Doctoral Program in Statistics, Optimization and Applied Mathematics

# Model-Informed Precision Dosing of adalimumab in patients with inflammatory bowel disease

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- 2024 -

# INDICIOS DE CALIDAD DE LA TESIS DOCTORAL

La presente Tesis Doctoral, titulada **Individualización farmacocinética del tratamiento con adalimumab en pacientes con enfermedad inflamatoria intestinal,** dentro del Programa de Doctorado en Estadística, Optimización y Matemática Aplicada, se presenta bajo la modalidad de **tesis por compendio** de las siguientes **publicaciones**:

- Marquez-Megias S, Ramon-Lopez A, Más-Serrano P, Diaz-Gonzalez M, Candela-Boix MR, Nalda-Molina R. *Evaluation of the Predictive Performance of Population Pharmacokinetic Models of Adalimumab in Patients with Inflammatory Bowel Disease*. **Pharmaceutics**. 2021; 13(8):1244. DOI: 10.3390/pharmaceutics13081244 / PMID: 34452204
- Marquez-Megias S, Nalda-Molina R, Sanz-Valero J, Más-Serrano P, Diaz-Gonzalez M, Candela-Boix MR, Ramon-Lopez A. *Cost-Effectiveness of Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease: A Systematic Review*. **Pharmaceutics**. 2022;14(5):1009. DOI: 10.3390/pharmaceutics14051009 / PMID: 35631594
- Marquez-Megias S, Nalda-Molina R, Más-Serrano P, Ramon-Lopez A. *Population Pharmacokinetic Model of Adalimumab Based on Prior Information Using Real World Data*. **Biomedicines**. 2023;11(10):2822. DOI: 10.3390/biomedicines11102822 / PMID: 37893195

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Que **Dña. Silvia Márquez Megías** ha realizado bajo nuestra supervisión el trabajo titulado ***Individualización farmacocinética del tratamiento con adalimumab en pacientes con enfermedad inflamatoria intestinal*** conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

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**INFORMA**:

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En Elche a ……. de …….. de 2024

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# FINANCIACIÓN DE LA TESIS DOCTORAL

La presente Tesis Doctoral ha sido financiada por las siguientes ayudas y/o contratos:

1. Ayudas a la iniciación a la investigación 2020 por la Universidad Miguel Hernández de Elche.

2. Contrato de personal de investigación de carácter temporal por la Universidad Miguel Hernández de Elche, con número de referencia PAR-00385/2021.

3. Ayudas para la Contratación de Personal Investigador en Formación 2021 por la Universidad Miguel Hernández de Elche.

4. Ayudas para la movilidad internacional del PDI Y PI 2023 por la Universidad Miguel Hernández de Elche.

# AGRADECIMIENTOS

Todo comenzó en cuarto de carrera, cuando conocí a mis futuros directores de Tesis, Amelia Ramón y Ricardo Nalda, que me introdujeron en el fascinante mundo de la farmacocinética poblacional y me ayudaron a elegir el camino de la investigación. Considero que he sido muy afortunada de haberme cruzado con ellos y de que confiaran en mí para realizar la Tesis Doctoral. Desde el principio, me integraron en su grupo de investigación y me trataron como una más. Siempre estaré enormemente agradecida por su disposición para trabajar conmigo, por los buenos ratos compartidos, por su constante paciencia y por la “familia burbuja” que formamos en el despacho durante estos años.

Me gustaría expresar mi más profundo agradecimiento al Dr. Ricardo Nalda. Son muchos momentos compartidos que no se pueden resumir en unas cuantas líneas, pero permanecerán imborrables en mi memoria, junto con todas las anécdotas vividas en congresos, conversaciones y momentos de risas en el despacho. Ha sido una gran fuente de inspiración y motivación, impulsándome a seguir trabajando y a enfrentar nuevos desafíos con determinación. Además de la ayuda incalculable prestada tanto en las facetas académicas como en las personales. Me faltan palabras para describir mi gratitud y admiración.

Igualmente, quiero mostrar mi sincero agradecimiento a la Dra. Amelia Ramón por su inestimable contribución a mi formación académica y personal. Aprecio mucho todos los conocimientos transmitidos y los consejos tan valiosos, tanto para el desarrollo de mi Tesis como para mi crecimiento personal, siempre acompañados de una sonrisa. También me gustaría darle las gracias por la oportunidad que me dio al iniciarme en el mundo de la docencia universitaria, un ámbito completamente nuevo para mí, pero apasionante y gratificante. Valoro enormemente la confianza y dedicación que ha depositado en mí desde el principio.

Sin duda, haber compartido este camino con vosotros ha hecho que mi experiencia como doctoranda haya sido mucho más enriquecedora y significativa. Ha sido un placer poder teneros como mis directores de tesis.

Además, deseo agradecer sinceramente a la unidad de Farmacocinética Clínica del Hospital General Universitario Dr. Balmis de Alicante, especialmente al Dr. Patricio Más. Aprecio profundamente el tiempo dedicado a revisar, colaborar y formar parte de cada uno de los artículos que forman esta Tesis Doctoral.

De igual manera, quiero expresar mi agradecimiento al Dr. Javier Sanz Valero por enseñarme y guiarme en la realización de revisiones sistemáticas. Ha sido un verdadero honor colaborar y trabajar con él, así como compartir la autoría en uno de los artículos incluidos en esta Tesis Doctoral.

Asimismo, deseo transmitir mi reconocimiento a Aris Dokoumetzidis por brindarme la oportunidad de realizar una estancia de investigación con él y su equipo en Atenas, así como por compartir sus conocimientos en el campo de la farmacocinética poblacional, su paciencia y dedicación. También quiero agradecer a todos mis compañeros de Grecia, especialmente a Eleni, Chris y Evans, quienes me acogieron y me integraron desde el primer momento, enseñándome lo increíble que es tener compañeros que compartan las mismas experiencias y que entiendan la investigación que realizas.

No puedo pasar por alto el respaldo constante de mi familia, especialmente el de mi hermana y mi padre. Han hecho un esfuerzo no solo por comprenderme a mí, sino también mi trabajo. Muchas gracias por vuestra paciencia, ánimos y por nunca cansaros de escucharme.

También, es importante para mí reconocer el apoyo incondicional de mis amigos, con especial mención a Adriana, por escuchar mis audios interminables, dándome su apoyo, comprensión y sus mejores consejos en todos los momentos. A Ana, también le agradezco estar siempre cerca, a pesar de la distancia, escuchando mis historias y ofreciéndome su ayuda, comprensión y sabiduría, convirtiéndose en mi otra hermana mayor. Y a Maribel, por acompañarme, animarme a seguir adelante y confiar en mí incluso cuando yo misma dudaba.

Por supuesto, no puedo dejar de agradecer a Javi, quien indudablemente ha sido la persona que más de cerca ha vivido mi tesis. Creo que se merece una estatua por su paciencia en todos los momentos de mi etapa doctoral, tanto los felices como los de incertidumbre y tensión. Gracias por creer en mí y por ser mi apoyo constante durante este camino, por celebrar mis logros y por formar parte de ellos. Has hecho posible que alcance mis objetivos y que pueda enfrentar cualquier desafío; sin ti, este camino no habría sido el mismo.

Finalmente me gustaría dar las gracias a mi madre, porque sé que estaría muy orgullosa de ver cómo he crecido personalmente y de todas las metas que he alcanzado, aunque sé que siempre lo estuvo. A pesar de que, por desgracia, no pudo vivir todo el proceso del doctorado a mi lado, siempre ha estado acompañándome en una parte de mí. Tengo claro que sin ella nada de esto hubiera sido posible. Muchas gracias, mamá.

# ÍNDICE

# LISTA DE ABREVIATURAS

| | |
|---|---|
| **AAA** | Antibodies Against Adalimumab |
| **BIREME** | Latin American and Caribbean Center on Health Sciences Information |
| **CD** | Crohn's Disease |
| **CHEERS** | Consolidated Health Economic Evaluation Reporting Standards |
| **CI** | Confidence Interval |
| **CL/F** | Apparent Clearance |
| **Cmax** | Maximum Plasma Concentration |
| **DeCS** | Health Sciences Descriptors |
| **EBES** | Empirical Bayesian Estimates |
| **EII** | Enfermedad Inflamatoria Intestinal |
| **IBD** | Inflammatory Bowel Diseases |
| **ICER** | Incremental Cost-Effectiveness Ratio |
| **IIV** | Interindividual Variability |
| **ka** | Absorption Rate Constant |
| **LILACS** | Caribbean Health Sciences Literature |
| **LOR** | Loss Of Response |
| **MEDES** | Medicina En Español |
| **MeSH** | Medical Subject Headings |
| **MIPD** | Model-Informed Precision Dosing |
| **MPE** | Mean Prediction Error |
| **NPC** | Numerical Predictive Check |
| **NPDE** | Normalized Prediction Distribution Errors |
| **OFV** | Objective Function Value |
| **pcVPC** | Predicted-Corrected Visual Predictive Check |
| **PK** | Pharmacokinetics |
| **PopPK** | Population Pharmacokinetic |

| | |
|---|---|
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **QALY** | Quality-Adjusted Life-Years |
| **QQ-plot** | Quantile-Quantile plot |
| **RMSPE** | Root Mean Square Prediction Error |
| RSE | Relative Standard Error |
| **SIGN** | Scottish Intercollegiate Guidelines Network Grading Review Group |
| **TDM** | Therapeutic Drug Monitoring |
| **Tmax** | Time to Maximum Plasma Concentration |
| **TNF** | Tumor Necrosis Factor |
| **TSC** | Trough Serum Concentration |
| **UC** | Ulcerative Colitis |
| **V/F** | Apparent Volume of Distribution |

# ABSTRACT

Inflammatory Bowel Diseases (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic autoimmune diseases characterized by intermittent destructive inflammation in different areas of the digestive tract because of the release of inflammatory mediators, such as cytokines, interleukins, and tumor necrosis factor (TNF) by the immune system.

Biological therapies, particularly anti-TNF drugs like adalimumab, have emerged as revolutionary options for the treatment of IBD. Adalimumab is a humanized IgG1 monoclonal antibody that specifically binds to the TNF and neutralizes its biological function. Despite its effectiveness, a significant proportion of patients annually face a loss of response (LOR), requiring dose adjustments or treatment changes. Prolonged subtherapeutic drug levels can lead to LOR or the development of antibodies against adalimumab (AAA) that reduce treatment response rates. Optimizing treatment through Model-Informed Precision Dosing (MIPD) is crucial to prevent immunogenicity and lead to reduced surgery rates and lower AAA risk, along with economic advantages.

In clinical settings, rich profiles of plasma drug concentration measurements are often unavailable, which limits the development of population pharmacokinetic (PopPK) models. Consequently, dosage individualization relies on existing PopPK models from the literature. However, the selected PopPK model must be developed from a population similar to the studied population and must be validated before using them in the clinical setting. The re-estimation of the PopPK parameters would lead to an improvement in the precision and accuracy of the model's plasma concentration predictions.

The first objective of this Thesis was to conduct a systematic review to evaluate studies on the cost-effectiveness analysis of Therapeutic Drug Monitoring (TDM) of anti-TNF in IBD. A cross-sectional descriptive study of studies found in the literature was conducted following the structure of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The quality of the included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. Thirteen studies from 2013 to 2021 were reviewed, with eight achieving very good to excellent rankings on the CHEERS checklist. This systematic review demonstrated the cost-effectiveness and potential cost-saving benefits of implementing TDM for anti-TNF drugs in IBD management.

The second objective of this Thesis was to evaluate the predictive performance of PopPK models of adalimumab in IBD patients, identified in the literature, to determine the PopPK model that best suited the target population of the Dr. Balmis General University Hospital

of Alicante to integrate it into clinical routines. A retrospective observational study involving 134 patients was conducted between 2014 and 2019. Model adequacy was assessed through individual PK parameter distribution and Normalized Prediction Distribution Errors (NPDE) plots, while predictive performance was assessed by calculating bias and precision. Additionally, stochastic simulations were performed to optimize maintenance doses in clinical protocols, to achieve a trough target of 8 mg/L in at least 75% of the population. Among the PopPK models for adalimumab in IBD found in the literature, two were superior in terms of model adequacy and predictive performance. Nevertheless, it was observed that the Empirical Bayesian Estimates (EBEs) were biased from the population mean values, suggesting the need for model refinement based on available data. Furthermore, stochastic simulations with these models suggested potential benefits in increasing the maintenance dose in the protocol to reach the 8 mg/L target.

The last objective of this Thesis was to optimize the selected PopPK model of adalimumab for IBD, looking for the improvement in predictive performance and clinical impact. In this study, the selected model from the previous objective was considered as a reference model. A retrospective observational study involving 54 IBD patients was conducted to refine the reference model. The refinement of the PK parameters was performed using two different methods: estimating the PK parameters without priors (estimated model) and incorporating informative priors in some parameters (prior model). The criterion for model selection were the evaluation of predictive performance and the clinical impact. This final model effectively characterized adalimumab PK in the studied population and improved by up to 50%, compared to the reference model in terms of bias and precision. The main structural difference between both models was the inclusion of the albumin as a meaningful covariate on CL/F. Moreover, the final model significantly improved the clinical impact on the target population, suggesting more accurate dose optimization and increased efficacy in adalimumab treatment.

# RESUMEN

La Enfermedad Inflamatoria Intestinal (EII) es una enfermedad autoinmune crónica caracterizada por episodios intermitentes de inflamación en diversas regiones del tracto digestivo. Esta inflamación es ocasionada por la liberación de mediadores inflamatorios, como citocinas, interleucinas y el factor de necrosis tumoral (TNF), por parte del sistema inmunológico. Dos tipos de enfermedades se abarcan dentro de la EII, la Enfermedad de Crohn y la Colitis Ulcerosa.

Los tratamientos biológicos, en particular los fármacos anti-TNF como el adalimumab, han emergido como opciones novedosas en el tratamiento farmacológico de la EII. Adalimumab es un anticuerpo monoclonal IgG1 humanizado que se une específicamente al TNF y neutraliza su función biológica. A pesar de su eficacia, una proporción significativa de pacientes experimenta anualmente una pérdida de respuesta al tratamiento, lo que implica ajustes de dosis o cambios de tratamiento farmacológico. La persistencia de concentraciones plasmáticas de adalimumab por debajo del intervalo terapéutico puede desencadenar la pérdida de respuesta o el desarrollo de anticuerpos anti-adalimumab (AAA), reduciendo la tasa de respuesta al tratamiento. La monitorización e individualización posológica de adalimumab resulta crucial para prevenir la inmunogenicidad, disminuir las tasas de cirugía y minimizar el riesgo de desarrollar AAA, además de ofrecer beneficios económicos.

En la práctica clínica rutinaria solo se suele disponer de un limitado número de determinaciones de las concentraciones plasmáticas de fármaco, por lo que no siempre es posible desarrollar un modelo farmacocinético poblacional (PopPK) y, por tanto, la individualización posológica se basa en modelos PopPK de la literatura científica. No obstante, el modelo PopPK seleccionado debe haberse desarrollado a partir de una población de pacientes similar a la población estudiada y es necesario que se valide previamente a su utilización en la práctica clínica. Posteriormente, la reestimación de los parámetros PopPK, conllevará una mejora en la precisión y exactitud con la que el modelo PopPK predice las concentraciones plasmáticas.

El primer objetivo de esta Tesis fue realizar una revisión sistemática para evaluar los estudios disponibles sobre el impacto coste-efectivo de la individualización posológica de anti-TNF en EII. Se realizó un estudio descriptivo transversal de estudios publicados en la literatura siguiendo la estructura de las guías Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). La calidad de los estudios incluidos se evaluó mediante la lista de verificación Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Se revisaron trece estudios realizados entre 2013 y

2021, y ocho de ellos obtuvieron clasificaciones de muy buena a excelente en la lista de verificación CHEERS. Esta revisión sistemática evidenció que realizar TDM en anti-TNF en el tratamiento de la EII es coste-efectivo y que además permite ahorrar gastos.

El segundo objetivo de esta Tesis fue evaluar la capacidad predictiva de los modelos PopPK de adalimumab en pacientes con EII, identificados en la literatura, para determinar el modelo PopPK que mejor se adapta a la población del Hospital General Universitario Dr. Balmis de Alicante y, así, incorporarlo en las rutinas clínicas de individualización posológica. Se realizó un estudio observacional retrospectivo con 134 pacientes entre 2014 y 2019. La adecuación del modelo se evaluó mediante la distribución de parámetros PK individuales y gráficos de Normalized Prediction Distribution Errors (NPDE), mientras que la capacidad predictiva se evaluó mediante el cálculo de la exactitud y la precisión. Además, se realizaron simulaciones estocásticas para optimizar las dosis de mantenimiento en protocolos clínicos, para lograr un objetivo terapéutico de una concentración plasmática valle de adalimumab de 8 mg/L en al menos el 75% de la población. Entre los modelos PopPK para adalimumab en EII encontrados en la literatura científica, dos obtuvieron mejores resultados que el resto en términos de adecuación del modelo y capacidad predictiva. Sin embargo, se observó que los Empirical Bayesian Estimates (EBEs) estaban sesgados en comparación con los valores medios poblacionales de los modelos seleccionados, lo que sugiere la necesidad de adaptar el modelo para la población estudiada. Además, las simulaciones estocásticas realizadas con estos modelos mostraron los posibles beneficios de aumentar la dosis de mantenimiento en los protocolos para alcanzar el objetivo terapéutico de 8 mg/L.

El último objetivo de esta Tesis fue optimizar el modelo PopPK de adalimumab para EII de la literatura, considerando mejoras en la capacidad predictiva y el impacto clínico. En este estudio se consideró como modelo de referencia el modelo seleccionado del objetivo anterior. Se realizó un estudio observacional retrospectivo con 54 pacientes con EII para refinar el modelo de referencia. El ajustado de los parámetros farmacocinéticos se realizó utilizando dos métodos diferentes: uno estimando los parámetros farmacocinéticos sin incluir priors (modelo estimado) y el otro incorporando información del modelo de referencia como priors en algunos parámetros (modelo prior). Para seleccionar el modelo PopPK se evaluó la capacidad predictiva y el impacto clínico. El modelo final caracterizó eficazmente la farmacocinética de adalimumab en la población estudiada y mejoró hasta en un 50%, con respecto al modelo de referencia en términos de la exactitud y precisión. La principal diferencia estructural entre ambos modelos fue la inclusión de la albúmina como una covariable significativa en el CL/F. Además, el

modelo final mejoró significativamente el impacto clínico en la población estudiada, lo que sugiere una individualización posológica más precisa y conlleva una mayor eficacia en el tratamiento farmacológico con adalimumab.

# 1. INTRODUCTION

## 1.1 Inflammatory Bowel Diseases

Inflammatory Bowel Diseases (IBD) are chronic autoimmune diseases characterized by intermittent destructive inflammation in different areas of the digestive tract. This inflammation occurs as a result of the release of inflammatory mediators, such as cytokines, interleukins, and tumor necrosis factor (TNF) by the immune system. Currently, the etiology and pathogenesis of IBD remain unclear. However, factors like gut microbiota, genetic predisposition, immune dysregulation, and environmental elements, such as diet and lifestyle are considered relevant to the development of the disease [1-3].

Symptomatic episodes in IBD manifest as flares, alternating with periods of remission. The frequency, duration, and severity of these flares are variable and unpredictable. The spectrum of symptoms associated with IBD is extensive, including abdominal pain, diarrhea, nocturnal defecations, tenesmus, weight loss, fatigue, and extraintestinal manifestations such as arthritis and skin disorders [4, 5].

Despite having a low mortality rate, the unpredictable nature, frequency of flares, and the prolonged duration of symptoms, which can extend significantly over time, produce a great limitation in the quality of life of patients, preventing the development of daily activities. Additionally, the need for ongoing medical treatments, dietary restrictions, and the potential long-term complications is considered a burden in managing this chronic condition [6, 7]. Therefore, IBD not only affects the physical health of individuals but also impacts their emotional and social well-being and affects their quality of life, interfering with their personal and work development.

IBD typically manifests during late adolescence and early adulthood, with a notable incidence peak between the ages of 15 and 30. Nevertheless, these conditions can affect individuals at any age, including children and older adults. [6, 7]. The diagnosis of IBD is based on a combination of clinical symptoms, endoscopic and histological findings [4-7] and include two pathologies: Crohn's disease (CD) and ulcerative colitis (UC). Both diseases share similarities in terms of clinical symptoms, diagnosis, risk factors, and treatment. However, they mainly differ in the location of inflammation.

CD is characterized by transmural inflammation that can affect any part of the digestive tract. The inflammation of the digestive tract wall in CD is discontinuous and asymmetrical, leading to complications such as obstruction, abscesses, and fistulas [6]. On the other hand, UC affects a more limited area, involving only the superficial layer of the colon, although in severe cases, the lesion may reach the muscular layer. Unlike CD,

the damaged area of the intestinal wall in UC is symmetrical and presents a continuous extension [7].

The global distribution of IBD reveals a high prevalence of IBD in North America and Europe with 6.8 million cases of IBD [9]. However, in the recent decades, there has been a notable increase in its occurrence in Asian countries possibly due to the change in dietary patterns, increased consumption of processed foods, excessive use of antibiotics, and overall improvements in hygiene [10, 11]. Consequently, IBD has become a global health problem with a substantial economic impact on healthcare [12, 13].

The inherent risks associated with IBD are substantial, extending beyond the gastrointestinal tract. Multiple European studies indicate that UC patients face an increased risk of colorectal cancer, while patients with CD have elevated risks of extraintestinal cancers compared to the general population. Additionally, IBD is linked to heightened mortality, with factors such as disease severity and complications contributing to adverse outcomes [14-17].

## 1.2 Pharmacological treatment

The current pharmacological treatments aim to reduce the intensity of flares, prevent complications, like surgery, and block disease progression, ultimately improving the quality of life for patients with minimal adverse effects. Several pharmacological alternatives are available, including aminosalicylates, corticosteroids, Immunomodulators, and biological therapies, which have shown clinical efficacy in treating these diseases [4, 5].

