, genome wide association studies (GWAS), and next generation sequencing (NGS). These new tools have made it possible to discover multiple polymorphisms capable of predicting the patients' response to antiTNFs at the time of diagnosis, i.e., even before they are deemed eligible for treatment with biological agents[10]. Their use is however not widespread in clinical practice.

The purpose of this systematic review is to analyze the potential benefits of proactive TDM and the pharmacogenetic analysis of biological drugs in IBD patients in clinical remission.

Methods

Literature search strategy

This systematic review was carried out by two independent reviewers[11] in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The databases consulted included PubMed, EMBASE and the Cochrane Central Register of Clinical Trials. The search was completed on 30th May 2021.

The studies to be included in the review were selected independently by the two authors. A third reviewer resolved any disagreement.

Search terms were selected from the *Subject Headings* (MeSH) thesaurus, developed by the U.S. National Library of Medicine. The selection process yielded the following MeSH descriptors: *inflammatory bowel disease*, *Crohn's disease* and *ulcerative colitis*. The final search equation, defined using Boolean connectors, was applied to the MEDLINE/Pubmed database in the following manner: (IBD [tiab] OR inflammatory bowel disease [Mesh] OR Crohn's disease [Mesh] OR ulcerative colitis [Mesh]) AND (proactive [tiab]) AND (therapeutic drug monitoring [tiab] OR TDM [tiab] OR drug monitoring [tiab]) AND (infliximab [tiab] OR adalimumab [tiab] OR certolizumab pegol [tiab] OR golimumab [tiab] OR vedolizumab [tiab] OR ustekinumab [tiab]). The search for pharmacogenetic analyses of patients with IBD was carried out manually.

Inclusion criteria

The study included randomized clinical trials (RCTs) published between January 2015 and May 2021 in English and Spanish, which met the following criteria: 1) They had to include a comparison of proactive vs. reactive TDM (or lack of TDM) in patients with IBD; 2) They had to include a pharmacogenetic analysis as a predictor of clinical response.

Exclusion criteria

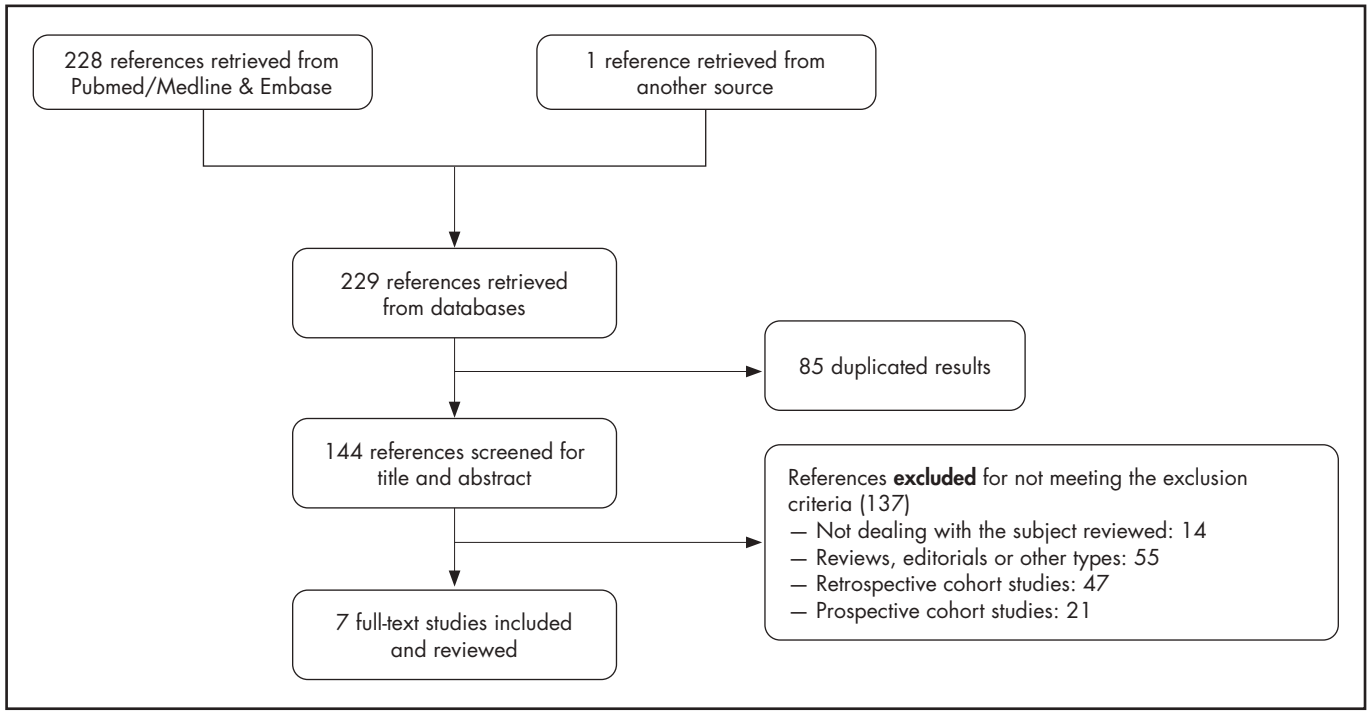
Articles not specifically dedicated to the purpose of this study as well as observational analyses, reviews and non-RCT studies were excluded from the search.

Methodological quality

The methodological quality of the selected studies was evaluated using the Jadad scale, a critical reading tool made up of five questions related with the design of clinical trials that rates the quality of studies on a 5-point scale whereby trials obtaining less than 3 points are considered low quality and those scoring 5 points are considered rigorous[12].

The Cochrane risk-of-bias tool was used to determine the internal validity of the trials included[13].

Figure 1. *Article selection process.*



Data extraction

The following data were extracted from the studies selected: design of the study, number of patients, mean or median patient age, therapeutic intervention, dosing regimen and main objective.

Results

The primary search yielded 228 journal and database citations. The secondary search produced one citation (Figure 1). Agreement between the reviewers regarding trial selection was excellent (kappa = 0.97).

The search strategy applied to the different databases yielded a total of 228 references. After removing 85 duplications and applying the inclusion and exclusion criteria a total of 143 references were obtained. Of these, 14 were rejected for not dealing with the subject being reviewed, 55 for not meeting the inclusion criteria (reviews, editorials, and other kinds of texts), and 68 because they were observational studies. Finally, seven studies were included after full-text reading (Figure 1). No RCT containing a pharmacogenetic analysis was found.

The assessment of the quality of the selected articles on the Jadad scale yielded scores between 1 and 5 points, with a median of 2 points (Table 1). The majority of trials included (71.4%) were open-label[14-18], which earned them a score of 2 points (low methodological quality). After analyzing the RCTs, it was established that two had a low risk of bias[19,20] (Figure 2). The most significant data in each study is summarized in table 2.

The population included in the different studies was rather heterogeneous, except for one article that was made up exclusively of pediatric subjects[17]. Nearly all the studies measured the same clinical variables. Analyzed drugs were IFX and adalimumab. The target plasma concentration was between 3 and 8 µg/mL for IFX and between 5 and 10 µg/mL for adalimumab. Mean duration of RCTs was 53 weeks.

Proactive versus reactive therapeutic drug monitoring

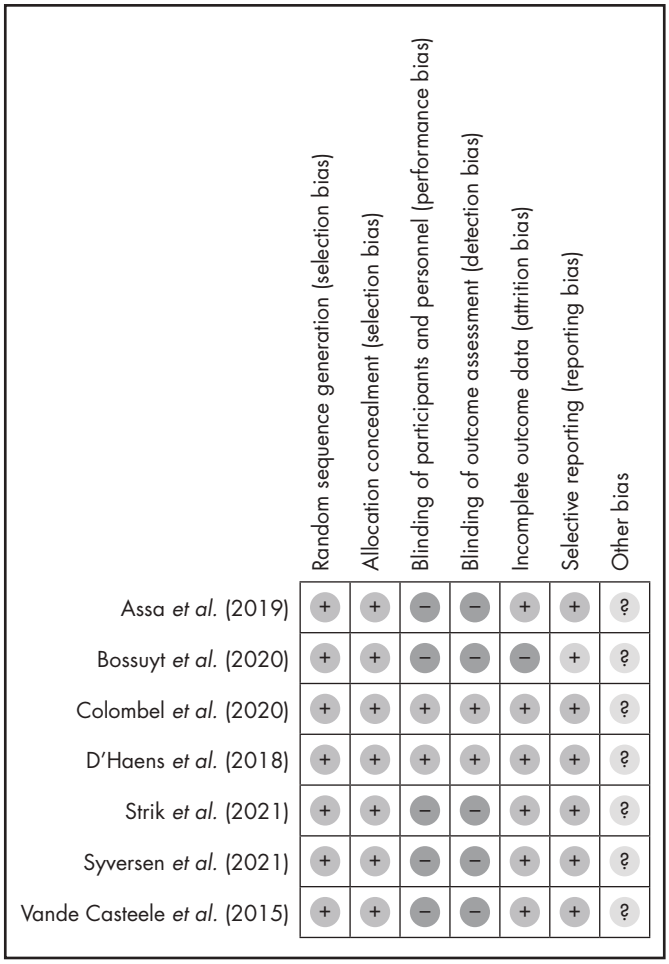
The TAXIT trial included 251 patients (173 with Crohn's disease [CD] and 78 with ulcerative colitis [UC]) randomized to receive IFX dosed accor-