Aminosalicylates, such as mesalamine and sulfasalazine, are particularly effective for mild to moderate cases of IBD and are often used as first-line treatments due to their local anti-inflammatory properties in the gastrointestinal tract. Their localized action minimizes systemic side effects, contributing to their favorable safety profile. Aminosalicylates have proven benefits in both the induction and maintenance phases of IBD treatment, offering patients a versatile and well-tolerated option [4, 5].

Corticosteroids, including prednisone and budesonide, are potent anti-inflammatory drugs used for short-term management of flares in IBD. By suppressing the immune response and reducing inflammation in the gastrointestinal tract, these drugs effectively reduce symptoms like abdominal pain and diarrhea. However, their effectiveness falls short of achieving mucosal healing. Despite their efficacy, even short-term use may be accompanied by significant adverse events, including bone loss, weight gain, insomnia,

hypertension, elevated blood glucose, and others. Historically, they have served as a temporary "bridge" to allow symptom control until immunomodulators and/or biologic agents become effective and enable mucosal healing [4, 5].

Immunomodulators, such as azathioprine, 6-mercaptopurine, and methotrexate, are prescribed to maintain remission in patients with moderate-to-severe IBD who remain symptomatic despite current or previous corticosteroid therapy. While these drugs are not suitable for short-term induction in active and symptomatic disease due to their relatively slow onset of action, they prove effective for sustaining long-term remission and preventing disease flares. Adverse effects may include allergic reactions, pancreatitis, myelosuppression, nausea, infections, and hepatotoxicity [4, 5].

Biological therapies have emerged as revolutionary options for the treatment of IBD, representing a significant advancement in IBD management and offering improved symptom control and quality of life for many patients. These therapies include anti-tumor necrosis factor (anti-TNF) agents (e.g., infliximab, adalimumab), anti-integrin agents (e.g., vedolizumab), and anti-interleukin agents (e.g., ustekinumab). These therapies target specific components of the immune system to reduce inflammation, inducing and maintaining remission in patients with moderate to severe IBD. Their specificity in targeting molecules involved in the inflammatory cascade not only enhances efficacy but also minimizes the non-specific immunosuppression associated with conventional treatments [4, 5].

### 1.3 Adalimumab

Anti-TNF drugs are monoclonal antibodies that specifically bind to the TNF and neutralize its biological function, thereby decreasing the inflammation process. Adalimumab is a humanized IgG1 monoclonal antibody indicated for both induction and maintenance in patients with moderate-to-severe IBD older than 6 years who do not respond to the treatment with corticosteroids, immunosuppressive agents, or other biologic therapy [18-21].

The dosage regimen of adalimumab consists of two phases: an induction phase, with a dosage of 160/80 mg or 80/80 mg at weeks 0/2; and a maintenance phase where patients receive 40 mg of adalimumab every other week. The dosage and administration frequency can be adjusted according to the individual patient’s needs with the aim of achieving the optimal efficacy during long-term treatment. The dosage regimen in the maintenance phase can be increased to 40 mg every 10 days, 40 mg every week, 80

mg every other week, or 80 mg every week. Conversely, the dosage regimen can be decreased to 40 mg every 3 weeks [20, 21].

Adalimumab exhibited linear pharmacokinetics (PK) with a mean half-life of approximately 2 weeks ranging from 10 to 20 days across studies [21]. This indicates a nearly complete elimination of the drug within 14 weeks. Adalimumab is administered subcutaneously, allowing patients to self-administer the treatment in an ambulatory setting. Its bioavailability is estimated to be 64% and the primary mechanism responsible for its removal is opsonization via the reticuloendothelial system [21,22]. In a single 40 mg subcutaneous administration of adalimumab to healthy adult subjects, the maximum serum concentration (Cmax) reached 4.7 ± 1.6 μg/mL, with a time to reach the maximum concentration (Tmax) of 131 ± 56 hours, which is approximately five days. This suggests a gradual and sustained release pattern, contributing to the extended therapeutic effect. Moreover, the clinical response is reached after 2-8 weeks of treatment [21].

Adalimumab is usually well tolerated and there were no dose-related adverse events. Patients in clinical trials have been administered doses up to 10 mg/kg without any observed dose-limiting toxicities. Nevertheless, in the event of an overdose, it is advisable to closely monitor the patient for any signs or symptoms of adverse reactions or effects. Immediate and appropriate symptomatic treatment should be initiated to address any potential complications [21]. The most reported side effects are localized at the injection site, presenting as erythema and/or itching, occasional bleeding, pain, or swelling. However, it is not necessary to discontinue treatment due to these reactions. On a systemic level, infections are potential adverse reactions because of the immunosupression. These infections often manifest in the respiratory tract, including pneumonia, sinusitis, and pharyngitis, among others. Despite these potential side effects, the benefits of adalimumab in managing IBD outweigh the risks, and careful monitoring allows for timely intervention when necessary [20, 21].

Although there are no specified contraindications, it is noteworthy that adalimumab has not been sufficiently studied in patients aged 4 years or younger or with a body weight less than 15 kg. Moreover, clinicians should avoid prescribing adalimumab in cases of hypersensitivity and patients with underlying active infection, such as tuberculosis, congestive cardiac failure, or hepatic dysfunction. Adalimumab has been associated with the reactivation of hepatitis B, due to the immunosuppressive effects of the drug [21].

## 1.4 Therapeutic Drug Monitoring and Model Informed Precision Dosing

Therapeutic drug monitoring (TDM) consists of optimizing the treatment of each patient, ensuring that the drug concentrations in the patient stay within the therapeutic range to achieve the maximum efficacy with the minimum toxicity. This strategy may also consider the variability in the drug response among different individuals, including factors such as age, sex, weight, comorbidities, and concomitant medications [23].

On the other hand, the utilization of the Model-Informed Precision Dosing (MIPD) approach stands out as a valuable strategy to optimize drug dosages, particularly for drugs with high PK variability. This strategy involves the application of population pharmacokinetic (PopPK) models and a prospective Bayesian approach to calculate the individual PK parameters for each patient. These PK parameters guide the determination of the optimal dosage regimen, striking a balance between efficacy and toxicity, and ultimately improving treatment outcomes for each patient [39].

The PK of anti-TNF plays a crucial role in determining the response in patients with IBD. Nearly 40% of IBD patients experience a loss of response (LOR) to anti-TNF treatment every year, requiring either dose intensification or switching to another drug [24]. When patients do not show any improvement from the treatment, it is identified as primary LOR [24-26]. Conversely, secondary LOR occurs when patients no longer respond to treatment, even after an initial positive response [25, 26]. Over the past decade, multiple studies have pointed out that, following extended periods of subtherapeutic drug levels may increase the probability to experience a LOR to adalimumab or develop antibodies against adalimumab (AAA) [27-31]. This underscores the critical role of individualized dosing, as the presence of AAA reduces the response rate to treatment, often preventing the use of another drug with a similar mechanism of action. Furthermore, a prospective study has indicated the challenges of achieving improved clinical outcomes through dose escalation once patients experience a LOR [30].

Numerous studies highlight the association between higher serum adalimumab concentrations and improved therapeutic outcomes [32-35]. The exposure target varies depending on whether patients are diagnosed with CD or UC and the specific therapeutic objective, such as clinical, endoscopic, biochemical, or histologic remission. Among these objectives, endoscopic remission is widely accepted as the most relevant target [35]. Several studies suggest that maintaining trough serum concentrations (TSC) of adalimumab within the range of 8–12 mg/L is necessary to achieve mucosal healing and endoscopic remission in 80–90% of IBD patients [35, 36]. Notably, a recent study found that patients with adalimumab TSCs below 8.3 mg/L were at a higher risk of developing

AAA and experiencing LOR by week 12 [32]. Therefore, a therapeutic range of 8–12 mg/L has been considered in the clinical setting for most groups.

Historically, adjusting adalimumab dosage was based on an empirical approach, involving the escalation of treatment for patients facing a LOR. This adjustment relied on their symptoms, which exhibit variability from one patient to another, making it a subjective and imprecise criterion. If this strategy proved ineffective, the next step was switching to another biological treatment. Nevertheless, the dosing guidance was predominantly conducted using algorithms [37, 38]. Nonetheless, predicting the progression of IBD through a standardized algorithm is challenging due to the occurrence of different and random events along a patient's disease trajectory, differing among individuals.

Given the considerable interindividual variability (IIV) in the PK of adalimumab, patients with IBD could experience substantial benefits through dose optimization [36, 38]. A multicenter retrospective study involving adalimumab-treated patients indicated that the MIPD approach could prevent immunogenicity and lead to superior long-term outcomes in IBD. These outcomes include reduced rates of surgery or hospitalization, a lower risk of developing AAA, and fewer serious infusion reactions [41]. Moreover, considering the mean direct cost per patient-year, estimated at approximately 3500 euros for CD patients and 2000 euros for UC patients, including diagnostic procedures, hospitalizations, and biological treatment in Europe [40], MIPD emerges as a particularly relevant tool for cost savings. Furthermore, the MIPD approach proved to be more cost-effective compared to empirical or reactive dose optimization programs [41].

In the clinical setting, the use of MDPI often relies on utilizing PopPK models available in the literature due to the lack of data for developing in-house models in many hospitals. In the literature, there are multiple PopPK models developed for adalimumab and IBD patients. The variety of models is due to several factors such as differences in the target population in age, disease severity, ethnicity, dietary habits, and more. Additionally, disparities in study protocols, analytical methods, sampling schedules, or follow-up durations, contribute to the heterogeneity in the PopPK models. Moreover, the utilization of distinct statistical and computational tools, along with the expertise of the pharmacometrics research group, further accentuates the variability. Consequently, PopPK models for the same drug could exhibit significant variations, resulting in different predicted concentration profiles for individual patients. Therefore, the key determinant for the successful implementation of MIPD lies in the selection of the appropriate PopPK model.

Thus, before incorporating a drug into the MIPD program, it is essential to validate these models within the target population. The aim is to obtain more precise and reliable outcomes during implementation, so the validation must involve assessing the predictive performance of the models under similar conditions to the clinical practice. However, many validations reported in the literature tend to focus on the model adequacy rather than evaluating its predictive performance. While model adequacy uses all the data available to validate the model, the assessment of predictive performance is calculated using TSCs that were not employed in calculating the Empirical Bayesian estimates (EBEs) of the PK parameters, providing a more realistic representation of real-world scenarios.

Even though a PopPK model implemented from the literature can suit a population in the clinical setting, it is convenient to refine the selected PopPK model to the specific study population. This adaptation involves re-estimating parameters and considering potential new covariates to improve the accuracy and precision in dose optimization. On the other hand, the incorporation of prior information in the PK model development can be valuable in stabilizing parameter estimations, particularly when dealing with limited available data. Multiple studies have demonstrated that employing priors in the PK parameter estimation allowed a better fit to the new data than fixing the parameters [42-46].

# 5. OBJECTIVES

The objectives of this Thesis are the following:

1. To conduct a systematic review to evaluate studies on the cost-effectiveness analysis of TDM of anti-TNF in IBD and to provide a critical analysis of the most current scientific knowledge regarding the use of TDM.

2. To assess the predictive performance of PopPK models of adalimumab in IBD patients and to determine the PopPK model that best suited the target population of the Dr. Balmis General University Hospital of Alicante, to subsequently, use it in the real-world using MIPD.

3. To optimize the PopPK model of adalimumab for IBD, previously selected from the literature, considering its improvement in predictive performance and clinical impact.

# 6. METHODS

## 3.1 Study design

The systematic review (*Article I*) consisted of a cross-sectional descriptive study and a critical analysis of studies found in the literature. The structure of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [47] (*Article I: Supplementary Table S1*), and the methodological framework proposed for scoping studies [48,49].

For *Articles II* and *III*, two retrospective observational studies were conducted at the Dr. Balmis General University Hospital of Alicante on patients diagnosed with IBD undergoing adalimumab treatment who followed an MIPD program. Data for the first study (*Article II*) were collected from patients enrolled in the MIPD program from 2014 to 2019, while data collection for the second study (*Article III*) was extended until 2022.

## 3.2 Literature Search

### *3.2.1 Source of Data Collection*

For both studies (*Article I* and *Article II*), data were sourced through direct consultation and online access to databases in the Health Sciences field. The databases included MEDLINE (via PubMed), Embase, and Scopus, with additional access for *Article I* to Cochrane Library, PsycINFO, Web of Science, Latin American & Caribbean Health Sciences Literature (LILACS), and Medicina en Español (MEDES).

### *3.2.2 Search strategies*

Search terms were selected using the Thesaurus of Health Sciences Descriptors (DeCS) developed by the Latin American and Caribbean Center on Health Sciences Information (BIREME) and equivalent terms established by the US National Library of Medicine, Medical Subject Headings (MeSH). For *Article I*, the following MeSH descriptors “Inflammatory Bowel Diseases”, “Tumor Necrosis Factor Inhibitors”, “Infliximab”, “Adalimumab”, “Cost-Benefit Analysis”, “Cost Savings” and “DrugMonitoring” were considered suitable, whereas for *Article II*, the used MeSH descriptors were “Chron Disease”, “Colitis, Ulcerative”, “adalimumab” and “pharmacokinetics”. In both studies, these terms were used to query the database using the title and abstract field (Title/Abstract) and it was not necessary to use filters (limits).

Both strategies were subsequently adapted to the characteristics of each database consulted, from the first available date in each of the selected databases until December 2021 (*Article I*) and May 2021 (*Article II*). Additionally, a manual search strategy was conducted by inspecting the reference lists of the articles that were selected

for the review to reduce the possibility of publication bias. Likewise, experts in the field were contacted to explore the potential presence of gray literature (materials and research generated by organizations outside conventional commercial or academic sources that are disseminated through alternative distribution channels). The search equations, for *Article I* and *II*, are available in Article I (Supplementary): Table S2 and *Article II: 2.1 Literature Search*, respectively.

### *3.2.3 Selection of Articles*

For the review and critical analysis, articles were selected based on specific criteria. In *Article I*, the inclusion criteria were original articles published in peer-reviewed journals that met the search objectives. Exclusion criteria were the unavailability of full-text articles, a lack of relationship between the intervention and the studied outcome (causality criterion), or articles focusing on diseases other than IBD, such as rheumatoid arthritis, psoriasis, or ankylosing spondylitis; studies regarding different drugs other than anti-TNF antagonists, like vedolizumab or ustekinumab, and studies conducted on animals. There was no language, publication date, or publication status restriction.

In the case of *Article II*, inclusion criteria comprised original articles published in peer-reviewed journals, works describing a new PopPK model, and relevant studies with full text available, written in either English or Spanish. The exclusion criteria were articles involving diseases other than CD or UC and studies conducted using animal models.

Two of the authors conducted the selection of relevant articles. To validate the inclusion of articles, an assessment of agreement between the authors using the kappa index was required to be greater than 0.60 [50]. In case of discrepancies, a third author was responsible for reaching a resolution and subsequent consensus amongst all the authors.

### *3.2.4 Quality Assessment, Level of Evidence and Grade of Recommendation*

For *Article I*, the quality of the included articles was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [51]. All studies were classified into four categories: "excellent" (85%), "very good" (70–84%), "good" (55–69%), and "insufficient" (<55%). The quality assessment was independently performed by two authors. It was determined that the inter-rater agreement among the authors, measured using the kappa index, should be higher than 0.60. In case of discrepancies, a third author was responsible for reaching a resolution and subsequent consensus amongst all the authors.

To evaluate the potential bias due to missing results, the methods and the results sections of the included articles were compared. The Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN) recommendations were used to establish the level of evidence and its corresponding degree of recommendation [52].

#### *3.2.5 Data Extraction*

For *Article I*, the extracted items included general information about the study (first author, country, and year of publication); study design (population, intervention, type of TDM approach used, time horizon, and methods of measuring outcomes); and results (primary outcomes). The primary outcomes collected included the cost-effectiveness of TDM strategies, expressed as total costs, cost savings, quality-adjusted life-years (QALY), or incremental cost-effectiveness ratio (ICER). To allow comparisons across studies, costs were converted to euros based on the year of publication of each study. Additionally, all costs were standardized over one year for result consistency. When data allowed, average costs per patient and per year were calculated by considering total costs and the number of patients within each treatment group in the respective studies.

The information collected for *Artic*le *II* was regarding patient characteristics, model structure, typical PopPK parameters, IIV, residual variability, and relevant covariates.

### 3.3 Patients and Data Collection

For the second and third studies (*Articles II* and *III*), data were collected from patients with IBD who underwent adalimumab treatment at the Dr. Balmis General University Hospital of Alicante, Spain. Participants diagnosed with IBD and with at least two adalimumab TSCs were eligible for inclusion. Patients treated with monoclonal antibodies other than adalimumab, such as infliximab, vedolizumab, or ustekinumab, and subjects who were diagnosed with other autoimmune diseases different from IBD such as rheumatoid arthritis, psoriasis, and ankylosing spondylitis, were excluded from both studies.

Relevant data were collected from the medical records and included age, sex, height, IBD type, body weight, lean body weight, body mass index, serum albumin, serum C-reactive protein, fecal calprotectin, AAA status, and AAA serum concentration, use of concomitant immunomodulators, previous anti-TNF treatment and whether adalimumab originator or biosimilar was used. For missing covariates, the mean value

of this covariate for a given patient was imputed. If any patient had no available value of a covariate, the mean value of that covariate of the rest of the patients was imputed.

Serum adalimumab concentrations and AAA were measured using an enzyme-linked immunosorbent assay (LISA TRACKER Duo Drug + ADAb from TheraDiag®) with a limit of quantification established to be 0.1 mg/L. Patients were considered as positive for AAA if titers were above 10 mg/L on at least one occasion.

## 3.4 Evaluation of Model Adequacy

For the second article (*Article II*), the evaluation of the model adequacy of the PopPK models found in the literature was performed by comparing how each PopPK model described the studied population using all the available TSCs. The distribution of the EBEs of the PK parameters for each of the PopPK models was calculated after performing a post-hoc analysis using the full dataset. Then, this distribution was compared to the theoretical distribution of these PK parameters according to each PopPK model. Additionally, Normalized Prediction Distribution Errors (NPDE) plots were performed to observe any trends that could indicate model misspecifications or inadequate model adequacy [53,54]. Models that showed a greater systematic bias in the EBEs of the PK parameters, or in the NPDE were excluded. The predictive performance of the models was further evaluated for those models that adequately described the studied population.

For the third article (Article III), an internal validation of model adequacy was conducted through a Numerical Predictive Check (NPC). This method quantitatively compares cumulative observed adalimumab concentrations corresponding to model-simulated percentiles with their expected concentrations, representing the 50th percentile of observed concentrations and the 95% confidence interval (CI) for the 50th percentile of predicted concentrations. Additionally, the accuracy and robustness of parameter estimates were assessed using a bootstrap with 500 replicates constructed by sampling individuals with replacements from the original dataset. Model parameters were estimated for each bootstrap replicate and were used to estimate the mean and 95% CI from the individual replicates.

## 3.5 Evaluation of Predictive Performance

For the second study (*Article II*), the predictive performance was only evaluated in those models that best described the studied population, according to the evaluation of the model adequacy.

To evaluate the predictive performance, the individual predictions of the last TSCs were estimated for each patient, using EBEs of the individual PK parameters. These last TSCs, named “last observed TSC”, were left out and not used to calculate the EBEs of the individual PK parameters. Then, bias and imprecision were calculated using the last observed TSCs by comparing them with their individual predictions calculated by each of the PK models. Two different scenarios were considered to evaluate the predictive performance: Scenario 1: EBEs were calculated from the previous TSC obtained from each patient; Scenario 2: EBEs were calculated from the two previous TSCs of each patient.

The mean prediction error (MPE, Equation (1)) and root mean square prediction error (RMSPE, Equation (2)) were calculated for bias and imprecision, respectively.

$$MPE = \frac{\sum(\hat{Y}-Y)}{n} \quad (1)$$

$$RMSPE = \sqrt{\frac{\sum(\hat{Y}-Y)^2}{n}} \quad (2)$$

In both equations, Y-hat represents the individual-predicted adalimumab concentration, Y represents the observed adalimumab concentration, and n is the number of observations.

Additionally, to evaluate graphically the predictive performance a Predicted-Corrected Visual Predictive Check (pcVPC) and graphical evaluation (residual vs. predicted, observed vs. predicted, and NPDE) were also performed. Finally, a bootstrap of the data was constructed to compare the statistical significance of the differences between bias and imprecision of the different models.

### 3.6 Model Development and Evaluation

The reference model to carry out the third study (*Article III*) was the one selected among all available models in the literature in *Article II* [55, 56]. The model considered as a reference model, developed with Monolix 4.3.2, consisted of a one-compartment model with first-order absorption and linear elimination and was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution (V/F) and absorption rate constant (ka) with a combined residual error model. The presence of AAA was included as a categorical covariate on CL/F.

Initially, the reference model was refitted by estimating the PK population parameters using all the available TSCs from patients in Monolix software V.2023R1 [57]. The model structure, including the covariate model, was the same as the reference

model. Ka and the effect of AAA on CL/F were fixed to their published value, while the others were estimated. The use of informative priors in the model was also considered by using the option of *Maximum a Posteriori Estimation* in Monolix with the estimated values and the relative standard error (RSE) of the reference model's parameter estimations.

To evaluate the appropriateness of including the prior for each parameter, priors were set individually as informative, while in the remaining parameters were kept as noninformative.

Regarding covariates, the analysis was based on physiological plausibility and visual graphical inspection of the relationships between EBEs of the PK parameters and the covariates. Statistical significance in the decrease of the Objective Function Value (OFV) ($p < 0.01$) was assessed individually for the inclusion of the covariates, using a stepwise forward addition and backward elimination covariate model-building methodology. The OFV is represented as minus twice the log of the likelihood, resulting in a single value that offers an overall summary of how well the model predictions, given a specific set of parameter values, align with the observed data. A lower OFV corresponds to a higher likelihood and implies a better fit of the model [58].

The improvement in predictive performance as well as the decrease in the OFV were the criterion for model selection in this study. A decrease in the RSE of the parameter estimation was also considered for the inclusion of informative priors in the development of the final PopPK model.

## 3.7 Clinical Impact

For the second article (*Article II*), stochastic simulations were performed to optimize the initial maintenance doses in the clinical protocols. Dosage regimens of 40 and 80 mg were simulated administered every week or every other week to observe whether at least 75% of the population reached the target.

For the third article (*Article III*), the clinical impact of PopPK models was assessed by determining the true and false positives positives of the predictions of the last TSCs compared to the last observed TSCs, for the developed final model and the reference model. True and false positives were calculated by comparing the coincidences and discrepancies between the predicted TSCs and the corresponding last observed TSCs for each PopPK model. Additionally, the 95% CI of true and false positives in each scenario for each model was calculated with bootstrap.

In both studies, the target interval of the TSCs considered was within 8–12 mg/L for clinical response or remission [32, 36].

## 3.8 Software

The PopPK models found in the literature were implemented in NONMEM® version 7.4 [59]. For model development, the software used was Monolix 2023R1® [57]. The statistical analysis, data visualization, and validation were performed using R software [60], implemented in RStudio [61].

## 3.9 Ethical Considerations

### *3.9.1 Ethics Approval*

All studies were conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Dr. Balmis General University Hospital of Alicante.

### *3.9.2 Consent*

The need for written consent was waived due to the retrospective nature of the studies.

# 4 RESULTS AND DISCUSSION

## 4.1 Cost-Effectiveness of Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease: A Systematic Review

### *4.1.1 Literature research*

This systematic review identified a total of 102 publications from Medline (via PubMed) (33), Embase (16), Cochrane Library (1), Scopus (18) and Web of Science (34). This review included a total of 13 original articles [62-74], after removing duplicates, applying the inclusion and exclusion criteria, and consulting the bibliographic lists of the selected articles. The inter-rater agreement for the selected studies, based on the kappa index, was 0.815 ($p < 0.001$). The list of excluded studies along with the reasons for their exclusion is provided in *Article I (Supplementary): Table S3.* The flowchart illustrating the study selection process is presented in *Article I: Figure 1*.

### *4.1.2 Study design*

All included studies (ST1-13) examined the health economics of TDM in IBD patients treated with anti-TNF from 2013 to 2021. Six of them (ST1–6) used a modeling and simulation approach based on the calculation of probabilities, obtained from the literature, associated with experiencing a flare or being included in a TDM strategy. The principal benefit of the simulation approach is the opportunity to assess an extensive patient cohort. However, the main weaknesses of these studies are the simplification of the events related to disease progression, uncertainties regarding the reliability of the external clinical results used in the modeling process, and challenges in accurately predicting or replicating a clinical setting.

Most of the studies (12 out of 13) were focused on infliximab and only one study (ST1) assessed the costs of using TDM for adalimumab with a modeling and simulation approach. Due to the limitations inherent to the modeling and simulation approach, further studies, either clinical trials or observational studies, are needed to provide a wider outlook. The summary of the characteristics of each study is listed in *Article I: Table 1.*

### *4.1.3 Population*

Concerning the study population, only one publication (ST1) was performed using a pediatric population. Nevertheless, this study approximated the utility values from research on adult populations. Eight studies exclusively considered patients with CD (ST1–4, 6, 11–13), while five included both CD and UC patients (ST7–11). None of the

selected studies recruited UC patients independently from CD, and that could indicate a notable gap in cost-effectiveness evaluations for TDM in UC.

#### *4.1.4 Interventions*

The included studies presented three different types of interventions: proactive TDM reactive TDM, and an empirical strategy:

1. Proactive TDM involves systematically measuring drug concentrations and AAA at predetermined intervals for all patients. This approach aims to optimize drug dosage, achieve a target concentration to improve response rates, and prevent both primary and secondary LOR, as well as the development of AAA [76].

2. Reactive TDM consists of measuring drug concentration and AAA levels only when patients exhibit primary or secondary LOR to a biological treatment. This information is used to understand the reasons for the LOR and guide subsequent therapeutic decisions, such as increasing the drug dosage, adding immunomodulators, or switching to another drug within or outside the same class [76].

3. An empirical strategy adjusts dosage based on clinical symptoms without monitoring drug concentrations or AAA [76].

The comparative analyses among these strategies in the included studies are diverse: four studies compared proactive TDM with reactive TDM (ST1, 7, 8, 10), three studies compared proactive TDM with an empirical strategy (ST3, 4, 11), five studies compared reactive TDM with an empirical strategy (ST5, 6, 9, 11–13), and one study integrated all three strategies as part of its intervention (ST2).

However, the application of the concept of proactive TDM varied among the included studies. For some studies (ST3, 7, 10), proactive TDM was implemented as a strategy for patients in disease remission, measuring drug TSCs and/or AAA levels only once. In contrast, other authors (ST1, 2, 4, 8, 11) adopted a more continuous approach, repeatedly measuring these levels to avoid LOR and manage the disease and its clinical symptoms.

On the other hand, the definitions of clinical response and LOR are crucial to classify patients into different groups and to decide their future treatment. Nonetheless, seven studies (ST1–5, 7, 8) did not provide explicit criteria for establishing a clinical response to the drug, while nine studies (ST2–8, 10, 11) omitted the criteria for defining LOR. Even in those studies that incorporated definitions for clinical response and LOR, there were substantial variations between them across the studies. The only item they

agreed with was to include the Crohn's Disease Activity Index to assess either treatment response or LOR.

Consequently, the comparison of results was challenging due to the lack of generalizability.

### *4.1.5 TDM*

All included studies used TDM to optimize the treatment of anti-TNF in IBD patients through an algorithm. TDM was defined as the evaluation of drug concentration and AAA [76]. However, MIPD is a more precise alternative, based on the use of PopPK models and a prospective Bayesian approach to increase the homogeneity in drug exposure in patients and, therefore, to improve outcomes of treatments [39].

In this line, predicting the progression of IBD through a standardized algorithm is difficult due to the unpredictable and varied events that may occur during a patient's disease course. However, all studies, whether with proactive or reactive TDM, implemented an algorithm to determine the subsequent treatment decision based on drug concentrations. Three studies developed and used their algorithm (ST2, 3, 12), while the others adapted or used existing algorithms from the literature. Consequently, applying different algorithms could lead to patients being switched to different treatment groups, significantly limiting generalizability and potentially biasing overall costs.

Furthermore, there is a lack of homogeneity in the decisions made by each algorithm, as five studies (ST2, 6, 9, 12, 13) did not consider supratherapeutic drug concentrations, and, therefore, increasing the dosage was the only possible option in their algorithms. On the contrary, other studies (ST3, 7) solely took into account high drug TSCs, and increasing the dosage was not an option. Standardizing the clinical use of these algorithms could facilitate uniform therapeutic decisions and cost comparisons.

### *4.1.6 Costs*

The analyzed costs varied across the studies, with outcomes measured differently in each, although the assessment of cost savings was a shared aspect among all studies. Nine studies (ST1–4, 6, 9, 11–13) quantified outcomes in terms of monetary costs, while five studies (ST1, 2, 4, 6, 11) measured the outcomes in QALY and ICER. Even though all the selected studies concluded that the TDM strategy was cost-effective compared to an empirical approach, it is difficult to compare results due to variations in patient numbers, adalimumab or AAA samples per patient, and diverse factors included in calculating final costs across studies.

Overall costs were closely related to drug expenses but varied across countries and health systems. Additionally, all selected studies focused only on direct medical costs, including drug costs, drug or AAA testing, surgery, and hospitalization. The exclusion of indirect costs, associated with flaring (e.g., workdays missed) and the likelihood of adverse events, may lead to an underestimation of the economic impact of TDM. A detailed summary of the costs of each study is provided in *Article I: Table 2*.

### *4.1.7 Quality Assessment*

The total scores on the CHEERS checklist for each study are presented in *Article I: Table 1*, with additional details in *Article I (Supplementary): Table S4*. Two studies (15.4%) were categorized as "excellent"; six studies (46.2%) as "very good"; and five studies (38.4%) as "insufficient". The inter-rater agreement for score determination was 0.806 ($p < 0.001$) based on the kappa index, and there was no observed risk of bias in the published papers.

Furthermore, in accordance with the SIGN recommendations [52], the level of evidence was determined to be 2++ (high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal). The degree of recommendation was assigned as B, indicating that studies rated 2++ and were directly applicable to the target population.

### *4.1.8 Limitations*

A notable limitation of this systematic review was the relatively high number of non-relevant articles (108) compared to the final selection (13). The initial retrieval from Scopus and Web of Science databases included numerous irrelevant works, possibly due to the lack of indexing and the search being performed in text format (querying title, abstract, and keywords). Another limitation relied on the fact that a meta-analysis was not conducted because of clinical and methodological heterogeneity. This heterogeneity included variations in study designs, applied algorithms, follow-up periods, diverse definitions of clinical criteria, and different TDM approaches.

## 4.2 Evaluation of the Predictive Performance of Population Pharmacokinetic Models of Adalimumab in Patients with Inflammatory Bowel Diseases

### *4.2.1 Literature research*

In this study, a total of 211 publications from PubMed (72), Embase (52), and Scopus (87) were found from 2003 to 2021. Six PopPK models for adalimumab for CD and/or UC patients [21, 55, 77-80], denoted as M1 to M6, were selected after removing duplicate articles and applying the inclusion and exclusion criteria. While all the PopPK models shared a one-compartment structure, they varied in the included covariates. All of them included patients with both induction and maintenance treatment, and only one was performed with data from a pediatric population. Only two of them (M1 and M6) were derived from complete profiles of serum concentrations of adalimumab. Five models were developed using NONMEM® software, and one model (M2) using Monolix®. Additional details can be found in *Article II: Table 1*.

The reported values for adalimumab CL/F in the included studies varied between 11.7 and 17.5 mL/h, with the lowest value observed in the study performed with a pediatric population (M3). The typical V/F ranged from 4.07 to 13.5 L. Regarding the ka, it was estimated in three models and fixed in the other three. All models estimated the IIV associated with adalimumab CL/F, with values ranging from 16.4% to 65%, while the IIV of V/F was estimated in only three models (M1, M2, and M5) ranging from 35.1% to 48%. The summary of the characteristics of each study is listed in *Article II: Table 2*.

### *4.2.2 Patients Characteristics*

The dataset comprised 134 patients with IBD treated with adalimumab with a minimum of two TSCs. Around 85% of the patients were diagnosed with CD. The analysis included a total of 398 TSCs during the maintenance phase. Of these, 25.4% exceeded 8 mg/L, 46.3% ranged between 3 and 8 mg/L, and 28.3% were below 3 mg/L in the initial measurement. AAA were detected in 11 patients (8%). Patients' characteristics are summarized in *Article II: Table 3.*

During the induction phase, 82 patients received a dose of 160/80 mg at weeks 0/2, 18 patients received 80/40 mg and, for the remaining patients, that information was unavailable. In the maintenance phase, all patients received 40 mg of adalimumab every other week. After that, dosage adjustments were implemented in response to treatment needs.

### *4.2.3 Evaluation of Model Adequacy*

The model adequacy showed that M2 and M4 performed better than the rest in terms of the similarity of the distribution of EBEs of CL compared with the theoretical distribution (*Article II: Figure 1*). However, the mean individual CL/F, derived from the Bayesian post-hoc estimation across all six PopPK models, was somehow higher than the expected mean CL/F. A plausible explanation for this systematic trend could be that the mean albumin value of the studied population was slightly lower compared to the mentioned in the literature models, which can suggest a worse disease control. Additionally, the NPDE and QQ-plot, available in *Article II: Figure 2*, also performed better in these models. Therefore, the predictive performance would be evaluated in M2 and M4 models.

The distribution of the individual V/F was not performed due to the absence of IIV of V/F in half of the models (M3, M4, and M6).

### *4.2.4 Evaluation of predictive performance*

Four out of the six models were excluded due to significant bias in the distribution of NPDE and the EBEs of PopPK parameters. Therefore, M2 and M4 were the candidates to assess the predictive performance. The predictive performance was conducted using the last observed TSCs. Those TSCs were not utilized to calculate the EBEs, mimicking real-world conditions. Both models demonstrated reasonable predictive performance, with bias less than -0.91, representing less than 13% of the trough target (8 mg/L). The bootstrap analysis of the predictive performance revealed no statistical difference between the two models. Therefore, both models could be considered equally suitable for clinical routine purposes. The predictive performance for M2 and M4 is represented in *Article II: Figure 3*. Additionally, the bias and precision for M2 and M4 and their confidence interval are shown in *Article II: Table 4*.

### *4.2.5 Clinical impact*

The recommended maintenance dose, according to the drug label, is 40 mg every other week [20]. However, based on stochastic simulations with M2 and M4 and considering the target TSCs over 8 mg/mL, that dose regimen was insufficient to reach the target for at least 75% of the population even in patients without AAA. Therefore, the recommended maintenance regimen dosage that should be included in protocols is 40 mg every week or 80 mg every other week, to ensure at least 75% of the population

reaches the target. These recommendations align with MDPI interventions in our population, where 75% of patients required a dose increase to reach the 8 mg/mL target.

#### *4.2.6 Limitations*

The main limitation of this study relied on its retrospective design, where patient selection for MDPI was determined based on the clinical decisions of the physician introducing a potential bias in disease severity, as evidenced by the mean albumin values in the studied population. Conducting a prospective study with a structured inclusion of patients for MDPI, regardless of their clinical status, is essential to avoid selection bias and validate these results in a wider population.

### 4.3 Population Pharmacokinetic Model of Adalimumab Based on Prior Information Using Real World Data

#### *4.3.1 Patients Characteristics*

In this study, the dataset consisted of 54 patients with IBD undergoing adalimumab treatment with a minimum of two TSCs. Approximately 85% of these patients were diagnosed with CD, while 15% had UC. As part of the induction phase, 43 patients received 160/80 mg at weeks 0/2, while 2 patients received 80/40 mg, and, for the rest nine patients, that information was unavailable. Following the induction phase, all patients received 40 mg of adalimumab every other week. A total of 148 TSCs were available for analysis, with 19 of them obtained during the induction phase. Among these TSCs, 68.2% fell below 8 mg/L, 16.2% were within the range of 8 to 12 mg/L, and 15.6% over 12 mg/L. AAA were detected in nine patients (17%). The summary of the characteristics of the studied population, in comparison to the population of the reference model, is presented in *Article III: Table 1*.

#### *4.3.2 Model Development, Covariate Analysis and Evaluation*

In the initial step, all parameters were estimated keeping the model structure of the reference model. The model structure consisted of a one-compartment model with first-order absorption and linear elimination. Due to the lack of serum concentrations during the absorption phase in the dataset and the limited number of patients with AAA, ka and the covariate of AAA on CL/F were fixed to the values of the reference model, 0.00625 1/h and 4.5, respectively.

A linear relationship between EBEs of CL/F and albumin was found ($p < 0.001$), illustrated in *Article III: Figure 1*. During the forward inclusion step of the covariate modeling, only albumin was found to be a significant covariate influencing CL/F.

The definition of CL/F was based on Equation (3). The inclusion of AAA and albumin as covariates on CL/F resulted in a statistically significant decrease in the OFV and the IIV in CL/F and significantly improved the predictive performance of the final model in terms of bias and imprecision. Model structure and code are available in *Article III (Supplementary): Figure S1*.

$$\mathrm{CL/F} = \mathrm{CL_{pop}} \cdot (1 + \mathrm{AAA} \cdot \mathrm{cov_{AAA-CL/F}}) \cdot (\frac{\mathrm{ALB}}{\mathrm{mALB}})^{\mathrm{cov_{ALB-CL/F}}} \qquad (3)$$

The inclusion of albumin as a covariate on CL/F revealed an association between lower albumin levels and increased CL/F. In this study, CL/F increased by a factor of 12 as albumin levels rose from their lowest (1.97 g/dl) to the highest (4.96 g/dl) values. Consequently, patients with lower albumin levels required higher doses to reach the desired therapeutic target. In fact, albumin was a significant covariate on CL in a considerable number of previously published PK models of infliximab for IBD [81]. In contrast, studies that developed PopPK models for adalimumab in CD [77, 79] or IBD patients [80] did not include albumin as a covariate, although they considered albumin as an influential inflammatory marker of adalimumab clearance.

As a second step of model development, the use of priors in different parameters was assessed. Prior information can be used to stabilize the estimation of the model parameters when dealing with limited available data. The inclusion of informative priors in the IIV of CL/F and the IIV of V/F led to a substantial reduction in RSE, not only for these parameters but also for those estimated without priors. The resulting RSE, when using priors, decreased from 30.6% to 3.4% for the IIV of CL/F and from 114.5% to 1.4% for the IIV of V/F. However, for the remaining parameters, the inclusion of priors did not improve the fit, neither in terms of RSE nor in predictive performance. Hence, this model would be considered the final model.

The results of predictive performance in terms of bias and imprecision were −1.79 and 4.14 for the reference model and −0.849 and 3.99 for the final model, respectively. Therefore, the final model behaved better in terms of bias and imprecision, compared to the reference model, and showed a comparable dispersion of IRES, as illustrated in *Article III: Figure 2*. The 95% CI of the differences, calculated with the bootstrap analysis, shown in *Article III: Table 2,* revealed statistical differences in bias but not in imprecision.

The pcVPC and NPC for both the reference and final models, represented in *Article III: Figure 3*, showed that the final model performs better than the reference model. The same results were observed in Observed vs. Predicted and NPDE plots, available in *Article III (Supplementary): Figure S2 and Figure S3*, respectively.

The RSE of the estimated PK parameters in the final model was below 50% in the bootstrap analysis. There were no significant differences between the mean values of the PK parameters in the bootstrap analysis of the final model. The values of each parameter of the final model compared to the reference model are detailed in *Article III: Table 3*.

### *4.3.3 Clinical impact*

The final model predicted better the need for dose adjustment across all scenarios since obtained 15% more true positives (39 vs. 33) and 30% less false positives than the final model (*Article III: Figure 4)*. The detailed overview of true and false positives in the predictions of the last TSCs, along with the differences between the reference and the final model for each scenario is presented in *Article III: Table 4*.

### *4.3.4 Limitations*

One of the main limitations of this study was its retrospective design, in which patient selection for MIPD was based on clinical decisions made by physicians, which implies a potential bias related to the disease severity. This potential bias could result in an underestimation of the mean values and variance of albumin, C-reactive protein, and fecal calprotectin in the IBD population. Another limitation inherent to the clinical setting was the availability of only TSCs since data were collected in a clinical context; therefore, there was a lack of serum concentrations during the absorption phase and, consequently, ka could not be estimated, so it was fixed to the value of the reference model.

# 5 CONCLUSIONS

1. The systematic review about the cost-effectiveness of the use of TDM of anti-TNF in IBD identified 13 health economic studies, eight of which met the criteria for very good to excellent quality work according to the CHEERS checklist. The comparison between the TDM strategy and an empirical strategy favor the former in terms of cost saving. The ICER indicated that the reactive TDM strategy was more favorable than the empirical approach. This systematic review demonstrated the cost-effectiveness and potential cost-saving benefits of implementing TDM for anti-TNF drugs in the management of IBD.

2. Among the PopPK models of adalimumab for IBD identified in the literature, two were found to be better in terms of model adequacy and predictive performance. Nevertheless, it was observed that the EBEs of the individual were biased from the population mean values in these models, suggesting the necessity for model refinement based on the available data. Furthermore, the stochastic simulations performed with these models recommended the potential benefits of increasing the maintenance dose in the protocol to reach the target of 8 mg/L.

3. The PopPK model of adalimumab, developed for IBD patients of the Dr. Balmis General University Hospital of Alicante, incorporated informative priors in IIV of CL/F and IIV of V/F, based on the reference model. This PopPK model effectively characterized adalimumab PK in the studied population and performed better than the reference model in terms of predictive performance. The main structural difference between both models was the inclusion of albumin as a meaningful covariate on CL/F. To our knowledge, this is the first PopPK model of adalimumab in IBD that identified albumin as a covariate on CL/F. Moreover, the final model significantly improved the clinical impact on the target population and could allow a more accurate dose optimization and increase the efficacy of adalimumab treatment.

# 6 CONCLUSIONES

1. La revisión sistemática sobre el coste-efectividad de realizar TDM en anti-TNF en la enfermedad inflamatoria intestinal (EII) identificó 13 estudios económicos, de los cuales ocho fueron clasificados de muy buenos a excelentes en términos de calidad según la lista de verificación CHEERS. La comparación entre realizar TDM con respecto a utilizar una estrategia empírica para optimizar la dosis de los pacientes con EII tratados con anti-TNF supuso un beneficio económico notable. El ICER indicó que la estrategia de TDM reactiva era más favorable que el enfoque empírico. Esta revisión sistemática demostró que realizar TDM para optimizar la dosis de anti-TNF en pacientes con EII es coste-efectivo y supone beneficios económicos en el manejo de la EII.

2. De los modelos PopPK de adalimumab para la EII disponibles en la literatura, dos presentaron mejores características de adecuación al modelo y capacidad predictiva. Sin embargo, se observó que los EBEs estaban sesgados en comparación con los valores medios poblacionales de los modelos seleccionados, lo que sugiere la necesidad de adaptar el modelo para la población estudiada. Además, las simulaciones estocásticas llevadas a cabo con dichos modelos mostraron los posibles beneficios de aumentar la dosis de mantenimiento en los protocolos para alcanzar el objetivo terapéutico de 8 mg/L.

3. Se desarrolló un modelo PopPK de adalimumab para la EII utilizando datos de pacientes del Hospital General Universitario Dr. Balmis de Alicante. Este modelo se basó en un modelo de referencia, incorporando priors informativos en la variabilidad interindividual del CL/F y del V/F. El modelo PopPK final caracterizó de manera adecuada la farmacocinética de adalimumab en la población estudiada y mostró mejores resultados que el modelo de referencia en la capacidad predictiva. La principal diferencia estructural entre ambos modelos consistió en la inclusión de la albúmina como una covariable significativa en el CL/F. Hasta la fecha, este es el primer modelo PopPK de adalimumab para la EII que incluye la albúmina como una covariable que en el CL/F. Además, el modelo final mejora significativamente el impacto clínico en la población estudiada, ofreciendo la posibilidad de una optimización más precisa de la dosis y un aumento en la eficacia del tratamiento con adalimumab.