Table 1. Assessment of the quality of the clinical trials included in the study using the Jadad scale

Study (year)	Q1* (0/1)	Q2* (0/1)	Q3* (0/1)	Q4** (+1/-1)	Q5**(+1/–1)	Final score
Vande Casteele *et al.* (2015)[18]	1	0	1	+1	–1	**2**
D'Haens *et al.* (2018)[20]	1	1	1	+1	+1	**5**
Assa *et al.* (2019)[17]	1	0	1	+1	–1	**2**
Colombel *et al.* (2020)[19]	1	1	1	+1	+1	**5**
Bossuyt *et al.* (2020)[16]	1	0	0	+1	–1	**1**
Strik *et al.* (2021)[15]	1	0	1	+1	–1	**2**
Syversen *et al.* (2021)[14]	1	0	1	+1	–1	**2**

Score = *0: no; 1: yes; **–1: no; 1: yes. **Abbreviations**: Q1: Was the study randomized?; Q2: Was it a double-blind study?; Q3: Does the study include a description of subjects lost to follow-up or who withdrew from the study?; Q4: Was the method used for generating the randomization sequence adequate and properly described?; Q5: Was the blinding method appropriate and properly, described? Scores < 3 indicate low quality.

Figura 2. *Risk-of-bias assessment.*



ding to either the patients' symptoms (*n* = 123) or a target trough plasma concentration (*n* = 128). The main endpoints were (CR) (Harvey-Bradshaw Index [HBI] ≤ 4 for CD and Mayo Score [MS] ≤ 2 for UC) and biochemical remission (C-reactive protein [CRP] ≤ 5 mg/L) a year after the optimization phase, which required the attainment of IFX plasma concentrations of 3-7 µg/mL. Subjects remained in the maintenance phase for at least 14 weeks, exhibiting a stable CR (total or partial responders). Seventy-four percent of patients in the target trough concentrations group achieved IFX concentrations of 3-7 µg/mL as compared with 57% in the symptoms-based dosing group ($p < 0.001$). 81 patients (66%) in the symptoms-based dosing group and 88 patients (69%) in the target trough levels group achieved CR and biochemical remission ($p = 0.686$). No statistically significant differences were observed between the two treatment arms with CD or UC[18].

The TAILORIX trial compared the effect of a proactive increase in the IFX dose based on frequently determined symptoms, biomarkers and/or trough levels (dose intensification groups 1 and 2 [DIS1 and DIS2], which differed in the intensification schedule) with conventional symptoms-based management (control group). A total of 122 untreated CD patients were randomized into three groups who would receive treatment with IFX every 8 weeks from week 14 to week 54. The main goal of the study was to determine the proportion of patients in CR who were not administered corticosteroids (Crohn's Disease Activity Index [CDAI] < 150) between weeks 22 and 54 who achieved endoscopic healing (absence of ulcers) by week 54, without abscesses or formation of new fistulas and without the need of bowel resection surgery. CDAI values were similar between the three groups (DIS1, DIS2 & control): 33%, 27% and 40% ($p = 0.5$). The main limitation of the study was its low statistical power resulting from the low number of patients included in each group. The increase in the IFX dose administered in this study, based on a combination of symptoms, biomarkers and/or IFX plasma levels, was not higher than that based only on symptoms[20].