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# ARTICLES

## ARTICLE I

Systematic Review

# Cost-Effectiveness of Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease: A Systematic Review

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**Pharmaceutics 2022; 14(5):1009**

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| Impact factor (2022) | 5.4 |
| Pharmacology & Pharmacy (Q1) | 50/278 |

## ABSTRACT

Infliximab and adalimumab are monoclonal antibodies against tumor necrosis factor (anti-TNF) used to manage inflammatory bowel disease (IBD). Therapeutic Drug Monitoring (TDM) has been proven to prevent immunogenicity, to achieve better long-term clinical results and to save costs in IBD treatment. The aim of this study was to conduct a systematic review on cost-effectiveness analyses of studies that apply TDM of anti-TNF in IBD and to provide a critical analysis of the best scientific knowledge available in the literature. The quality of the included studies was assessed using Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Cost-effectiveness of the TDM strategies was presented as total costs, cost savings, quality-adjusted life-years (QALY) and incremental cost-effectiveness ratio (ICER). Thirteen studies that examined the health economics of TDM of anti-TNF in IBD from 2013 to 2021 were included. Eight of them (61.5%) achieved a score between 17 and 23 on the CHEERS checklist. The comparison between the TDM strategy and an empirical strategy was cost saving. The ICER between reactive TDM and an empirical strategy was dominated (favorable) by reactive TDM, whereas the ICER value for proactive TDM compared to an empirical strategy ranged from EUR 56,845 to 3,901,554. This systematic review demonstrated that a TDM strategy is cost-effective or cost-saving in IBD.

## Keywords

inflammatory bowel diseases; drug monitoring; pharmacokinetics; tumor necrosis factor inhibitors; adalimumab; infliximab; cost–benefit analysis; cost-effectiveness

## 1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are autoimmune inflammatory bowel diseases (IBD) characterized by the chronic inflammation of the intestinal tract [1,2]. In 2017, there were 6.8 million cases of IBD globally [3–5]. According to several European studies, the risk of colorectal cancer is two times higher in UC patients than in the general population, whereas patients with CD have a higher risk of extraintestinal cancers and increased mortality compared to the general population [6–10].

Infliximab and adalimumab are monoclonal antibodies against tumor necrosis factor (anti-TNF), which are increasingly used to treat patients with moderate-to-severe IBD older than 6 years who had an inadequate response with corticosteroids or immunomodulators [11,12]. However, nearly 40% of IBD patients experience a loss of response (LOR) to anti-TNF treatment every year, requiring either dose intensification or switching to another drug [13].

Numerous studies reveal that higher serum drug concentrations are associated with better therapeutic outcomes, including mucosal healing [14–18]. Related to this, some authors have shown that patients can experience LOR to anti-TNF due to developing antibodies against anti-TNF (AAA) after long periods of subtherapeutic drug levels [19–22].

In this line, Therapeutic Drug Monitoring (TDM) of anti-TNF has been proven to prevent immunogenicity and to achieve better long-term outcomes in terms of IBD-related surgery or hospitalization [23–25]. Since the mean direct cost per patient-year is around EUR 3500 for CD patients and EUR 2000 for UC patients including diagnostic procedures, hospitalizations and biological treatment in Europe [26], TDM could be a tool of special relevance to optimize the treatment and save costs.

In the literature, other systematic reviews confirmed that TDM of anti-TNF is cost-effective in rheumatoid arthritis [27,28]. Recently, another systematic review of the TDM of immunomodulators and anti-TNF therapy in IBD proved to be cost-effective or cost-saving compared with an empirical strategy without TDM. However, the main limitation of this review is the inclusion of only model-based analyses with simulations of patients [29].

The aims of this systematic review are to evaluate studies concerning the cost-effectiveness analysis of TDM of anti-TNF in IBD and to provide a critical analysis of the best scientific knowledge available on the use of TDM.

## 2. Materials and Methods

### 2.1. Literature Search

This systematic review consisted of a cross-sectional descriptive study and a critical analysis of studies found in the literature. The structure of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30] (Supplementary Table S1), and the methodological framework proposed for scoping studies [31,32].

### 2.2. Source of Data Collection

The data were obtained from direct consultation and access, via the Internet, to the following bibliographic databases in the field of health sciences: MEDLINE (via PubMed), Embase, Cochrane Library, PsycINFO, Scopus, Web of Science, and Latin American & Caribbean Health Sciences Literature (LILACS) and Medicina en Español (MEDES). The published articles were analyzed and retrieved from the indicated bibliographic databases.

### 2.3. Information Processing

Search terms were selected using the Thesaurus of Health Sciences Descriptors (DeCS) developed by the Latin American and Caribbean Center on Health Sciences Information (BIREME) and equivalent terms established by the US National Library of Medicine, Medical Subject Headings (MeSH). The MeSH descriptors “Inflammatory Bowel Diseases”, “Tumor Necrosis Factor Inhibitors”, “Infliximab”, “Adalimumab”, “Cost-Benefit Analysis”, “Cost Savings” and “DrugMonitoring” were considered suitable. Likewise, these terms were used to query the database using the title and abstract field (Title/Abstract). It was not necessary to use filters (limits). The search equations are available in Supplementary Table S2. This review was not registered; although, the protocol was developed before the research began.

This strategy was subsequently adapted to the characteristics of each database consulted, from the first available date in each of the selected databases until December 2021. Additionally, a complimentary search strategy was performed to reduce the possibility of publication bias by manually searching the reference lists of the articles that were selected for the review. Likewise, experts in the subject under study were contacted to determine the possible existence of gray literature (materials and research produced by organizations outside traditional commercial or academic publications that are disseminated through other distribution channels).

### 2.4. Final Selection of Articles

For the review and critical analysis, articles that met the following criteria were chosen:

Inclusion: original articles published in peer-reviewed journals and articles that met the objectives of the search.

Exclusion: full text could not be found; no relationship between the intervention and the outcome under study (causality criterion); articles that included any diseases different to IBD such as rheumatoid arthritis, psoriasis or ankylosing spondylitis; studies regarding different drugs to anti-TNF antagonists such as Vedolizumab or Ustekinumab and studies developed in animals.

There was no language, publication date or publication status restriction. The selection of relevant articles was performed by two authors of the present review (S.M.-M. and A.R.-L.). To validate the inclusion of the articles, the assessment of the agreement between the authors using the kappa index, had to be greater than 0.60 [33]. In case of discrepancies, a third reviewer (R.N.-M.) was responsible for reaching a resolution and subsequent consensus amongst all the authors.

### 2.5. Quality Assessment, Level of Evidence and Grade of Recommendation

The quality of all identified studies was evaluated by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [34], which consists of 24 items to appraise the quality of the included studies. For each item, it was assigned one point for each item present (if not applicable, it was not scored). The percentage of total scores assigned to each study was used to evaluate the study quality. All studies were classified into four categories: “excellent” (85%), “very good” (70–84%), “good” (55–69%), and “insufficient” (<55%).

The quality assessment was conducted by two reviewers (S.M.-M. and A.R.-L.) independently. It was established that the inter-rater agreement for the authors (using the kappa index) should be higher than 60%. In case of discrepancies, a third reviewer (R.N.-M.) was responsible for reaching a resolution and subsequent consensus amongst all the authors.

To assess the risk of bias due to missing results, the methods and the results sections of the selected articles were compared. To determine the level of evidence and its degree of recommendation, the recommendations of the Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN) [35] were used.

### 2.6. Data Extraction

Data from eligible articles were collected to systematize and facilitate the interpretation of the results. Data were extracted by one reviewer and verified by a second reviewer. The following items were extracted: general information of study (first author, country of the study and year of publication); study design (population, intervention, type of TDM approach used, time horizon and methods of measuring outcomes); and results (primary outcomes). The primary outcomes collected were the cost-effectiveness of the TDM strategies, presented as the total costs, cost savings, quality-adjusted life-years (QALY) or incremental cost-effectiveness ratio (ICER). Costs were converted to the same currency (euros) in the year of publication of each study to allow the comparison between the different studies. Moreover, all the costs were normalized to a one-year period to homogenize the results. If the information was available, average costs per patient per year were calculated according to the total costs and the number of patients in each group of treatment in each study.

## 3. Results

This systematic review identified a total of 102 publications: 33 were found in Medline (via PubMed), 16 in Embase, 1 in Cochrane Library, 18 in Scopus and 34 in Web of Science. No article was retrieved from PsycINFO, LILACS and MEDES. A total of 13 original articles were included in this review [36–48] after removing duplicates, applying the inclusion and exclusion criteria and consulting the bibliographic lists of the selected articles from the search strategy. The list of excluded studies and the reasons for exclusion is available in Supplementary Table S3. The inter-rater agreement for the selected studies was 0.815 ($p < 0.001$) according to the kappa index. The process of study selection is presented in a flowchart in Figure 1.

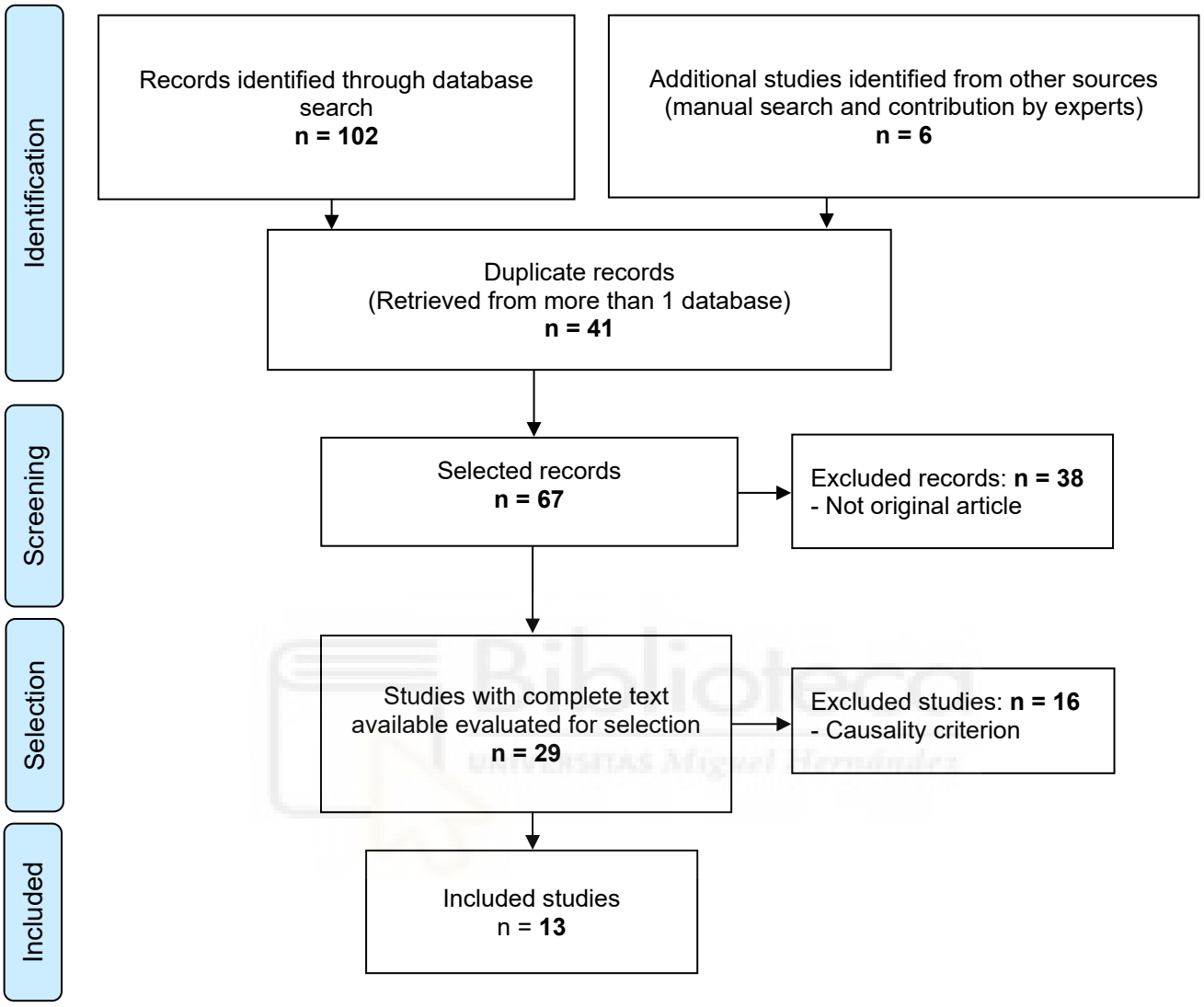


**Figure 1.** Selection procedure of the studies

All included studies examined the health economics of TDM in IBD patients treated with anti-TNF from 2013 to 2021. Moreover, 12 of them evaluated the TDM of infliximab and only one (ST1) evaluated the use of adalimumab. The summary of the characteristics of each study is listed in Table 1.

**Table 1.** Summary of the characteristics of the included studies.

| Study | Authors, year | Country | Study design | Drug studied | Study population (n, m/f, age) | Study duration | Measure of outcomes | Intervention | CHEERS (n, %) |
|---|---|---|---|---|---|---|---|---|---|
| **ST1** | Yao et al, 2021 [36] | US | Modeling approach | Adalimumab | 20,000 simulated CD pediatric biologic-naïve patients | 3 years and 4 weeks | Costs<br>Cost savings<br>QALY<br>ICER | Proactive TDM (n=10,000) vs Reactive TDM (n=10,000) | 21 (87.5%) Excellent |
| **ST2** | Negoescu et al, 2020 [37] | US | Modeling approach | Infliximab | 100,000 CD simulated patients | 5 years | Costs<br>Cost savings<br>QALY<br>ICER | Proactive TDM (n=NA) vs Reactive TDM (n=NA) vs Empirical strategy (n=NA) | 19 (79.2%) Very good |
| **ST3** | Attar et al, 2019 [38] | France | Modeling approach | Infliximab | 40,000 CD simulated adult patients | 2 years | Costs<br>Cost savings | Proactive TDM (n=20,000) vs Empirical strategy (n=20,000) | 7 (29.2%) Insufficient |
| **ST4** | Freeman et al, 2016 [39] | UK | Modeling approach | Infliximab | Simulations of CD patients in maintenance treatment of infliximab | 10 years | Costs<br>Cost savings<br>QALY<br>ICER | Proactive TDM (n=NA) vs Empirical strategy (n=NA) | 23 (95.8 %) Excellent |
| **ST5** | Roblin et al, 2015 [40] | France | Modeling approach | Infliximab | 10,000 Simulations of CD patients with LOR to infliximab | 1, 3 and 5 years | Cost savings | Reactive TDM (n=NA) vs Empirical strategy (n=NA) | 10 (41.7%) Insufficient |
| **ST6** | Velayos et al, 2013 [41] | US | Modeling approach | Infliximab | 10,000 simulations of CD patients with LOR to infliximab | 1 year | Costs<br>Cost savings<br>QALY<br>ICER | Reactive TDM (n=NA) vs Empirical strategy (n=NA) | 17 (70.8%) Very good |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **ST7** | Wu et al, 2021 [42] | Australia | Prospective observational study | Infliximab | 428 IBD patients (322/296, 36 ±18.7 yo) | 56 weeks | Cost savings | Proactive TDM (n=181) vs Reactive TDM (n=247) | 12 (50.0%) Insufficient |
| **ST8** | Ganesnanthan et al, 2020 [43] | UK | Retrospective observational study | Infliximab | 85 IBD patients (54/31, 39.13 ±14.25 yo) | NA | Cost savings | Proactive TDM (n=NA) vs Reactive TDM (n=NA) vs Proactive TDM post-induction (n=NA) | 7 (29.2%) Insufficient |
| **ST9** | Guidi et al, 2018 [44] | Italy | Prospective observational study | Infliximab | 148 IBD patients in treatment for at least 4 months with LOR to infliximab (75/73, 40.8 (37.05 – 42.5) yo) | 12 weeks | Costs Cost savings | Reactive TDM (n=96) vs Empirical strategy (n=52) | 17 (70.8%) Very good |
| **ST10** | Taks et al, 2017 [45] | The Netherlands | Non-randomized clinical trial | Infliximab | 33 IBD adult patients (20/13, 43 (32-59) yo) | 1 year | Cost savings | Proactive TDM (n=28) vs Reactive TDM (n=33) | 4 (16.7%) Insufficient |
| **ST11** | Vande Castelee et al, 2015 [46] | Belgium | Randomized controlled clinical trial | Infliximab | 251 IBD adult patients with a stable clinical response for at least 14 weeks (138/113, 41 (34.5-49.0) yo) | 2 years and 16 weeks | Costs Cost savings QALY ICER | Proactive TDM (n=128) vs Empirical strategy (123) | 18 (75.0%) Very good |
| **ST12** | Steenholdt et al 2015 [47] | Denmark | Randomized controlled clinical trial | Infliximab | 69 CD adult patients with LOR to infliximab (27/69, 37 (19-81) yo) | 20 and 52 weeks | Costs Cost savings | Reactive TDM (n=33) vs Empirical strategy (n=36) | 17 (70.8%) Very good |
| **ST13** | Steenholdt et al, 2014 [48] | | | | | 12 weeks | | | 17 (70.8%) Very good |

*M: male; f: female; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CD: Crohn's disease; QALY: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio; IBD: inflammatory bowel disease; yo: years old; NA: not available; LOR: loss of response*

### 3.1. Study Design

Regarding the study design, three were randomized controlled clinical trials (ST11–13), one was a non-randomized clinical trial (ST10), two were prospective observational studies (ST7, 9) and one was a retrospective observational study (ST8).

Alternatively, six studies considered simulated patients using a modeling approach, based on a Markov model (ST1, 4, 6), a stochastic simulation model (ST2) and a discrete event model (ST3, 5).

### 3.2. Population

Twelve studies were carried out on adult patients (ST3, 10, 4–6, 11–13) while only one studied the pediatric population (ST1). Eight studies considered only CD patients (ST1–4, 6, 11–13), whereas five included IBD patients (CD and UC) (ST7–11). Eight studies included patients only in a maintenance phase of treatment (ST3, 4, 6, 7, 9, 10, 12, 13), and in the others, patients were in both induction and maintenance stages.

### 3.3. Interventions

The included studies show three types of intervention: proactive TDM, reactive TDM and an empirical strategy. Proactive TDM can be defined as the measurement of concentrations and AAA levels in all patients, at specific time points, to optimize drug dosage and to achieve a threshold drug concentration that can improve response rates and prevent secondary LOR and the development of AAA [49]. Reactive TDM is the measurement of drug concentration and antibody levels only when patients had experienced primary or secondary LOR to a biological treatment to inform about reasons for the lack of response and to facilitate the next therapeutic decisions such as increasing drug, adding immunomodulators or switching to another drug either in or out of class [49]. Another approach is an empirical strategy that bases its dosage changes on clinical symptoms. Four compared a proactive TDM versus a reactive TDM (ST1, 7, 8, 10), three compared a proactive TDM versus an empirical strategy (ST3, 4, 11), five compared a reactive TDM versus an empirical strategy (ST5, 6, 9, 11–13) and one study included the three strategies as part of its intervention (ST2).

### 3.4. TDM

All studies, either proactive or reactive TDM, applied an algorithm to decide the next decision in the treatment based on drug concentrations. Three studies developed and used their own algorithm (ST2, 3, 12) while the rest adapted or used others found in the literature. Five of the algorithms included an optimal drug concentration interval (ST1, 4, 7, 10, 11), five considered a threshold (ST3, 5, 9, 12, 13), whereas three did not

mention the interval or threshold used to change the dosage or to switch drug (ST2, 6, 8). Seven algorithms took into account the use of immunomodulators (ST1, 2, 4, 5, 9, 12, 13); although, four of them did not include their cost in the analysis (ST5, 9, 12, 13).

Six studies defined the clinical or biochemical criteria to establish response (ST6, 9–13) while four described the criteria to determine LOR (ST1, 9, 12, 13). Even though they were distinct from each other, all of them included the Crohn's Disease Activity Index to determine either response or LOR. In relation to LOR, four out of five studies that included induction patients considered the primary LOR and the discontinuation of the drug due to adverse events (ST1, 2, 5, 11). Regarding secondary LOR, three studies (ST1, 5, 6) included the cost of the treatment with another drug after switching from the main drug, whereas one study (ST8) did not include this cost in the final result.

The analytical assay to measure AAA and trough concentrations differed in each study: five (ST3–5, 7, 9) used LISA TRACKER duo (Theradiag, Marne la Vallée, France); one (ST8) IDK monitor ELISA kit; one (ST10) homemade ELISA (Sanquin, Amsterdam, The Netherlands); two (ST12, 13) radioimmunoassay (Biomonitor A/S, Copenhagen, Denmark); and the rest did not specify it. In addition to this, three studies only measured AAA if trough concentrations were below an established threshold (ST7, 10, 11), one study only measured trough concentrations in absence of AAA (ST6), whereas the others tested the levels of both AAA and trough concentrations simultaneously at every measurement, which considerably affected the cost.

### 3.5. Costs

The costs analyzed varied from each study. The outcomes were measured as costs in nine studies (ST1–4, 6, 9, 11–13), as cost savings in all included studies, as QALY and as ICER in five studies (ST1, 2, 4, 6, 11). Eight studies (ST1–4, 6, 9, 12, 13) included an extensive detailed amount of costs such as clinic visits, hospitalization, surgery and diagnosed tests, among others. The cost of the anti-TNF treatment was evaluated in all of the included studies; although, in some studies patients were treated with biosimilars such as Inflectra (ST8), CT-P13 (ST3, 9) and another study (ST7) did not specify it. Attar et al. (ST3) defined two scenarios to calculate the cost of the treatment with all patients treated with the originator (Remicade) and with the biosimilar CT-P13, whereas Guidi et al. (ST9) added a third scenario to calculate half patients treated with each one. The summary of the costs of each study is listed in Table 2.