The PAILOT trial was designed to determine whether proactive TDM was associated with higher rates of CR in pediatric CD patients under 18 treated with adalimumab. The primary endpoint was evidence of corticosteroid-free CR (Pediatric Crohn's Disease Index [PCDAI] < 10 points) at all follow-up visits from week 8 to week 72. The study compared a group subjected to proactive TDM of adalimumab (*n* = 38) with a reactive monitoring group (*n* = 40). In the first, concentrations were measured at weeks 4 and 8 and every two months thereafter until the end of the study. The target concentration was 5 µg/mL. Anti-adalimumab antibodies were detected in patients with concentrations below 0.3 µg/mL. Patients in the reactive TDM group were only tested for levels if there were signs that they were not responding to the treatment. Adalimumab concentrations were higher in the proactive TDM group (7.1 µg/mL vs 6.2 µg/mL; $p = 0.001$) and 31 patients (82%) achieved a PCDAI < 10 points in the proactive TDM group as compared with 19 (48%) in the reactive TDM group ($p = 0.002$). At week 72, 33 patients (87%) in the proactive TDM group had their adalimumab dosing intensified vs. 24 (60%) in the reactive TDM group ($p = 0.001$)[17].

In the SERENE-UC study, Colombel *et al.* compared a high-dose adalimumab regimen (40 mg a week) with a standard regimen (40 mg every 2 weeks) in adult patients with active severe-to-moderate UC. At the end of induction at week 8, patients were randomized in a 2:2:1 ratio to 40 mg adalimumab once a week, to 40 mg every two weeks, and to an exploratory arm where 40 mg of adalimumab was administered, with the dose being adjusted during the maintenance phase based on proactive TDM (to achieve concentrations > 10 µg/mL) and the symptoms observed (rectal bleeds ≥ 1). The primary endpoint was the CR rate at 52 weeks in patients who responded to the treatment at week 8. The CR rate at week 52 was 39.5% for patients treated with weekly adalimumab, 29% for patients on adalimumab every two weeks, and 36.5% for patients where adalimumab was dosed based on monitoring[19].

Bossuyt *et al.* compared an algorithm-based proactive monitoring strategy (*n* = 115) with a reactive monitoring strategy (*n* = 72) of IFX. The primary endpoint was the treatment failure rate. The secondary endpoint was CR at 6 and 12 months from initiation of the study. After one year, the treatment failure rate in the proactive TDM group was 19% vs 10% ($p = 0.08$) for the reactive TDM group. CR rates were similar in both groups (75% vs 83%; $p = 0.17$)[16].

The PRECISION trial randomized 80 CD and UC patients in CR (MS ≤ 2 and HBI ≤ 4) after at least 14 weeks on IFX to receive it adjusted on the basis of pharmacokinetic Bayesian estimations to keep trough levels above 3 µg/mL (BE group) or to continue with the same treatment without any dose and/or dosing interval adjustments (control group). After one year into the trial, 28/32 (88%) of patients in the BE group were in CR as compared with 25/39 (64%) of patients in the control group ($p = 0.017$). However, no differences were observed in the median IFX plasma levels (3.8 µg/mL in the BE group vs 2.9 µg/mL in the control group; $p = 0.563$). Median concentrations of fecal calprotectin were significantly lower in the BE group than in the control group (47 µg/g vs 144 µg/g; $p = 0.031$)[15].

The NOR-DRUM trial evaluated whether proactive TDM during induction improved the efficacy of treatment as compared with standard unmonitored IFX therapy in chronic immune-mediated diseases (including CD and UC) treated with IFX. This was a 38-week-long open-label RCT whose main goal was to evaluate the CR rate achieved at week 30. Although blood samples were drawn from patients in the standard therapy arm to determine IFX plasma levels, only clinical parameters were evaluated. CR was set at a MS ≤ 2 for UC and a HBI ≤ 4 for CD. The CR rate in patients with UC was 64.1% in the proactively monitored group and 70.7% in the reactively monitored one. In CD patients, the CR rate was 58.6% in the proactive TDM group and 60.7% in the reactive group, without statistically significant differences being observed between the groups[14].

Pharmacogenetic analysis

Evaluation of genetic markers associated to the efficacy and tolerance of biological medications has become increasingly common in patients with CD and UC. No randomized studies were found that could be included in this section. Only two cohort studies were identified that did not meet the inclusion criteria.

Table 2. Randomized clinical trials on proactive therapeutic drug monitoring

Trial (year)	Design	Drug	Clinical intervention	Concomitant IM (AZA, 6-MP, MTX)	*N*	Mean age (SD) Median (range)	Results of the primary variable
Vande Casteele *et al.* (2015)[18]	RCT, open-label, 52w, phase IV	IFX	Symptom-based R-TDM	7 (5.7%)	CD: 82 & UC: 4	42.0 (32.0-48.0)	CR at one year after optimization
	2011-002061-38 (TAXIT)		P-TDM to maintain plasma concentrations between 3-7 µg/mL	6 (4.7%)	CD: 91 & UC: 37	41.0 (30.0-50.3)	R-TDM: 81/123 (66%). In CD 55% & in UC 88% vs P-TDM 88/128 (69%) ARR 2.9% (95% CI: –8.7-14.5) (p = 0.686). In CD 63% ARR 7.8% 95% CI (–6.9-22.4) (p = 0.353) & in UC 84% RAR –4.0% (95% CI: –19.6-11.5) (p = 0.748)
D'Haens *et al.* (2018)[20]	RCT, double-blind, phase IV, 54w NCT01442025 (TAILORIX)	IFX	*DIS1:* Dose increase by increments of 2.5 mg/kg maximally two times to a maximum dose of 10 mg/kg (according to a specific algorithm)	122 (100%)	CD: 45	29.1 (22.7-44.5)	CR without corticosteroids (CDAI < 150) from w22 to w54 + endoscopic healing at w54
			DIS2: Dose increase by increments of 5 mg/kg, maximally one time to a maximum dose of 10 mg/kg (according to a specific algorithm)		CD: 37	30.2 (24.0-47.6)	DIS1: 33% vs DIS2: 27% vs Control: 40% (p = 0.5)
			Control: Dose increase of 5-10 mg/kg if CDAI > 220 at current appointment or if CDAI = 150-220 during the two weeks prior to current appointment		CD: 40	28.7 (21.5-39.9)	DIS1 vs control ARR –6.7% (95% CI: –27-2-13.8) DIS2 vs control ARR –13% (95% CI: –33.8-7.9%)
Assa *et al.* (2019)[17]	RCT, phase IV, open-label, 72w	ADA	R-TDM	17 (43%)	40	14.6 (2.6)	CR (PCDA I< 10) from w8 to w72 without corticosteroids
	NCT02256462 (PAILOT)		P-TDM to maintain plasma concentrations above 5 µg/mL	17 (45%)	38	14.0 (2.6)	R-TDM: 19/40 (48%) vs P-TDM 31/38 (82%) ARR: 34.1% (95% CI: 14.3-53.9) **(p = 0.002)**
Colombel *et al.* (2020)[19]	RCT, double-blind, phase III, 52w, NCT02065622 (SERENE-UC)	ADA	ST: 40 mg qw; 40 mg q2w P-TDM: maintenance of plasma concentrations above 10 µg/mL	NA	151 (UC)	NA	CR with q5w regimen in responders at w8 ST: 40 mg qw: 39.5% (1) 40 mg q2w: 29.0% (2) P-TDM: 36.5% ARR (1) –3.0% (95% CI: –16.4 to 10.5) ARR (2): 7.5% (95% CI: –5.7 to 20.7)
Bossuyt *et al.* (2020)[16]	RCT, open-label, phase IV, 52w NCT04775732	IFX	P-TDM-cohort to maintain plasma concentrations between 3-7 µg/mL	NA	115	NA	CR between 6mos & 12mos
			R-TDM cohort		72*		P-TDM 75% vs R-TDM 83% ARR –8.6% (95% CI: –20.3 to 3.2) (p = 0.17)
Strik *et al.* (2021)[15]	RCT, phase IV, open-label, 52w	IFX	ST: 5 mg/kg q8w	17 (42.5%)	CD: 33; UC: 7	37 (25-52)	CR at one year
	NCT02453776 (PRECISION)		P-TDM: to maintain plasma concentrations at 3 µg/mL 1-10 mg/kg and the q4w-q12w interval	15 (37.5%)	CD: 33; UC: 7	38 (29-51)	ST: 25/39 (64%). In CD: 63.6% and in UC 71.4% vs P-TDM: 28/32 (88%) ARR: –23.4% (–42.3 to –4.5) **(p = 0.017)**. In CD: 90.9% ARR 27.3% (95% CI: 8.2% to 46.4%) **(p = 0.008)** & in UC: 85.7% ARR 14.3% (95% CI: –28.0 to 56.6) (p = 0.515)