**Table 2.** Summary of the economic outcomes of each study per year.

| Study | Authors, year | Total cost | Cost savings | Average cost savings per patient | QALY | ICER |
|---|---|---|---|---|---|---|
| **ST1** | Yao et al, 2021 [36] | PA: $110,851.18 USD (€94,223.50)<br>RA: $111,508.01 USD (€94,781.81) | PA: $656.83 USD (€558.31) compared to RA | PA: €0.06 compared to RA | PA: 0.81<br>RA: 0.74 | RA-PA: Dominated by PA |
| **ST2** | Negoescu et al, 2020 [37] | PA: $16,585.42 USD (€14,926.88)<br>RA: $15,847.69 USD (€14,262.92)<br>ES: $15,853.68 USD (€14,268.31) | RA: $737.73 USD (€663.96) compared to PA and $5.99 USD (€5.39) compared to ES | NA | PA: 0.74<br>RA: 0.73<br>ES: 0.73 | RA-PA: $146,509.12 USD (€131,858.21)<br>ES-RA: Dominated by RA |
| **ST3** | Attar et al, 2019 [38] | PA: €186,635,650<br>ES: €201,879,000 | PA: €15,243,350 compared to ES | PA: €0.76 compared to ES | NA | NA |
| **ST4** | Freeman et al, 2016 [39] | PA: £13,980 (€18,174)<br>ES: £15,050 (€19,565) | PA: £1,070 (€1,391) compared to ES | NA | PA: 0.63<br>ES: 0.65 | ES-PA: £43,727.01 (€56,845.12) |
| **ST5** | Roblin et al, 2015 [40] | NA | RA: €26,260,058.60 compared to ES | NA | NA | NA |
| **ST6** | Velayos et al, 2013 [41] | RA: $31,870 USD (€23,902.5)<br>ES: $37,266 USD (€27,949.5) | RA: $5,396 USD (€4,047) compared to ES | NA | RA: 0.80<br>ES: 0.80 | ES-RA: Dominated by RA |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ST7** | Wu et al, 2021 [42] | NA | PA: $304,916.95 AUD (€196,394.48) compared to RA | NA | NA | NA |
| **ST8** | Ganesnanthan et al, 2020 [43] | NA | PA: £56,865 (€62,551) compared to ES<br>PA post-induction: £51,595 (€56,754.50) compared to ES<br>RA: £318.61 (27,081.85) compared to ES | NA | NA | NA |
| **ST9** | Guidi et al, 2018 [44] | RA: €3,230,810.44<br>ES: €3,788,285.67 | RA: €557,475.23 compared to ES | RA: €39,197.38 compared to ES | NA | NA |
| **ST10** | Taks et al, 2017 [45] | NA | PA: €47,026 compared to RA | NA | NA | NA |
| **ST11** | Vande Castelee et al, 2015 [46] | PA: €5,201,473<br>ES: €5,276,773 | PA: €75,300 compared to ES | PA: €300 compared to ES | PA: 0.82<br>ES: 0.84 | ES-PA: €3,901,554.40 |
| **ST12** | Steenholdt et al 2015 [47] | RA: $22,066 USD (€17,652.80)<br>ES: $29,072 USD (€23,257.60) | RA: $7,006 USD (€5,604.8) compared to ES | RA: €111.11 compared to ES | NA | NA |
| **ST13** | Steenholdt et al, 2014 [48] | RA: $26,164.67 USD (€19,623.5)<br>ES: $39,771.33 USD (€29,828.5) | RA: $13,606.67 USD (€10,205) compared to ES | RA: €233.92 compared to ES | NA | NA |

*QALY: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio; PA: proactive TDM; RA: reactive TDM; ES: empirical strategy; NA: not available; USD: United States Dollars; AUD: Australian dollars*

Total costs ranged from EUR 14,927 to 186,635,650 per year for a proactive TDM strategy; from EUR 14,263 to 3,230,810 per year for a reactive TDM strategy; and from EUR 14,268 to 201,879,000 per year for an empirical strategy. In this line, cost savings of proactive TDM compared to reactive TDM ranged from EUR 558 to 196,394 per year; cost savings of proactive TDM compared to an empirical strategy ranged from EUR 1391 to 15,243,350 per year; and cost savings of reactive TDM compared to an empirical strategy ranged from EUR 5.39 to 26,260,059 per year (Table 2).

On the other hand, QALY ranged from 0.63 to 0.82 for a proactive TDM strategy; from 0.73 to 0.80 for a reactive TDM strategy; and from 0.65 to 0.84 for an empirical strategy. The ICER between reactive TDM and an empirical strategy was dominated (favorable) by reactive TDM in two studies (ST2, 6). When it comes to ICER between proactive TDM and reactive TDM, the proactive TDM dominated in one study (ST1) while in another study (ST2) its value was EUR 131,858 (below the cost-effective thresholds in the United States). The ICER between proactive TDM compared to an empirical strategy ranged from EUR 56,845 to 3,901,554.

### 3.6. Quality Assessment

The total score of the CHEERS checklist of each study is included in Table 1 and more details are available in Supplementary Table S4. The scores ranged from 4 to 23. The number of studies categorized as “excellent”, very good” and “insufficient” was 2 (15.4%), 6 (46.2%) and 5 (38.4%), respectively.

The inter-rater agreement for the determination of each score was 0.806 ($p < 0.001$) according to the kappa index. No risk of bias was observed in the published papers.

Furthermore, following the recommendations of the Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN) [35], the level of evidence was 2++ (high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal) and its degree of recommendation was B (studies rated 2++ directly applicable to the target population).

## 4. Discussion

The objective of this systematic review was to identify and synthesize the scientific evidence published around the cost-effectiveness analyses of the use of TDM of anti-TNF in IBD. This review includes both model-based and trial-based studies. With the object of minimizing publication bias, the database searches were exhaustive, with neither language nor date restrictions. Moreover, the PRISMA guideline was followed to

minimize bias and the quality of identified studies was evaluated with the CHEERS checklist. The results of the CHEERS checklist show that eight of thirteen (61.5%) included studies achieved very good to excellent rankings.

After performing an exhaustive search in numerous databases, thirteen studies were found in the literature. Six of them (ST1–6) used a modeling approach based on the calculation of probabilities of having a flare or being included in a TDM strategy, obtained from the literature. A modeling approach allows for the evaluation of large cohorts of patients, which would be very difficult to acquire in real life. However, the main weaknesses of these studies are the simplification of the events related to disease progression, the reliability of the external clinical results used for the modeling and the difficulties in predicting or reflecting a clinical setting.

With regard to the drug studied, 12 studies were focused on infliximab. Therefore, there is a lack of evidence on the cost-effectiveness of using TDM of adalimumab since only one study (ST1) found in the search evaluated the costs with a modeling approach. Due to the limitations of the modeling approach, further studies, either clinical trials or observational studies, are needed to provide a wider outlook.

Five studies (ST6, 9, 10, 12, 13) reported data with a follow-up lower than or equal to 1 year but, as IBD is a chronic disease, a higher follow-up is required to understand the long-term impact on the costs of a TDM strategy [44,50].

Regarding the population, there is only one published study (ST1) based on a pediatric population. Moreover, this study approximated the utility values of health states from studies on adult patients. For that reason, future cost–benefit analyses in pediatric populations are needed to confirm the results of this study.

None of the selected studies recruited UC patients separately from CD and, consequently, the cost-effectiveness evaluation of TDM in UC is lacking. In fact, there may be differences in the response to infliximab between CD and UC patients since infliximab could be more immunogenic and reach lower trough concentrations in UC patients than in CD patients, affecting considerably the cost-effectiveness of TDM of anti-TNF in this group of patients [43].

It has been shown that AAA are clinically relevant for disease progression or applying TDM [19–22]; however, one study (ST3) did not include the presence of AAA to infliximab because of the complexity generated in its model. Moreover, AAA to infliximab frequently appear in the first year [39]; although, most studies included patients just in a maintenance phase of treatment. Therefore, TDM including the induction of the

treatment could lead to more benefits and be more cost-effective since it would prevent flares and decrease hospitalizations and surgery rates [45,51–53].

Concerning the intervention, a proactive TDM strategy was included as one of the interventions in eight studies (ST1–4, 7, 8, 10, 11). However, some of them (ST3, 7, 10) applied this concept differently and interpreted it as a strategy for patients that had disease remission and only measured drug trough concentrations and/or AAA levels once. Other authors (ST1, 2, 4, 8, 11) repeatedly measured these levels to avoid LOR and to restrain the disease and its clinical symptoms. In fact, an adequate sample schedule has not been established so far. Consequently, every one of these studies differed in that schedule and used either 8 weeks (ST1), 6 months (ST2) or 1 year (ST4). Therefore, the comparison of the results is difficult due to the lack of generalizability and the fact that a high frequency of TDM could increase the total cost of a proactive TDM strategy as was observed by Yao et al. [36].

The progression of IBD is difficult to predict using a standardized algorithm because different and random events may occur along a patient's disease course and differ from one patient to another. Conversely, each study applied a different algorithm to achieve a dosage optimization with variations in the interval or threshold used. In this context, patients can be switched to different groups of treatment when applying different algorithms and this could considerably limit the generalizability and bias the overall costs. Moreover, there is no homogeneity in the decisions taken by every algorithm since five studies (ST2, 6, 9, 12, 13) did not consider supratherapeutic drug concentration and, therefore, increasing the dosage was the only possible decision in their algorithm. On the contrary, other studies (ST3, 7) took into account only high drug trough concentrations and, therefore, increasing the dosage was not an option. So far, the exposure target for anti-TNF is highly dependent on the therapeutic objective (clinical, endoscopic, biochemical or histologic remission) and whether patients are diagnosed with CD or UC [17]. Based on the currently available evidence, an interval of 6–10 mg/L of infliximab trough concentrations is recommended to achieve clinical response [25,54,55]. Regarding adalimumab, a target of 8–12 mg/L adalimumab trough concentrations is required to achieve mucosal healing in 80–90% of IBD patients [25,54,55]. In fact, a recent study showed that patients with adalimumab trough concentrations lower than 8.3 mg/L had more risk to develop AAA and to experience LOR by week 12 [56]. The generalization of the clinical use of these intervals would allow the therapeutic decisions and to compare costs to be standardized.

Related to the dosages, 12 studies (ST1, 3–13) administered doses of 5 mg/kg and 10 mg/kg. Nevertheless, Negoescu et al. (ST2) included a medium dose of 7.5

mg/kg of infliximab as an option and observed that smaller dose increases would decrease the overall cost of the drug and still achieve therapeutic trough concentrations [39]. Recently, adding immunomodulators to the anti-TNF therapy has shown clinical relevance in the decrease or disappearance of AAA [39,57]. However, not all studies included this option in their algorithm (ST3, 6–8, 10, 11) and some of those that included the algorithm did not consider its costs (ST5, 9, 12, 13), which could considerably affect the cost-effectiveness analysis.

The analytical assay varied from each study and, consequently, the limit to consider undetectable AAA and trough concentrations and its cost differed largely from each other. The selected intervals or thresholds are directly dependent on assay type and whether or not AAA are measured. However, none of the assays can be classified as a gold standard. Moreover, four studies (ST1, 2, 6, 11) did not mention which analytical assay was applied, which is essential due to its direct impact on the cost-effectiveness of any TDM strategy.

The definitions of clinical response and LOR are essential to classify patients into different groups and to decide their future treatment. However, seven studies (ST1–5, 7, 8) did not define the criteria to determine a clinical response to the drug and nine studies (ST2–8, 10, 11) did not define the criteria to establish LOR. In those that included a definition for either clinical response and LOR, there are significant variations between them across the studies that have large implications for the generalizability of study outcomes. Moreover, some studies (ST1, 2, 4, 6) carried out procedures such as endoscopies or colonoscopies that significantly increased the overall costs.

Regarding the economic outcomes, it is difficult to compare the results given the different number of patients, the number of drug or AAA samples per patient and the different items included in the calculation of the final costs of each study. The overall costs are closely related to the drug cost, but it is not homogeneous and varied between countries and health systems. Furthermore, all selected studies only included direct medical costs of health care such as drug cost, drug or AAA testing, surgery and hospitalization. As none of them considered the indirect costs associated with flaring (e.g., time missed from work) and the likelihood of experiencing an adverse event, the economic implications of TDM might be underestimated. Moreover, biosimilars would enhance a more cost-effective strategy due to their lower price [58,59]; although, all the selected studies concluded that the TDM strategy is cost-effective compared to an empirical strategy.

All included studies used TDM to optimize the treatment of anti-TNF in IBD patients through an algorithm. According to Papamichael et al., TDM was defined as the evaluation of drug concentration and anti-drug antibodies [60]. However, Model-Informed Precision Dosing (MIPD) is a more precise alternative, based on the use of population pharmacokinetics (PopPK) models and a prospective Bayesian approach to increase the homogeneity in the drug exposure in patients and, therefore, to improve outcomes of treatments [61]. Some authors have carried out MIPD of adalimumab and infliximab in IBD patients, applying PopPK models found in the literature [62,63]. However, further investigations in this line are required to estimate its cost and compare it with the ones obtained from a TDM strategy.

One limitation of this systematic review could be the high rate of non-relevant articles (108) in relation to the final selection made (13). Scopus and Web of Science databases initially retrieved many works that were finally irrelevant, which could be due to the lack of indexing (the search was performed in text format querying the title, abstract and keywords). Despite performing a comprehensive search, it cannot be ruled out that some studies were not identified by the bibliographic databases searched or the manual search.

Another limitation of the present review relies on the fact that a meta-analysis was not performed owing to clinical and methodological heterogeneity such as different study designs, significant differences in the algorithms applied and follow-up periods, variability in definitions of clinical criteria and different TDM approaches applied.

## 5. Conclusions

In conclusion, this systematic review identified 13 health economic studies, eight of which were very good to excellent quality work per the CHEERS checklist.

The comparison between the TDM strategy and an empirical strategy was cost saving. The ICER between reactive TDM and an empirical strategy was dominated (favorable) by reactive TDM, whereas the ICER value for proactive TDM compared to an empirical strategy ranged from EUR 56,845 to 3,901,554. This systematic review demonstrated that TDM of anti-TNF drugs is a cost-effective or cost-saving tool in the management of IBD.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmaceutics14051009/s1, Table S1. PRISMA 2020 Checklist; Table S2. Search strategies; Table S3. List of excluded studies and reasons *[64–

110]*; Table S4. CHEERS checklist assessment. References [64–110] are cited in the Supplementary Materials.

**Author Contributions:** Conceptualization, R.N.-M. and A.R.-L.; methodology, J.S.-V., S.M.-M., R.N.-M. and A.R.-L.; formal analysis, S.M.-M. and A.R.-L.; investigation, S.M.-M. and A.R.-L.; supervision, R.N.-M.; writing—original draft, S.M.-M., J.S.-V. and A.R.-L.; writing—review and editing, R.N.-M., P.M.-S., M.D.-G. and M.R.C.-B. All authors have read and agreed to the published version of the manuscript.

**Funding:** S.M.-M. received a predoctoral fellowship from Miguel Hernandez University ("Ayudas a la contratación de personal investigador en formación 2021").

**Institutional Review Board Statement:** Not applicable

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data are available from the corresponding author on reasonable request.

**Conflicts of Interest:** The authors declare no conflict of interest.

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*Supplementary material*

# Cost-effectiveness of therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease: a systematic review

**Table S1.** PRISMA 2020 Checklist

**Table S2.** Search strategies

**Table S3.** List of excluded studies and reasons

**Table S4.** CHEERS checklist assessment

**Table S1.** PRISMA 2020 Checklist

| Section and topic | Item # | Checklist item | Location where ítem is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Title page |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract, Title page |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Introduction: paragraph 1-4 |
| Objectives | 4 | Provide an explicit statement of the objective or question the review addresses. | Introduction: paragraph 5 |
| **METHODS** | | | |
| Eligible criteria | 5 | Specify the inclusión and exclusión criteria for the review and how studies were grouped for the syntheses | Methods 2.5 |
| Information sources | 6 | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods 2.2. 2.4 paragraph 4 |
| Search strategy | 7 | Present the full search strategies for all databases, registers, and websites, including any filters and limits used. | Supplementary Table S2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods 2.5 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods 2.7 |

| | | | |
|---|---|---|---|
| Data ítems | 10 | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Methods 2.7 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Methods 2.5 Paragraph 4 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results | Methods 2.7 |
| Syntesis methods | 13 | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Methods 2.5 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods 2.6 paragraph 3 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Methods 2.6 paragraph 3 |
| **RESULTS** | | | |
| Study selection | 16 | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure 1 Supplementary table S3 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 1 Results 3.1, 3.2, 3.3, 3.4, 3.5, 3.6 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Results Paragraph 1 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Table 1 |
| Results of syntheses | 20 | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. | NA |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Results 3.6 |

| | | | |
|---|---|---|---|
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Results 3.6 paragraph 3 |
| **DISCUSSION** | | | |
| Discussion | 23 | Provide a general interpretation of the results in the context of other evidence. Discuss any limitations of the evidence included in the review. Discuss any limitations of the review processes used. Discuss implications of the results for practice, policy, and future research. | Discussion pages |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24 | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Methods 2.4 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Declarations Funding |
| Competing interests | 26 | Declare any competing interests of review authors. | Declarations |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Declarations |

*NA: Not applicable*

**Table S2.** Search strategies for each data base.

| Database | Search strategy |
|---|---|
| Medline (via PubMed) | • Target population (Inflammatory bowel diseases)<br><br>"Inflammatory Bowel Diseases"[Mesh] OR "Inflammatory Bowel Disease*"[Title/Abstract] OR "Idiopathic Proctocolitis"[Title/Abstract] OR "Ulcerative Colitis"[Title/Abstract] OR "Colitis Gravis"[Title/Abstract] OR "Colitis Ulcerativa"[Title/Abstract] OR "Colitis Ulcerosa"[Title/Abstract] OR "Histiocytic Ulcerative Colitis"[Title/Abstract] OR "Mucosal Colitis"[Title/Abstract] OR "Ulcerative Colorectitis"[Title/Abstract] OR "Ulcerative Proctocolitis"[Title/Abstract] OR "Ulcerous Colitis"[Title/Abstract] OR "Crohn's Enteritis"[Title/Abstract] OR "Regional Enteritis"[Title/Abstract] OR "Crohns Disease"[Title/Abstract] OR "Crohn's Disease"[Title/Abstract] OR "Granulomatous Enteritis"[Title/Abstract] OR "Ileocolitis"[Title/Abstract] OR "Granulomatous Colitis"[Title/Abstract] OR "Terminal Ileitis"[Title/Abstract] OR "Regional Ileitis"[Title/Abstract] OR "Enteritis Regionalis"[Title/Abstract] OR "Morbus Crohn*"[Title/Abstract] OR "Regional Enterocolitis"[Title/Abstract]<br><br>• Intervention (Tumor necrosis factor inhibitors)<br><br>"Tumor Necrosis Factor Inhibitors"[Mesh] OR "Tumor Necrosis Factor Inhibitor*"[Title/Abstract] OR "Tumor Necrosis Factor Blocker*"[Title/Abstract] OR "TNF Inhibitor*"[Title/Abstract] OR "TNF Blocker*"[Title/Abstract] OR "Tumor Necrosis Factor Antagonist*"[Title/Abstract] OR "TNF Antagonist*"[Title/Abstract] OR "TNF Inhibitor*"[Title/Abstract] OR "Tumor Necrosis Factor-a"[Title/Abstract] OR "TNF-a" [Title/Abstract] OR "anti TNF"[Title/Abstract] OR "TNF Alpha Inhibitor*"[Title/Abstract] OR "Anti Tumor Necrosis Factor Agent*"[Title/Abstract] OR "Tumour Necrosis Factor Alpha Inhibitor*"[Title/Abstract] OR "Adalimumab"[Mesh] OR "Adalimumab"[Title/Abstract] OR "Humira"[Title/Abstract] OR "Adalimumab-adbm"[Title/Abstract] OR "Amjevita"[Title/Abstract] OR "Adalimumab-atto"[Title/Abstract] OR "Cyltezo"[Title/Abstract] OR "Infliximab"[Mesh] OR "Infliximab"[Title/Abstract] OR "Monoclonal Antibody cA2"[Title/Abstract] OR "MAb cA2"[Title/Abstract] OR "Infliximab-abda"[Title/Abstract] OR "Renflexis"[Title/Abstract] OR "Infliximab-dyyb"[Title/Abstract] OR "Inflectra"[Title/Abstract] OR "Remicade"[Title/Abstract]<br><br>• Results (Cost effectiveness of drug monitoring)<br><br>"Cost-Benefit Analysis"[Mesh] OR "Cost-Benefit Analysis"[Title/Abstract] OR "Cost Benefit Analyses"[Title/Abstract] OR "Cost Effectiveness"[Title/Abstract] OR "Cost Benefit Data"[Title/Abstract] OR "Cost Utility Analysis"[Title/Abstract] OR "Cost-Utility Analyses"[Title/Abstract] OR "Economic Evaluation*"[Title/Abstract] OR "Marginal Analysis"[Title/Abstract] OR "Marginal Analyses"[Title/Abstract] OR "Cost Benefit"[Title/Abstract] OR "Costs and Benefit*"[Title/Abstract] OR "Benefits and Cost*"[Title/Abstract] OR "Cost Effectiveness Analysis"[Title/Abstract] OR "Cost Analysis"[Title/Abstract] OR "Cost Benefit"[Title/Abstract] OR "Cost Benefit Ratio"[Title/Abstract] OR "Cost Savings"[Mesh] OR "Cost |