Table 2 *(cont.).* Randomized clinical trials on proactive therapeutic drug monitoring

Trial (year)	Design	Drug	Clinical intervention	Concomitant IM (AZA, 6-MP, MTX)	*N*	Mean age (SD) Median (range)	Results of the primary variable
Syversen *et al.* (2021)	RCT, open-label, 38w NCT03074656 (NOR-DRUM)	IFX	ST: 5 mg/kg at w0, w2 & w6 and q8w thereafter. Adjustments according to clinical parameters	14 (50%) (CD) 17 (41%) (UC)	CD:28; UC:41	CD: 41.0 (11.5) UC: 41.3 (16.2)	CR at 30w
			P-TDM: 5 mg/kg at w0. After that, the dose is adjusted depending on plasma concentrations using a specific algorithm	23 (79%) (CD) 15 (38%) (UC)	CD: 29; UC: 39	CD: 35.4 (11.0) UC: 38.8 (14.5)	ST: CD:17/28 (60.7%) & UC: 29/41 (70.7%) vs P-TDM CD: 17/29 (58.6%) ($p > 0.05$) AD (95% CI): 4.7 (–21.1-30.4) UC: 25/39 (64.1%) ($p > 0.05$) AD (95% CI): 4.9 (–15-6-25.5)

ADA: adalimumab; AD: adjusted difference; ARR: absolute risk reduction; AZA: azathioprine; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CR:clinical remission; CRP: C reactive protein; 95% CI: 95% confidence interval; HBI: Harvey-Bradshaw index; IFX: infliximab; IM: immunomodulation; mos: months; 6-MP: 6-mercaptopurine; MS: Mayo score; MTX: methotrexate; N: number of subjects in the cohort; NA: not available; PCDAI: Pediatric Crohn's Disease Activity Index; qw: every week; q2w: every two weeks; q6w: every six weeks; q8w: every 8 weeks: P-TDM: proactive therapeutic drug monitoring; RCT: randomized controlled trial; R-TDM: reactive therapeutic drug monitoring; ST: standard therapy; UC: ulcerative colitis; w: week.
*CD: 135 and UC:51 overall.

Discussion

The present systematic review analyzed a series of clinical trials dedicated to investigating the results of proactive TDM and the advances made in the pharmacogenetic analysis of IBD patients.

Only two of the studies analyzed found proactive TDM to be superior to reactive strategy as no concentration-guided dose adjustments were made[15,17]. It should nonetheless be remembered that the first of these studies used IFX in adult patients whereas the second used adalimumab in pediatric patients, which precludes drawing any hard-and-fast conclusions. The study by Strik *et al.*[15] is the only one in the series to include a Bayesian estimation strategy with a population-based pharmacokinetic model to achieve the target plasma level. These systems make it possible not only to consider patient-related data but also factors that affect the pharmacokinetic profile of these drugs (doses and previous concentrations, anti-drug antibody concentrations, etc.), which makes them appropriate dosage individualization tools.

In 2017 the American Gastroenterological Association published a series of recommendations[21], which limited the use of reactive TDM to patients with active IBD treated with antiTNFs. Proactive TDM was not recommended as the information available was deemed insufficient. Since then, no further recommendations have been issued by other associations in their guidelines[22,23] probably due to the absence of high quality studies in large cohorts contributing conclusive results. Borren *et al.* recently sought to determine whether IFX levels measured in the context of clinical and endoscopic remission were able to predict loss of response over a 2-year follow-up period. These authors did not observe any differences between IFX plasma levels in patients with and without loss of response[24]. Despite the uncertainly, it would seem appropriate to measure biological drug concentrations in these cases as personalization of treatment does allow economic savings based on optimizing the administered doses[25-27].

Furthermore, in 2019 an expert panel recommended proactive TDM for antiTNF in IBD patients at the end of the induction phase and at least once during the maintenance phase. In patients with primary or secondary loss of response they recommended a reactive monitorization strategy. As regards the new drugs for IBD (e.g., vedolizumab and ustekinumab) proactive TDM may be appropriate at the end of the induction phase and reactive monitoring in case of secondary loss of response. Evidence for this is however still very limited[4].