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|---|---|
| | Saving*"[Title/Abstract] OR "Cost Audit"[Title/Abstract] OR "Cost Containment"[Title/Abstract] OR "Cost Control"[Title/Abstract] AND "Drug Monitoring"[Mesh] OR "Drug Monitoring"[Title/Abstract] OR "Therapeutic Drug Monitoring"[Title/Abstract] OR "Medication Monitoring"[Title/Abstract]<br><br>The final search equation was developed for use in MEDLINE via PubMed through the Boolean union of the 3 proposed equations (Population AND Intervention AND Result). |
| Embase | ● Target population (Inflammatory bowel diseases)<br><br>('inflammatory bowel disease'/exp OR 'inflammatory bowel disease' OR 'inflammatory bowel diseases' OR 'crohn disease'/exp OR 'crohn disease' OR 'crohn's disease' OR 'crohns disease' OR 'cleron disease' OR 'enteritis regionalis' OR 'intestinal tract, regional enteritis' OR 'morbus crohn' OR 'regional enteritis' OR 'regional enterocolitis' OR 'ulcerative colitis'/exp OR 'chronic ulcerative colitis' OR 'colitis ulcerativa' OR 'colitis ulcerosa' OR 'colitis ulcerosa chronica' OR 'colitis, mucosal' OR 'colitis, ulcerative' OR 'colitis, ulcerous' OR 'colon, chronic ulceration' OR 'histiocytic ulcerative colitis' OR 'mucosal colitis' OR 'ulcerative colitis' OR 'ulcerative colorectitis' OR 'ulcerative procto colitis' OR 'ulcerative proctocolitis' OR 'ulcerous colitis')<br><br>● Intervention (Tumor necrosis factor inhibitors)<br><br>('tumor necrosis factor inhibitor'/exp OR 'tnf alpha inhibitor' OR 'tnf inhibitor' OR 'anti tnf agent' OR 'anti tnf alpha agent' OR 'anti tumor necrosis factor agent' OR 'anti tumour necrosis factor agent' OR 'tumor necrosis factor alpha inhibitor' OR 'tumor necrosis factor inhibitor' OR 'tumor necrosis factor inhibitors' OR 'tumour necrosis factor alpha inhibitor' OR 'tumour necrosis factor inhibitor' OR 'adalimumab'/exp OR 'abp 501' OR 'abp501' OR 'abrilada' OR 'abt d2e7' OR 'abtd2e7' OR 'adalimumab' OR 'adalimumab adaz' OR 'adalimumab adbm' OR 'adalimumab afzb' OR 'adalimumab atto' OR 'adalimumab beta' OR 'adalimumab bwwd' OR 'adalimumab fkjp' OR 'adalimumab-adaz' OR 'adalimumab-adbm' OR 'adalimumab-afzb' OR 'adalimumab-atto' OR 'adalimumab-bwwd' OR 'adalimumab-fkjp' OR 'adaly' OR 'amgevita' OR 'amjevita' OR 'amsparity' OR 'avt 02' OR 'avt02' OR 'bat 1406' OR 'bat1406' OR 'bax 2923' OR 'bax 923' OR 'bax2923' OR 'bax923' OR 'bcd 057' OR 'bcd057' OR 'bi 695501' OR 'bi695501' OR 'chs 1420' OR 'chs1420' OR 'cinnora' OR 'ct p17' OR 'ctp17' OR 'cyltezo' OR 'da 3113' OR 'da3113' OR 'dmb 3113' OR 'dmb3113' OR 'exemptia' OR 'fkb 327' OR 'fkb327' OR 'fyzoclad' OR 'gp 2017' OR 'gp2017' OR 'hadlima' OR 'halimatoz' OR 'hefiya' OR 'hlx 03' OR 'hlx03' OR 'hulio' OR 'humira' OR 'hyrimoz' OR 'ibi 303' OR 'ibi303' OR 'idacio' OR 'imraldi' OR 'kromeya' OR 'lu 200134' OR 'lu200134' OR 'm 923' OR 'm923' OR 'mabura' OR 'monoclonal antibody d2e7' OR 'msb 11022' OR 'msb11022' OR 'ons 3010' OR 'ons3010' OR 'pf 06410293' OR 'pf 6410293' OR 'pf06410293' OR 'pf6410293' OR 'qletli' OR 'raheara' OR 'sb 5' OR 'sb5' OR 'solymbic' OR 'trudexa' OR 'yuflyma' OR 'zrc 3197' OR 'zrc3197' OR 'infliximab'/exp OR 'abp 710' OR 'abp710' OR 'avakine' OR 'avsola' OR 'flixabi' OR 'gp 1111' OR 'gp1111' OR 'inflectra' OR 'infliximab' OR 'infliximab abda' OR 'infliximab axxq' OR 'infliximab dyyb' OR 'infliximab qbtx' OR 'infliximab-abda' OR 'infliximab-axxq' OR 'infliximab-dyyb' OR 'infliximab-qbtx' OR 'ixifi' OR 'pf 06438179' OR 'pf 6438179' OR 'pf06438179' OR |

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| | 'pf6438179' OR 'remicade' OR 'remsima' OR 'renflexis' OR 'revellex' OR 'ta 650' OR 'ta650' OR 'zessly')<br><br>● Results (Cost effectiveness of drug monitoring)<br><br>('cost benefit analysis'/exp OR 'cost analysis' OR 'cost benefit' OR 'cost benefit analysis' OR 'cost benefit ratio' OR 'cost-benefit analysis') AND ('drug monitoring'/exp OR 'drug monitoring' OR 'medication monitoring' OR 'monitoring, drug' OR 'therapeutic drug monitoring')<br><br>The final search equation was developed for use in EMBASE through the Boolean union of the 3 proposed equations (Population AND Intervention AND Result). |
| Cochrane Library | #1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees<br>#2 ("Inflammatory Bowel Diseases"):ti,ab,kw (Word variations have been searched)<br>#3 MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees<br>#4 ("Tumor Necrosis Factor Inhibitors"):ti,ab,kw (Word variations have been searched)<br>#5 MeSH descriptor: [Cost-Benefit Analysis] explode all trees<br>#6 ("Cost-Benefit Analysis"):ti,ab,kw (Word variations have been searched)<br>#7 MeSH descriptor: [Drug Monitoring] explode all trees<br>#8 ("Drug Monitoring"):ti,ab,kw (Word variations have been searched)<br>#9 (#1 OR #2) AND (#3 OR #4) AND ((#5 OR #6) AND (#7 OR #8)) |
| PsycINFO | S1 MA inflammatory bowel disease OR TI inflamatory bowel disease OR AB inflamatory bowel disease<br>S2 MA tumor necrosis factor inhibitors OR TI tumor necrosis factor inhibitors OR AB tumor necrosis factor inhibitors<br>S3 MA cost benefit analysis OR TI cost benefit analysis OR AB cost benefit analysis<br>S4 MA drug monitoring OR TI drug monitoring OR AB drug monitoring<br>S5 S1 AND S2 AND (S3 AND S4) |
| Scopus | ● Target population (Inflammatory bowel diseases)<br><br>TITLE-ABS-KEY("Inflammatory Bowel Diseases" OR "Inflammatory Bowel Disease" OR "Idiopathic Proctocolitis" OR "Ulcerative Colitis" OR "Colitis Gravis" OR "Colitis Ulcerativa" OR "Colitis Ulcerosa" OR "Histiocytic Ulcerative Colitis" OR "Mucosal Colitis" OR "Ulcerative Colorectitis" OR "Ulcerative Proctocolitis" OR "Ulcerous Colitis" OR "Crohns Enteritis" OR "Regional Enteritis" OR "Crohns Disease" OR "Crohn's Disease" OR "Granulomatous Enteritis" OR "Ileocolitis" OR "Granulomatous Colitis" OR "Terminal Ileitis" OR "Regional Ileitis" OR "Enteritis Regionalis" OR "Morbus Crohn" OR "Regional Enterocolitis")<br><br>● Intervention (Tumor necrosis factor inhibitors)<br><br>TITLE-ABS-KEY("Tumor Necrosis Factor Inhibitor" OR "Tumor Necrosis Factor Blocker" OR "TNF Inhibitor" OR "TNF Blocker" OR "Tumor Necrosis Factor Antagonist" OR "TNF Antagonist" |

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|---|---|
| | OR "TNF Inhibitor" OR "Tumor Necrosis Factor-a" OR "TNF-a" OR "anti TNF" OR "TNF Alpha Inhibitor" OR "Anti Tumor Necrosis Factor Agent" OR "Tumour Necrosis Factor Alpha Inhibitor" OR "Adalimumab" OR "Humira" OR "Adalimumab-adbm" OR "Amjevita" OR "Adalimumab-atto" OR "Cyltezo" OR "Infliximab" OR "Monoclonal Antibody cA2" OR "MAb cA2" OR "Infliximab-abda" OR "Renflexis" OR "Infliximab-dyyb" OR "Inflectra" OR "Remicade")<br><br>● Results (Cost effectiveness of drug monitoring)<br><br>TITLE-ABS-KEY("Cost-Benefit Analysis" OR "Cost Benefit Analyses" OR "Cost Effectiveness" OR "Cost Benefit Data" OR "Cost Utility Analysis" OR "Cost-Utility Analyses" OR "Economic Evaluation" OR "Marginal Analysis" OR "Marginal Analyses" OR "Cost Benefit" OR "Costs and Benefit" OR "Benefits and Cost" OR "Cost Effectiveness Analysis" OR "Cost Analysis" OR "Cost Benefit Ratio" OR "Cost Saving" OR "Cost Audit" OR "Cost Containment" OR "Cost Control") AND TITLE-ABS-KEY("Drug Monitoring" OR "Therapeutic Drug Monitoring" OR "Medication Monitoring")<br><br>The final search equation was developed for use in SCOPUS through the Boolean union of the 3 proposed equations (Population AND Intervention AND Result). |
| Web of Science | ● Target population (Inflammatory bowel diseases)<br><br>"Inflammatory Bowel Diseases" OR "Inflammatory Bowel Disease" OR "Idiopathic Proctocolitis" OR "Ulcerative Colitis" OR "Colitis Gravis" OR "Colitis Ulcerativa" OR "Colitis Ulcerosa" OR "Histiocytic Ulcerative Colitis" OR "Mucosal Colitis" OR "Ulcerative Colorectitis" OR "Ulcerative Proctocolitis" OR "Ulcerous Colitis" OR "Crohns Enteritis" OR "Regional Enteritis" OR "Crohns Disease" OR "Crohn's Disease" OR "Granulomatous Enteritis" OR "Ileocolitis" OR "Granulomatous Colitis" OR "Terminal Ileitis" OR "Regional Ileitis" OR "Enteritis Regionalis" OR "Morbus Crohn" OR "Regional Enterocolitis" (Topic)<br><br>● Intervention (Tumor necrosis factor inhibitors)<br><br>"Tumor Necrosis Factor Inhibitor" OR "Tumor Necrosis Factor Blocker" OR "TNF Inhibitor" OR "TNF Blocker" OR "Tumor Necrosis Factor Antagonist" OR "TNF Antagonist" OR "TNF Inhibitor" OR "Tumor Necrosis Factor-a" OR "TNF-a" OR "anti TNF" OR "TNF Alpha Inhibitor" OR "Anti Tumor Necrosis Factor Agent" OR "Tumour Necrosis Factor Alpha Inhibitor" OR "Adalimumab" OR "Humira" OR "Adalimumab-adbm" OR "Amjevita" OR "Adalimumab-atto" OR "Cyltezo" OR "Infliximab" OR "Monoclonal Antibody cA2" OR "MAb cA2" OR "Infliximab-abda" OR "Renflexis" OR "Infliximab-dyyb" OR "Inflectra" OR "Remicade" (Topic)<br><br>● Results (Cost effectiveness of drug monitoring)<br><br>"Cost-Benefit Analysis" OR "Cost Benefit Analyses" OR "Cost Effectiveness" OR "Cost Benefit Data" OR "Cost Utility Analysis" OR "Cost-Utility Analyses" OR "Economic Evaluation" OR |

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| | "Marginal Analysis" OR "Marginal Analyses" OR "Cost Benefit" OR "Costs and Benefit" OR "Benefits and Cost" OR "Cost Effectiveness Analysis" OR "Cost Analysis" OR "Cost Benefit Ratio" OR "Cost Saving" OR "Cost Audit" OR "Cost Containment" OR "Cost Control" (Topic) and "Drug Monitoring" OR "Therapeutic Drug Monitoring" OR "Medication Monitoring" (Topic)<br><br>The final search equation was developed for use in WEB OF SCIENCE through the Boolean union of the 3 proposed equations (Population AND Intervention AND Result). |
| LILACS | (Inflammatory Bowel Diseases [Subject descriptor] or Inflammatory Bowel Diseases [Words]) and (Tumor Necrosis Factor Inhibitor [Subject descriptor] or Tumor Necrosis Factor Inhibitor [Words]) and (Cost-Benefit Analysis [Subject descriptor] or Cost-Benefit Analysis [Words]) and (Drug Monitoring [Subject descriptor] or Drug Monitoring [Words]) |
| MEDES | ("Enfermedades Inflamatorias del Intestino"[título/resumen/palabras_clave]) AND ("Inhibidores del factor de Necrosis Tumorales"[título/resumen/palabras_clave]) AND ("Cost-Benefit Analysis "[título/resumen/palabras_clave]) AND ("Drug Monitoring"[título/resumen/palabras_clave]) |

**Table S3**. List of excluded studies and reasons

| Reason of exclusion | Excluded studies |
|---|---|
| Not original article | Bhattacharya A, et al [64]; Alsound D, et al[65]; Fobelo MJ, et al [66]; Felice C, et al [67]; Peyrin-Biroulet L, et al [68]; Martelli L, et al [27]; Mitrev N, et al [69]; Franco DL, et al [70]; Hoseyni H, et al [71]; Lega S, et al [72]; Papamichael K, et al [73]; Teml A, et al [74]; Khanna R, et al [75]; Ricciuto A, et al [76]; Yao J, et al [29]; Yanai H, et al [77]; McNeill RP, et al [78]; Papamichael K, et al [79]; Andrews JM, et al [80]; Tavis S [81]; Rentsch CA et al [82]; Rentsch C et al [83]; Rentsch C et al [84]; Kozak J et al [85]; Janko N, et al [86]; Wright EK et al [87]; Steenholdt C et al [88]; Lee JM, et al [89]; Doherty J, et al [90]; Steen J, et al [91]; Yang SK [92]; Mehta P, et al [93]; Sanchez-Hernandez JG, et al [94]; Zandvliet ML, et al [95] |
| Causality criterion | Patel RN, et al [96]; Syversen SW, et al [97]; Drobne D, et al [98]; Selinger CP, et al [99]; Thomas PWA, et al [100]; Grossberg LB, et al [101]; Nigam GB, et al [102]; Langford T, et al [103]; Crane H, et al [104]; Stein BN, et al [105]; Sparrow M [106]; Park KT, et al [107]; Kelly OB, et al [108]; Scharnhorst V, et al [109]; Jourdil JF, et al [110] |

**Table S4.** CHEERS checklist assessment.

| | | Yao et al | Wu et al | Ganesana-nthan et al | Negoescu et al | Attar et al | Guidi et al | Taks et al | Roblin et al | Freeman et al | Vande Casteele et al | Steenholdt et al | Steenholdt et al | Velayos et al |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Title | Y | Y | Y | Y | Y | N | N | Y | Y | N | Y | Y | Y |
| 2. | Abstract | Y | Y | N | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 3. | Background & Objectives | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4. | Target Population & Subgroups | Y | Y | Y | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 5. | Setting & Location | Y | Y | Y | N | N | Y | Y | N | Y | Y | N | N | Y |
| 6. | Study Perspective | Y | Y | N | Y | N | N | N | N | N | Y | Y | Y | N |
| 7. | Comparators | Y | Y | N | Y | Y | Y | N | Y | Y | Y | Y | Y | Y |
| 8. | Time Horizon | N | N | N | N | N | N | N | Y | Y | N | N | N | Y |
| 9. | Discount Rate | Y | N | N | Y | N | N | N | N | Y | Y | N | N | N |
| 10. | Choice of Health Outcomes | Y | N | Y | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 11. | Measurement of Effectiveness | Y | N | N | N | N | N | N | Y | Y | Y | N | N | N |
| 12. | Measurement & Valuation of Preference-based Outcomes | Y | Y | N | N | N | Y | Y | N | Y | Y | Y | Y | N |
| 13. | Estimating Resources & Costs | Y | N | N | Y | N | Y | N | N | Y | N | Y | Y | Y |
| 14. | Currency, Price Date & Conversion | Y | N | N | Y | N | N | N | N | Y | Y | Y | Y | N |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15. | Choice of Model | Y | Y | N | Y | Y | Y | N | Y | Y | N | N | N | Y |
| 16. | Assumptions | Y | N | N | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 17. | Analytic Methods | Y | Y | N | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 18. | Study Parameters | Y | Y | N | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 19. | Incremental Costs & Outcomes | Y | N | N | Y | N | Y | N | N | Y | Y | Y | Y | Y |
| 20. | Characterising Uncertainty | Y | N | N | Y | N | N | N | Y | Y | N | N | N | N |
| 21. | Characterising Heterogeneity | Y | N | N | N | N | Y | N | N | Y | N | N | N | N |
| 22. | Study findings, limitations, generalisability and current knowledge | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y |
| 23. | Source of funding | N | N | N | Y | Y | Y | N | Y | Y | Y | Y | Y | Y |
| 24. | Conflicts of Interest | N | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| | Total (%) | 21 (87.5%) | 12 (50%) | 7 (29.2%) | 19 (79.2%) | 7 (29.2%) | 17 (70.8%) | 4 (16.7%) | 10 (41.7%) | 23 (95.8%) | 18 (75.0%) | 17 (70.8%) | 17 (70.8%) | 17 (70.8%) |

## ARTICLE II

Article

# Evaluation of the Predictive Performance of Population Pharmacokinetic Models of Adalimumab in Patients with Inflammatory Bowel Disease

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**Pharmaceutics 2021;13(8):1244**

| | |
|---|---|
| Impact factor (2021) | 6.525 |
| Pharmacology & Pharmacy (Q1) | 39/279 |

## ABSTRACT

Adalimumab is a monoclonal antibody used for inflammatory bowel disease. Due to its considerably variable pharmacokinetics, the loss of response and the development of anti-antibodies, it is highly recommended to use a model-informed precision dosing approach. The aim of this study is to evaluate the predictive performance of different population-pharmacokinetic models of adalimumab for inflammatory bowel disease to determine the pharmacokinetic model(s) that best suit our population to use in the clinical routine. A retrospective observational study with 134 patients was conducted at the General University Hospital of Alicante between 2014 and 2019. Model adequacy of each model was evaluated by the distribution of the individual pharmacokinetic parameters and the NPDE plots whereas predictive performance was assessed by calculating bias and precision. Moreover, stochastic simulations were performed to optimize the maintenance doses in the clinical protocols, to reach the target of 8 mg/L in at least 75% of the population. Two population pharmacokinetic models were selected out of the six found in the literature which performed better in terms of adequacy and predictive performance. The stochastic simulations suggested the benefits of increasing the maintenance dose in protocol to reach the 8 mg/L target.

## Keywords

pharmacokinetics; drug monitoring; adalimumab; inflammatory bowel diseases; Crohn's disease; colitis; ulcerative

## 1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) characterized by the intermittent destructive inflammation of the intestinal tract associated with significant morbidity, high burden of hospitalization and a severe impact on the quality of life of patients. There are several pharmacological alternatives available, including corticosteroids, immunosuppressive agents (methotrexate or azathioprine) and monoclonal antibodies that have shown clinical response in the treatment of these diseases [1–3].

Adalimumab is a human monoclonal antibody that binds specifically to the tumor necrosis factor (TNF) and neutralizes its biological function, decreasing the process of inflammation. Adalimumab is effective for induction and maintenance of remission in patients with moderate-to-severe IBD older than 6 years who fail with corticosteroids, immunosuppressive agents or other biologic therapy [4–6].

Several published studies of adalimumab have shed light on the clinical relevance of individualized dosing. Historically, the empiric approach to adapt the adalimumab dosage consists of intensifying the treatment in patients with loss of response and later, if this fails, switching to another biological treatment. In the last decade, several studies have shown that some patients can experience a loss of response to adalimumab or can develop antibodies against adalimumab (AAA) after long periods of subtherapeutic drug levels [7–14]. However, most of the time, the serum concentration guide dosing was done through algorithms [15,16].

In this line, Model-Informed Precision Dosing (MIPD) is the approach based on the use of population PK (PopPK) models and prospective Bayesian approach to increase the homogeneity in the drug exposure in patients in order to improve outcomes of treatments by achieving the optimal balance between efficacy and toxicity for each individual patient [17]. IBD patients could benefit from dose optimization because adalimumab has highly variable pharmacokinetics (PK) [16,18].

Recently, a multicenter retrospective study showed that the potential importance of early monitoring levels of adalimumab and MIPD approach can prevent immunogenicity and achieve better long-term outcomes in terms of IBD-related surgery or hospitalization, lower risk of developing AAA or serious infusion reactions and also it proved to be more cost-effective in comparison to empirical and/or reactive dose optimization program dose escalation [19]. However, the selection of the appropriate PopPK model is fundamental to apply MIPD, especially when there are multiple models in the literature in patients with IBD. The structural model is defined, in most of them, as

one-compartment model with linear kinetics in the absorption and elimination processes, although the value of the PopPK parameters, and the covariates included in the model, vary significantly. Therefore, the aim of this study is to evaluate the predictive performance of PopPK models of adalimumab found in literature, in patients with IBD to determine the pharmacokinetic model(s) best suited for our population to subsequently use it in the clinical setting using MIPD.

## 2. Materials and Methods

### 2.1. Literature Search

A systematic literature search was conducted of databases in the field of Health Sciences: MEDLINE (via PubMed), Embase and Scopus. To define the search terms, the Medical Subject Headings (MeSH), a thesaurus developed by the U.S. National Library of Medicine, was used. The MeSH descriptors “Chron Disease”, “Colitis, Ulcerative”, “adalimumab” and “pharmacokinetics” were considered suitable. Likewise, these terms, “inflammatory bowel diseases” and “pharmacokinetics” were used to query the databases using the title and abstract field (Title/Abstract). The search was performed from the first available date until May 2021 according to the characteristics of each database. Additionally, a manual search for population models was conducted by inspecting the bibliographies of relevant journal articles to minimize the number of unrecovered papers by the review.