In this regard, Papamichael *et al.* demonstrated that proactive monitoring was superior to reactive TDM in patients on adalimumab[20]. Similarly, proactive TDM for IFX showed itself to be superior to reactive TDM when comparing the data with that of a retrospective cohort[28]. It should be mentioned that most of the information available in the literature comes from observational cohort studies on IFX, data on adalimumab being scarce. Syed *et al.* observed that proactive TDM for both IFX and adalimumab was superior to reactive strategy [odds ratio (OR): 4.76; 95% CI: 1.65-13.67; $p = 0.0019$) and to the control group [OR: 6.10; 95% CI: 2.19-17.02; $p = 0.0002$] in achieving persistence of treatment at one year[29].

Giráldez-Montero *et al.* recently reviewed the TDM strategies for antiTNFs as well as the use of individualized dosing methods in IBD patients. The authors did not describe the inclusion or exclusion criteria of the studies on TDM strategies, with both randomized and observational studies being selected. The conclusion was that there is a trend toward the use of proactive TDM at the expense of reactive one as the former is associated with a longer response to treatment and a lower rate of relapses and discontinuations, although the available evidence is still limited and of poor quality[30].

Performance of genetic tests prior to initiating treatment with biological drugs in patients with IBD may constitute one more step on the way towards treatment individualization. The advantages of such tests include an increase in patient safety; a higher effectiveness of the treatment; and less expenses for the health system. One of the most significant findings to date was made by the PANTS prospective study, performed in 1,240 untreated patients. The study revealed an association between the *HLA-DQA1*05* (rs2097432) locus and a higher rate of immunogenicity (hazard ratio (HR) 1.90; 95% CI:1.60-2.25; $p < 0.001$) and of anti-IFX and anti-adalimumab antibody development. The authors observed higher immunogenicity rates at one year (92%) in patients on IFX monotherapy who were carriers of the *HLA-DQA1*05* haplotype. The lowest immunogenicity was observed in patients on adalimumab combined with an immunomodulator who were not carriers of that allele[31].

Another retrospective study on 252 patients with IBD showed the *HLA-DQA1*05* haplotype to significantly increase the risk of anti-IFX antibody formation (HR 7.29; 95% CI 2.97-17.191; $p < 0.001$) independently of the patient's age, sex, and weight and immunomodulator use, such factors being typically associated with a faster clearance of monoclonal antibodies. It was estimated that including immunomodulators in the patients' dosing regimen reduced the immunogenicity risk by 38% in both carriers and non-carriers (HR 0.62; 95% CI: 0.30-1.28)[32].

A *GWAS* study identified genetic variants in the *CD96* locus (rs9828223; $p < 0.001$) associated with immunogenicity and with a loss of clinical response[33].

A study from the Netherlands reported on a genetic test that included several polymorphisms (among them *HLA-DQA1*05*, *TPMT*; *NUDT15*) associated with the immunogenicity of antiTNF agents or with toxic effects in thiopurines (e.g., myelosuppression or pancreatitis)[34]. These findings should prompt research into other disciplines where IFX plays a key role in treatment algorithms (e.g., rheumatology). The results of the INHERIT

study (NCT04109300), which explores the prospective value of determining the *HLA-DQA1*05* haplotype in IBD patients who may be amenable to IFX treatment, may also be relevant in this regard as evaluation of the *HLA-DQA1*05* haplotype could be routinely carried out prior to initiating treatment with antiTNF agents[35].

The limitations of the present review are related to the differences between the various RCTs included regarding their design and population characteristics, analyzed drugs, activity scores and the phase at which the measurements were performed (induction or maintenance). This heterogeneity prevented a joint analysis of the results of the different trials. There is therefore a need to carry out prospective RCTs with more homogeneous designs and larger patient cohorts to come up with a more robust analysis of the benefits of proactive TDM in IBD patients.

To conclude, TDM allows an individualized adjustment of treatment with biological drugs in patients with IBD. The available evidence is still limited and low-quality, which prevents making hard-and-fast conclusions about the superiority of proactive vs. reactive TDM. On the other hand, the recent development of pharmacogenetic analysis techniques could allow an ex-ante selection of the patients most likely to derive a greater benefit from a specific technique as a function of their genotype. When more data is available, the combination of both strategies could herald a significant transformation in the way IBD patients are managed. It will be essential for pharmacists to play a key role in the multidisciplinary teams taking care of IBD patients.

Funding

No funding.

Acknowledgements

The authors would like to thank SEFH's PKGen Group for inviting them to contribute this paper to the Revista's special issue on personalized pharmacokinetics in clinical practice.

Conflict of interest

No conflict of interests.

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