The following search was used in Pubmed, and it was adapted to the other databases: (((((“Inflammatory Bowel Diseases”[Mesh]) OR (Inflammatory Bowel Diseases[Title/ Abstract])) OR (((Crohn Disease[Title/Abstract]) OR (Crohn’s Disease[Title/Abstract])) OR (“Crohn Disease”[Mesh]))) OR ((ulcerative colitis[Title/Abstract]) OR (“Colitis, Ulcerative”[ Mesh]))) AND ((Adalimumab[Title/Abstract]) OR (“Adalimumab”[Mesh]))) AND ((Pharmacokinetics[Title/Abstract]) OR (“Pharmacokinetics”[Mesh])).

The inclusion criteria were the following: original articles published in peer-reviewed journals, articles that describe a novel population pharmacokinetic model and pertinent works with the available complete text, which must be written in English or Spanish. Additionally, the full text of the document should be accessible and only one version of each document was included. The following were the exclusion criteria: articles that included different diseases to CD or UC and studies developed in animal models.

The following information was extracted from the articles: patient characteristics, model structure, typical PopPK parameters, inter-individual variability (IIV), residual variability (RV) and covariates.

### 2.2. Study Design

A retrospective observational study was conducted at the General University Hospital of Alicante, performed on patients diagnosed with IBD undergoing treatment with adalimumab and who followed a dose optimization program developed between 2014 and 2019.

### 2.3. Patients and Data Collection

Trough serum concentrations (TSC) were collected from patients diagnosed with moderate or severe IBD treated with adalimumab in General University Hospital of Alicante, Spain. The following inclusion criteria were applied: participants had to be diagnosed with IBD, treated with adalimumab, and there had to be at least two adalimumab TSC in their medical history. Exclusion criteria included patients treated with other monoclonal antibodies different to adalimumab like infliximab, vedolizumab and ustekinumab and subjects who were diagnosed with other autoimmune diseases different to IBD such as rheumatoid arthritis, psoriasis and ankylosing spondylitis.

Relevant data were collected from the medical records and included age, sex, height, body weight, lean body weight (LBW), body mass index (BMI), AAA status and AAA serum concentration, dose of adalimumab, adalimumab serum concentration, serum albumin levels, serum C-reactive protein (CRP) levels, fecal calprotectin (FCP), type of disease, use of concomitant immunomodulators and time of the event recorded. Missing values of continuous covariates were imputed by their expected mean values. Data were excluded from the analysis if there was uncertainty about any relevant information such as the time of dosing or the time of drug concentration measurement and the loss to follow-up during their treatment.

Serum adalimumab concentrations and AAA were measured using an enzyme-linked immunosorbent assay (LISA TRACKER Duo Drug + ADAb from TheraDiag®) with a limit of quantification established to be 0.1 mg/L. Patients were considered as positive for AAA if titers were above 10 mg/L on at least one occasion.

### 2.4. Evaluation of Model Adequacy

The first step in the evaluation of the different PopPK models found in the literature was the evaluation of the model adequacy by analyzing and comparing how the different PopPK models describe the studied population using all the available TSC

in the dataset (full dataset). Models that show the greater systematic bias in the Empirical Bayesian estimate (EBEs) of the PK parameters, or in the Normalised Prediction Distribution Errors (NPDE) [20,21] will be discarded. Only the models that described properly our population will be used to evaluate the predictive performance later.

Therefore, the distribution of the EBEs of the PK parameters for each of the PopPK models was calculated after performing a post-hoc analysis using the full dataset. Then, this distribution would be compared with the theoretical distribution of these PK parameters according to each of the PopPK models.

On the other hand, any trends observed in the NPDE plots (e.g., cone-shaped graph) might indicate model misspecifications and inferior model adequacy.

### 2.5. Evaluation of Predictive Performance

The evaluation of predictive performance was only performed in those models which best describe the studied population, according to the evaluation of the model adequacy.

To evaluate the predictive performance, the individual predictions of the last TSC were estimated for each patient, using the EBEs. These last TSC concentrations, named “last observed TSC”, were left out and not used to calculate the EBEs. To evaluate the predictive performance, the bias and the precision were calculated with the last observed TSC by comparing them with their individual predictions calculated by each of the PK models. The predictive performance of the patients was evaluated considering two different scenarios;

Scenario 1: The EBES were calculated from the previous TSC obtained from each patient.

Scenario 2: The EBES were calculated from the two previous TSC of each patient.

The mean prediction error (MPE, Equation (1)) and root mean square prediction error (RMSPE, Equation (2)) were calculated for bias and precision, respectively.

$$MPE = \frac{\sum(\hat{Y}-Y)}{n} \quad (1)$$

$$RMSPE = \sqrt{\frac{\sum(\hat{Y}-Y)^2}{n}} \quad (2)$$

In both equations Y-hat represents the model-predicted adalimumab concentration, Y represents the observed adalimumab concentration, and n is the number of observations.

A bootstrap of the data was performed to compare the statistical significance of the differences between bias and precision among the selected models.

### 2.6. Clinical Impact

Stochastic simulations were performed to optimize the initial maintenance doses in the clinical protocols, in order to acquire the target TSC in at least 75% of the population.

The dosage regimens that were simulated were 40 and 80 mg administered subcutaneously every week or every other week. The target TSC that were considered were 8 mg/L for clinical remission [18,22].

### 2.7. Software

The PopPK models found in the literature were implemented in NONMEM® version 7.4 software package [23]. The posterior statistical analysis and graphics were performed using R software v4.0.3 [24], implemented in R-studio v1.3.1093 [25].

### 2.8. Ethical Considerations

*2.8.1. Ethics Approval*

All studies were conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and were approved by the Human Investigational Review Board of each study center.

*2.8.2. Consent*

The need for written consent was waived because of the retrospective nature of the study.

## 6. Results

### 3.1. Literature Search

A total of 211 publications 72, 52 and 87 from PubMed, Embase and Scopus, respectively, from 2003 to 2021, were found and collected in the search of databases using the keywords mentioned in the methods section. After removing duplicate articles and applying the inclusion and exclusion criteria, six PopPK models [26–31] were selected. The models were numbered from 1 to 6 and are referred to as M1 to M6. All selected PopPK models were one-compartment models. Four of them included only trough levels of adalimumab (M2, M3, M4 and M5) whereas the others (M1 and M6)

derived from complete profiles of serum concentrations of adalimumab. Five of the six models were developed using NONMEM® software, while one model (M2) was developed using Monolix® software. Further information can be found in Table 1.

**Table 1.** Summary of specifications of selected models.

| Model no. | Study | No. of patients (total no. of samples) | Parameter values and covariate relationships included | IIV (CV) | Residual Variability |
|---|---|---|---|---|---|
| **M1** | FDA, 2008 | 646 adult patients (NA) | $CL/F\ (L/h) = 0.0127$<br>$V/F\ (L) = 9.39 + 0.126 \cdot (WT - 72))$<br>$ka\ (1/h) = 0.027\ FIX$ | IIV-CL/F: 16.4 %<br>IIV- V/F: 35.1 % | Prop = 31.6 % |
| **M2** | Ternant D et al, 2015 | 65 adult CD patients (341) | $CL/F\ (L/h) = 0.0175 \cdot (1 + 4.5 \cdot AAA)$<br>$V/F\ (L) = 13.5$<br>$ka\ (1/h) = 0.00625$ | IIV-CL/F: 65 %<br>IIV- V/F: 48 % | Add = 1.8 mg/L<br>Prop = 16 % |
| **M3** | Sharma S et al, 2015 | 189 pediatric CD patients (852) | $CL/F\ (L/h) = 0.0117 \cdot (1 + 1.08 \cdot AAA) \cdot (WT/45.2)^{0.48}$<br>$V/F\ (L) = 4.75 \cdot (WT/45.2)^{0.904}$<br>$ka\ (1/h) = 0.00833$ | IIV-CL/F: 21.1 % | Add = 1.9 mg/L<br>Prop = 7.1 % |
| **M4** | Berends SE et al, 2018 | 96 adult CD patients (181) | $CL/F\ (L/h) = 0.0133 \cdot (1 + 3.14 \cdot AAA) \cdot (1 + 0.4 \cdot DOSING)$<br>$V/F\ (L) = 4.07$<br>$ka\ (1/h) = 0.00833\ FIX$ | IIV-CL/F: 49.1 % | Add = 1.02 mg/L<br>Prop = 9 % |
| **M5** | Vande Castelee et al, 2019 | 28 adult CD patients (185) | $CL/F\ (L/h) = 0.01375 \cdot (1 + 1.59 \cdot AAA) \cdot (LBW/47.8)^{1.97}$<br>$V/F\ (L) = 7.8$<br>$ka\ (1/h) = 0.0143$ | IIV-CL/F: 32.6 %<br>IIV- V/F: 35.6 %<br>IIV- ka: 103.9 % | Prop = -16.6% |
| **M6** | Sánchez-Hernández et al, 2020 | 104 adult IBD patients (303) | $CL/F\ (L/h) = 0.0157 \cdot (BMI/23.7)^{1.11} \cdot (1 + 1.20 \cdot UDASC) \cdot (1 + 0.24 \cdot PEN) \cdot (FCP/74)^{0.064}$<br>$V/F\ (L) = 11.2$<br>$ka\ (1/h) = 0.00625\ FIX$ | IIV-CL/F: 23.2 % | Prop = 21.7 % |

*IIV: inter-individual variability; CV: coefficient of variation; CD: Crohn's disease; IBD: Inflammatory Bowel Disease; WT: weight; AAA: antibodies against adalimumab; DOSING: adalimumab dosing regimen (0: every other week, 1: every week); UDASC: unexplained decline in adalimumab serum concentrations (0: NO, 1: YES); PEN: administration pen device during maintenance phase (0:40 mg, 1:80 mg); FCP: fecal calprotectin; add: additive error; prop: proportional error; NA: not available. The M numbers represent the selected models.*

Typical values for adalimumab apparent clearance (CL/F) in the studies ranged from 11.7 to 17.5 mL/h, with the lowest value being reported in studies performed with pediatric population (M3). The typical apparent volume of distribution (V/F) ranged from 4.07 to 13.5 L. The absorption rate constant (ka) was estimated in three models and fixed in the others. All models estimated the IIV (coefficient of variation [CV], in percent) associated with adalimumab CL/F, with values ranging from 16.4% to 65%. Three models (M1, M2 and M5) estimated the IIV of V/F ranged from 35.1% to 48%. The summary of the characteristics of each study is listed in Table 2.

### 3.2. Patients

The dataset included 134 IBD patients in treatment with adalimumab with at least two TC. Baseline demographics, disease characteristics and missing values for the different covariates of the patient population are listed in Table 3. 75% of the patients are below 57 years old and 75 kg. Approximately 85% of the patients were diagnosed as CD and 8% of them developed AAA.

82 patients were treated subcutaneously with 160/80 mg and 18 with 80/40 mg at weeks 0/2 as an induction phase. For the rest, the information regarding the induction phase was not available in their medical histories. Following this phase, as a maintenance phase, all patients were treated with 40 mg of adalimumab every other week. A total of 398 TSC in the maintenance phase were available for the analysis, where 25.4% of these concentrations were over 8 mg/L, 46.3% between 3 and 8 mg/L and 28.3% below 3 mg/L in the first measure. AAA were detected in 11 patients. 73 patients were on a concomitant immunomodulator (azathioprine, 6 mercaptopurine, methotrexate or prednisone).

The dosage regimen was increased to 40 mg every 10 days or 40 mg every week, on 31 and 70 dose adjustments, respectively. Similarly, the dosage regimen was increased to 80 mg every other week or 80 mg every week, on 7 and 11 dose adjustments, respectively. On the other hand, on 7 dose adjustments, the dosage regimen was decreased to 40 mg every 3 weeks, at any time during their treatment. In 36 patients the dosage regimen was maintained at 40 mg every other week.

### 3.3. Evaluation of Model Adequacy

The distribution of the individual CL/F obtained in the post-hoc analysis compared with their theoretical distribution is represented in Figure 1. The distribution of the individual V/F was not performed because half of the models (M3, M4 and M6) did not include IIV in the V/F. The QQ-plot of the NPDE and their distribution versus time are depicted in Figure 2.

**Table 2.** Summary of patient characteristics of selected models.

| Model no. | Age (yr) | Weight (kg) | Disease (cd/uc) | Sex (m/f) | AAA positive (%) | Albumin (g/dl) | Dosage regimen | Measured adalimumab concentration | Measured AAA |
|---|---|---|---|---|---|---|---|---|---|
| **M1** | NA | NA | NA | NA | NA | NA | - Induction phase: 160/80 mg or 80/40 at weeks 0/2<br>- Maintenance phase: 40 every other week | ELISA | ELISA |
| **M2** | 37 (17-61) | 68 (43-109) | 100/0 | 17/48 | 9 (13.8 %) | NA | - Induction phase: 160/80 mg or 80/40 at weeks 0/2<br>- Maintenance phase: 40 mg every other week | ELISA | Double-antigen ELISA |
| **M3** | 13.6 (6-17) | 45.2 (18-119) | 100/0 | 105/84 | 83 (43.9 %) | 4.0 (2.4-5.3) | - Induction phase:<br>• ≥40 kg: 160/80 mg at weeks 0/2<br>• <40 kg: 80/40 at weeks 0/2<br>- Maintenance phase:<br>• ≥40 kg: 40 or 20 mg every other week<br>• <40 kg: 20 or 10 mg every other week | Double-antigen ELISA | Bridging ELISA |
| **M4** | 38 (32-44) | 65 (58-76) | 100/0 | 35/96 | 17 (18%) | 4.3 (4.05-4.5) | - Maintenance phase: 40 mg every week or every other week | TNF ELISA | Antigen-binding test |
| **M5** | 37 (30-49) | 66 (55-73) | 100/0 | 13/28 | 5 (17.9 %) | 3.99 (3.6-4.4) | - Induction phase: 160/80 mg at weeks 0/2<br>- Maintenance phase: 40 mg every other week | In-house developed TNF-coated ELISA | In-house developed drug resistant AAA assay |
| **M6** | 43 (32-56) | 68 (56-80) | 84/20 | 58/46 | 0 | 4.5 (4.3-4.7) | - Induction phase: 160/80 mg at weeks 0/2<br>- Maintenance phase: dose adjustment according to TDM | ELISA | ELISA |

*CD: Crohn's disease; UC: ulcerative colitis; AAA: antibodies against adalimumab; NA = not available. The M numbers represent the models described in Table 1.*

**Table 3.** Summary of characteristics of included patients.

| Characteristics | Count (%) / Median (percentile 25th – 75th ) | Missings, n (%) |
|---|---|---|
| Patients | 134 | 0 |
| Age (yr) | 45 (34 – 57) | 0 |
| Sex, male, n (%) | 70 (52.2 %) | 0 |
| Weight (kg) | 66 (58 – 75) | 1 (0.75 %) |
| Body mass index (kg/m$^2$) | 23.85 (20.52 – 27.36) | 10 (7.46 %) |
| Lean Body Weight (kg) | 46.84 (42.60 – 52.10) | 10 (7.46 %) |
| Albumin (g/dL) | 3.84 (3.53 – 4.12) | 5 (3.73 %) |
| CRP (mg/dL) | 0.64 (0.25 – 2.1) | 37 (27.61 %) |
| FCP (mg/kg) | 487 (217.11 – 884.68) | 37 (27.61 %) |
| IBD type, CD, n (%) | 115 (85.8 %) | 0 |
| Concomitant immunomodulator, n (%) | | |
| Aminosalicylate | 7 (5.2 %) | 0 |
| Methotrexate | 10 (7.5 %) | 0 |
| Azathioprine | 53 (39.6 %) | 0 |
| 6-Mercaptopurine | 6 (4.5 %) | 0 |
| Corticosteroids | 16 (11.9 %) | 0 |
| Combined | 14 (10.4 %) | 0 |
| Adalimumab serum samples | 398 | 0 |
| Adalimumab serum concentrations (mg/L) | 6.75 (4.58 – 8.65) | 0 |
| AAA serum concentrations (mg/L) | 29 (4.53 – 76.30) | 0 |
| AAA positive, n (%) | 11 (8%) | 0 |

*CRP: C-reactive protein; FCP: fecal calprotectin; IBD: inflammatory bowel disease; CD: Crohn's disease; AAA: antibodies against adalimumab.*

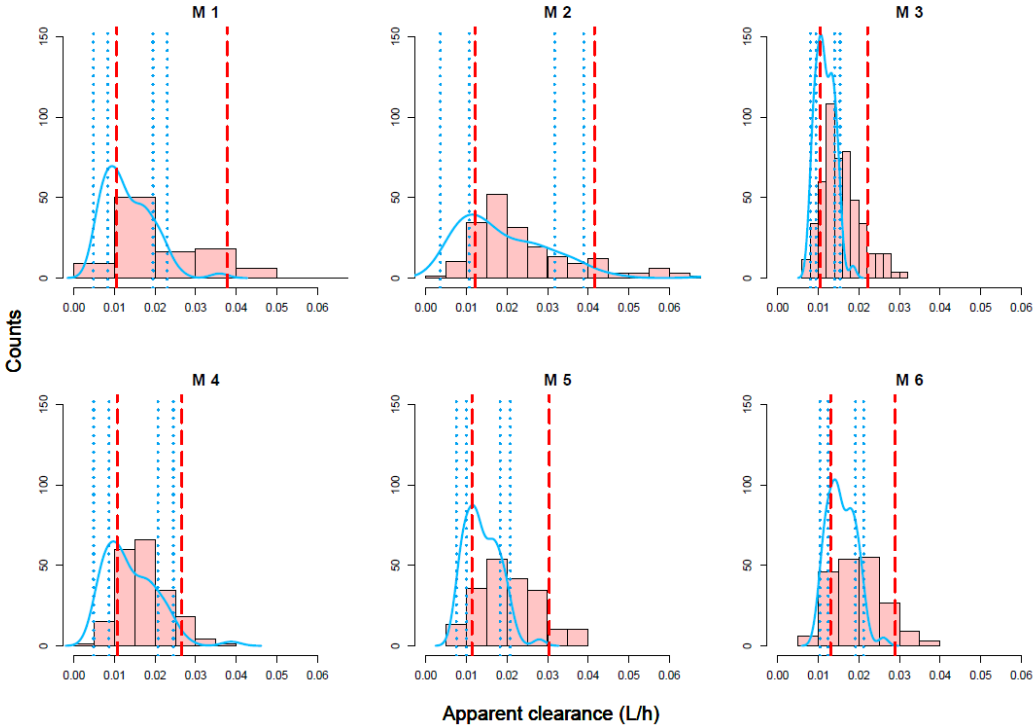


**Figure 1.** Histograms of EBEs for CL/F. Red dashed line; 20th and 80th percentile of EBEs CL/F; blue solid line represents the density of the simulated CL/F; blue dotted line, 95% confidence interval (CI) for the 20th and 80th percentiles of simulated CL/F. The M numbers represent the models described in Table 1.

In M2 and M4, the 20% and 80% percentiles of the EBE of CL/F are close to the 95% confidence interval of the 20% and 80% percentiles of the simulated distribution of CL/F for these models. Moreover, the NPDE performed better in these models. Hence, M2 and M4 were the models that best described the studied population, with less bias and better NPDE performance. Therefore, the predictive performance would be evaluated in these models.

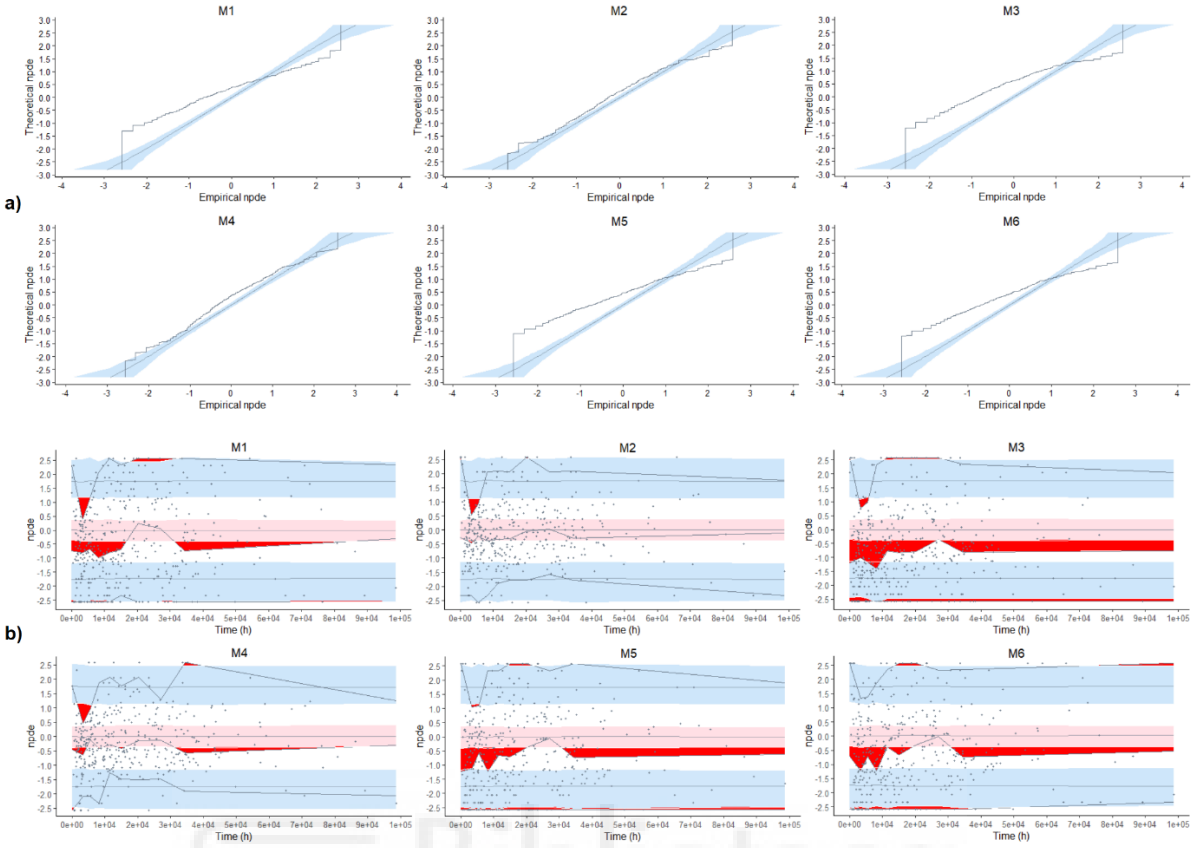


**Figure 2.** NPDE for each model. (a) Quantile-quantile plot of the NPDE versus the corresponding quantiles of a normal distribution. (b) Plot of NPDE versus time. Solid horizontal lines are the lines corresponding to 0, 5% and 95% critical values; gray solid lines, prediction intervals; blue-shaded area, 90% confidence interval (CI) of the 5% and 95% critical values; pink-shaded area, 90% CI of 0; red-shaded area, outliers of the bounds of the CI. The M numbers represent the models described in Table 1.

### 3.4. Evaluation of Predictive Performance

Figure 3 shows the predictive performance for M2 and M4 represented as the IRES vs. the model-based prediction of the last observed TSC. Both models behave similarly, with a limited bias and a similar dispersion of the IRES. Table 4 also shows the bias and precision for M2 and M4 and their confidence interval. M2 and M4 are statistically better ($p < 0.05$) than the other models in terms of bias and precision in both scenarios (data not shown).

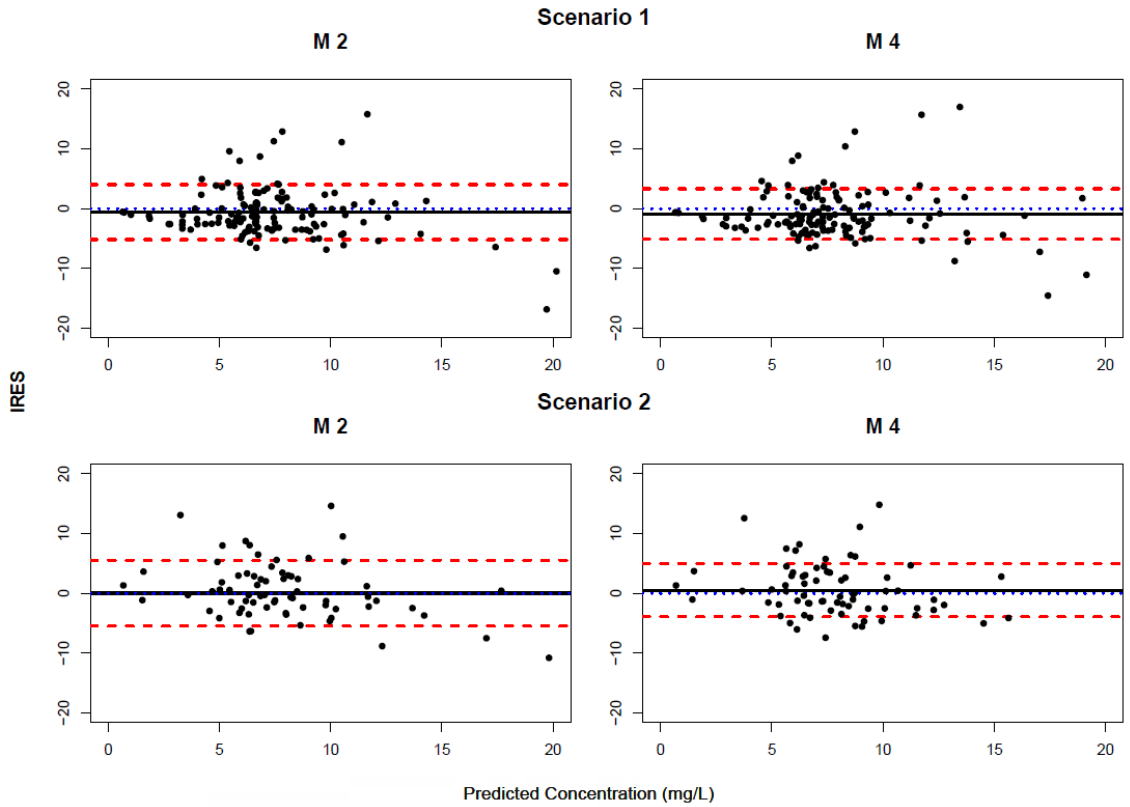


**Figure 3.** Individual residual (IRES) versus the individual predicted concentrations for M2 and M4 in Scenario 1 and Scenario 2. The mean IRES (black solid line) represents the bias of each model; red dashed line, 5th and 95th percentile for IRES; blue dotted line to highlight the line corresponding to 0. The M numbers represent the models described in Table 1.

**Table 4.** Values of bias and precision with its 95% confidence interval for each model in both scenarios.

| Model | Scenario 1 | | Scenario 2 | |
|---|---|---|---|---|
| | Bias | Precision | Bias | Precision |
| **M2** | -0.59 (-1.37 : 0.19) | 4.61 (3.55 : 5.67) | 0.012 (-1.27 : 1.29) | 5.43 (3.81 : 7.06) |
| **M4** | -0.91 (-1.62 : -0.19) | 4.30 (3.47 : 5.12) | 0.52 (-0.52 : 1.56) | 4.43 (3.49 : 5.37) |

*The M numbers represent the models described in Table 1.*

### 3.5. Clinical Impact

The results of the stochastic simulations of different dosage regimens using M2 and M4 are summarized in Figure 4. None of the dosage regimens could reach the desired target (TSC > 8 mg/mL) in at least 75% of the population that developed AAA. Similarly, 40 mg every other week was insufficient to reach the target for at least 75% of the population without AAA, although it is the standard dose recommended by protocol.

40 mg every week or 80 mg every week or every other week are enough to reach the target in at least 75% of the population. Interestingly, according to M2, the plasma concentration profiles of 40 mg every week or 80 mg every other week are very similar, which is not the case in M4.

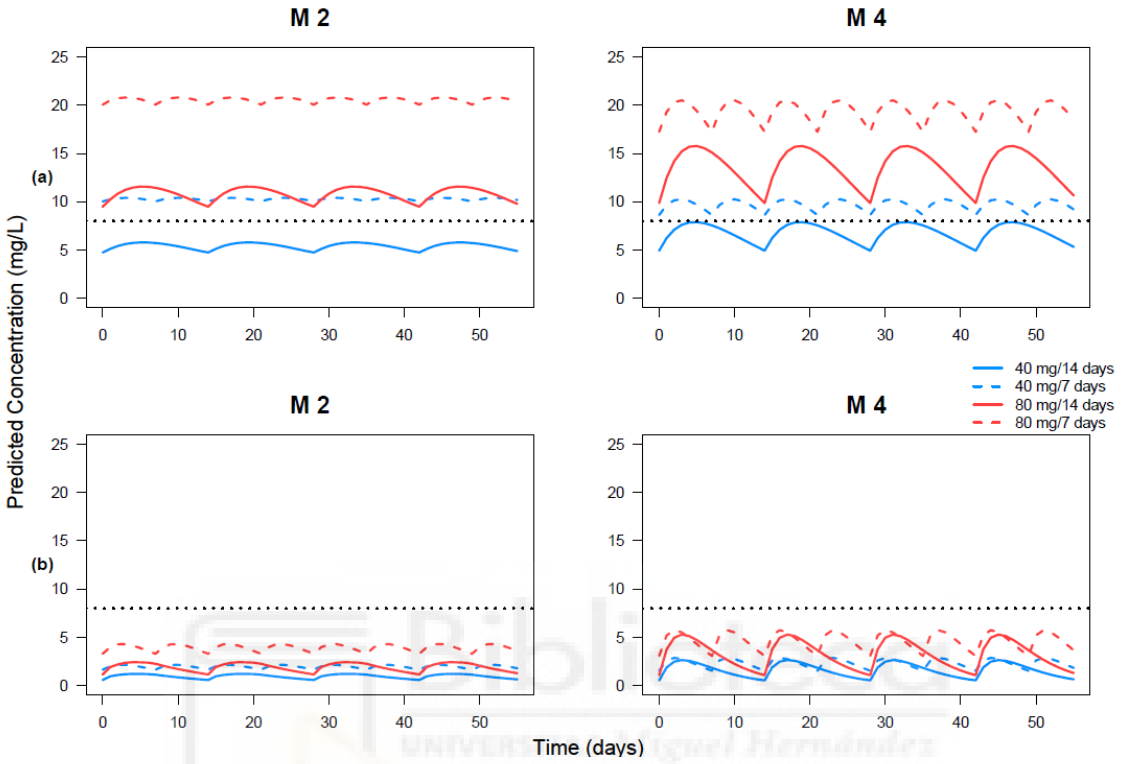


**Figure 4.** Stochastic simulation of the 25th percentile of serum concentrations over time for M2 and M4. Black dotted line was drawn to highlight the line corresponding to 8 mg/L. (a) Serum concentrations of patients without AAA. (b) Serum concentrations of patients with AAA. The M numbers represent the models described in Table 1.

## 7. Discussion

The MDPI applied in the clinical routine commonly makes use of PopPK models found in literature, given the lack of data available to develop in-house models in most of the hospitals. However, these models must be validated in the target population. An important aspect to validate is the predictive performance of the models, in similar conditions to the clinical routine. Many validations published in the literature do not really validate the predictive performance, but rather evaluate the model adequacy to the data. In the present work, the predictive performance was done with TSC that has not been used to calculate the EBEs, mimicking the real-world scenario. To our knowledge, this is the first validation and comparison of the PopPK models of adalimumab in the literature for their use in clinical routine. Six PopPK models for adalimumab were found in the literature for CD and/or UC patients, with similar structure (one-compartment model),

although the covariates included differ among them. The PopPK models included patients with both induction and maintenance treatment, and only one was performed with data from pediatric population.

The model adequacy showed thatM2 andM4 performed better than the rest. However, the mean individual CL/F obtained in all six PopPK models after the Bayesian post-hoc estimation (Figure 1) is somehow higher than the expected mean CL/F. One possible explanation for this systematic trend is that the mean albumin value of our population is slightly lower than the referenced in the models found in literature, which indicates a worse disease control. There are several studies that demonstrate the correlation between low levels of albumin and an increase in the clearance of other similar drugs like infliximab [32,33].

Consequently, four out of the six models were discarded due to the significant bias in the distribution of the NPDE as well as the EBEs of the PopPK parameters, therefore, the models M2 and M4 were the candidates to evaluate the predictive performance. The predictive performance of both models performed reasonably well, with a bias less than -0.91, which is less than 13% of the trough target (8 mg/L). The bootstrap analysis of the predictive performance showed no statistical difference between both models, so, with the available data, both models could be considered as equally good for the clinical routine purposes. AAA is considered the covariate with the highest impact in the pharmacokinetic parameters, according to the results of the stochastic simulations.

According to the drug label, the recommended maintenance dose after the induction phase is 40 mg every other week [5]. This scheme results in a mean steady-state TSC of approximately 7 mg/L in Crohn's disease patients, which agrees with the mean steady-state TSC observed in our population (7.3 mg/L). So far, the exposure target is highly dependent on the therapeutic objective (clinical, endoscopic, biochemical or histologic remission) and whether patients are diagnosed with CD or UC [34]. A recent study showed that patients with concentrations <8.3 mg/L had more risk to develop AAA by week 12 and experienced less clinical benefit from dose escalation due to a loss of response [22]. Another study indicates that 8–12 mg/L TSC of adalimumab are required to achieve mucosal healing in 80–90% of IBD patients [18]. According to the stochastic simulations performed with M2 and M4 and considering a target TSC over 8 mg/mL, the recommended maintenance regimen dosage that should be included in the protocols is 40 mg every week or 80 mg every other week, in order to reach the target in, at least, 75% of the population. These recommendations are in line with the MDPI interventions

in our population, where 75% of the patients needed a dose increase to reach the 8 mg/mL target.

The limitation of this study relies on its retrospective design, where patients were selected for MDPI based on the clinical decision of the physician, which implies a bias in the severity of the disease, reflected in the mean albumin values of our population. A prospective study in which patients were included for MDPI in a structured way regardless of the clinical situation of the patients should be carried out to avoid selection bias and validate these results in a wider population.

In summary, two of the PopPK models found in the literature were found to be better than the others in terms of model adequacy and predictive performance. However, the EBEs of the individual CL/F were found biased when compared with the population mean values in the models. That suggested the need to update the model with the available data. On the other hand, the stochastic simulations performed with these models suggested the benefits of increasing the maintenance dose in protocol to reach the 8 mg/L target.

**Author Contributions:** Conceptualization, R.N.-M., A.R.-L. and P.M.-S.; data curation, R.N.-M., P.M.-S., M.D.-G. and M.R.C.-B.; formal analysis, S.M.-M. and A.R.-L.; investigation, S.M.-M. and A.R.-L.; methodology, S.M.-M., A.R.-L., R.N.-M.; supervision, R.N.-M.; writing—original draft, S.M.-M. and A.R.-L.; writing—review and editing, R.N.-M., P.M.-S., M.D.-G. and M.R.C.-B. All authors have read and agreed to the published version of the manuscript.

**Funding**: This research was funded by a research grant offered by the Miguel Hernandez University. Reference number [PAR-00385/2021].

**Institutional Review Board Statement**: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Alicante University General Hospital.

**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of the study.

**Data Availability Statement:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Acknowledgments**: The authors thank Gastroenterology Department of the Alicante University General Hospital for the support in the treatment clinical approach.

**Conflicts of Interest:** The authors declare no conflict of interest.

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## ARTICLE III

Article

# Population Pharmacokinetic Model of Adalimumab Based on Prior Information Using Real World Data

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**Biomedicines 2023;11(10):2822**

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|---|---|
| Impact factor (2022) | 4,7 |
| Pharmacology & Pharmacy (Q1) | 68/278 |
| Biochemistry & Molecular Biology (Q2) | 54/136 |
| Medicine, Research & Experimental (Q2) | 92/285 |

## ABSTRACT

Adalimumab is a fully human monoclonal antibody used for the treatment of inflammatory bowel disease (IBD). Due to its considerably variable pharmacokinetics and the risk of developing antibodies against adalimumab, it is highly recommended to use a model-informed precision dosing approach. The aim of this study is to develop a population pharmacokinetic (PopPK) model of adalimumab for patients with IBD based on a literature model (reference model) to be used in the clinical setting. A retrospective observational study with 54 IBD patients was used to develop two different PopPK models based on the reference model. One of the developed models estimated the pharmacokinetic population parameters (estimated model), and the other model incorporated informative priors (prior model). The models were evaluated with bias and imprecision. Clinical impact was also assessed, evaluating the differences in dose interventions. The developed models included the albumin as a continuous covariate on apparent clearance. The prior model was superior to the estimated model in terms of bias, imprecision and clinical impact on the target population. In conclusion, the prior model adequately characterized adalimumab PK in the studied population and was better than the reference model in terms of predictive performance and clinical impact.

## Keywords

pharmacokinetics; drug monitoring; adalimumab; monoclonal antibodies; inflammatory bowel diseases; Crohn’s disease; ulcerative colitis

## 1. Introduction

Adalimumab is a fully human recombinant immunoglobulin G (IgG) monoclonal antibody that inhibits the binding of tumor necrosis factor (TNF) to its receptors, decreasing the process of inflammation. Adalimumab is increasingly used for the treatment of moderate-to-severe inflammatory bowel disease (IBD) patients both in induction and maintenance phases that had an inadequate response to corticosteroids, immunomodulators or other biologic therapies [1,2].

Numerous studies have demonstrated the association between higher serum drug levels of adalimumab and better clinical outcomes [3,4]. The exposure target depends on whether patients are diagnosed with Crohn's disease or ulcerative colitis and on the desired therapeutic objective, such as clinical, endoscopic, biochemical or histologic remission, although the most accepted target is the endoscopic remission [5]. In relation to this, some studies indicated that 8–12 mg/L trough serum concentrations (TSC) of adalimumab are required to achieve mucosal healing and endoscopic remission in 80–90% of IBD patients [5,6]. In fact, several studies have shown that after long periods of subtherapeutic drug levels, approximately 40% of patients with IBD can experience an irreversible disease worsening or develop antibodies against adalimumab (AAA) and, therefore, require dose escalation or even a switch to another drug [7–14]. A prospective study evidenced that having an improvement in clinical outcomes from dose escalation is difficult to achieve once they experience a loss of response [15]. Consequently, a therapeutic range of 8–12 mg/L has been considered as the therapeutic target in the clinical setting.

Model-Informed Precision Dosing (MIPD) is a Bayesian approach based on the use of population pharmacokinetic (PopPK) models to calculate the individual pharmacokinetic (PK) parameters for each patient. These individual PK parameters are used to achieve the optimal dose regimen to balance efficacy and toxicity and improve the treatment outcomes for each individual patient [16]. A multicenter retrospective study in patients treated with adalimumab indicated that the MIPD approach can prevent immunogenicity, lowering the risk of developing AAA and achieving better long-term outcomes in terms of IBD-related surgery or hospitalization. Moreover, it also proved to be more cost-effective compared to empirical and/or reactive dose optimization [17].

However, there are six PopPK models for adalimumab and IBD patients published in the literature. All models had a similar structure (one-compartment model), although the included covariates and the values of the PopPK parameters differ among them [1,18–22]. Even though a PopPK model implemented from the literature can suit a population

in the clinical setting, it is convenient to adapt this PopPK model to the studied population, to re-estimate the parameters and to evaluate the inclusion of potential new covariates to obtain more accurate results in the dose optimization. In a previous study, the predictive performance of these PopPK models was externally evaluated in the clinical setting [23]. This study, conducted by our research group, concluded that the PopPK model developed by Ternant et al. (reference model) was better than the others in terms of model adequacy and predictive performance [18]. However, the EBEs of the individual CL/F were found to be biased when compared with the mean population values in the models.

Therefore, the aim of this study is to optimize a PopPK model of adalimumab for IBD, previously selected from the literature, considering its improvement in predictive performance and clinical impact, with the subsequent application in the clinical setting for MIPD.

## 2. Materials and Methods

### 2.1. Study Design

A retrospective observational study was conducted at the Dr. Balmis General University Hospital of Alicante on patients with IBD in treatment with adalimumab who followed an MIPD program between 2014 and 2022.

### 2.2. Patients and Data Collection

This study included patients with IBD who underwent adalimumab treatment at the Dr. Balmis General University Hospital of Alicante, Spain. Participants with at least two adalimumab TSC were eligible for inclusion. Patients treated with monoclonal antibodies other than adalimumab, such as infliximab, vedolizumab or ustekinumab, and subjects who were diagnosed with autoimmune diseases other than IBD, such as rheumatoid arthritis, psoriasis or ankylosing spondylitis, were excluded from this study.

The covariates evaluated in this study included age, sex, height, body weight, body mass index, IBD type, serum albumin, serum C-reactive protein, fecal calprotectin, AAA status and AAA serum concentration, use of concomitant immunomodulators, previous anti-TNF treatment and whether adalimumab originator or biosimilar was used. For missing covariates, the mean value of this covariate for a given patient was imputed. If any patient had no available value of a covariate, the mean value of that covariate of the rest of the patients was imputed.

TSC and AAA were determined using an enzyme-linked immunosorbent assay LISA TRACKER Duo Drug + ADAb (TheraDiag®, Paris, France). The limits of quantification

for TSC and AAA were 0.1 mg/L (range 0.1–16 mg/L) and 10 ng/mL (range 10–2000 ng/mL), respectively. Patients were considered as positive for AAA if titers were above 10 ng/mL on at least one occasion.

### 2.3. Model Development and Evaluation

The reference model was the one selected among all available models in the literature, according to a predictive performance evaluation published elsewhere [18,23]. Briefly, the model, developed with Monolix 4.3.2, comprises a one-compartment model with first-order absorption and linear elimination and was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution (V/F) and absorption constant (ka) with a combined residual error model. The presence of AAA was included as a categorical covariate on CL/F.

Initially, the reference model was refitted by estimating the PK population parameters using all the available TSC of patients in Monolix software V.2023R1 [24]. The model structure was the same as the reference model, including the covariate model. Ka and the effect of AAA on CL/F were fixed to the published value.

The use of informative priors in the model was also considered by using the option of maximum a posteriori estimation in Monolix. The estimated values and the relative standard error (RSE) of the estimation of the parameters of the reference model were used to define the prior. To evaluate the appropriateness of the prior for each parameter, priors were set individually using an informative prior, whereas the rest of the parameters were kept as noninformative. The informative priors that reduce the RSE of the parameter estimations and result in better predictive performance would be retained in the model.

### 2.4. Covariate Analysis

Covariate analysis was based on physiological plausibility and visual graphical inspection of the relationships between Empirical Bayes Estimates (EBEs) of the PK parameters and the covariates. Statistical significance ($p < 0.01$) was further evaluated individually in the PK model using a stepwise forward addition and backward elimination covariate model-building methodology.

### 2.5. Model Selection

The improvement in predictive performance was the criterion for model selection. A decrease in the RSE of the parameter estimation was also considered for the inclusion of informative priors.

To evaluate predictive performance, the individual predictions of the last TSC were estimated for each patient, using EBEs of the individual PK parameters. These last TSCs, named the “last observed TSC”, were left out and not used to calculate the EBEs of the individual PK parameters. Bias and imprecision were then calculated using the last observed TSC by comparing them with their individual predictions.

The mean prediction error (MPE, Equation (1)) and root mean square prediction error (RMSPE, Equation (2)) were calculated for bias and imprecision, respectively.

$$MPE = \frac{\sum(\hat{Y}-Y)}{n} \quad (1)$$

$$RMSPE = \sqrt{\frac{\sum(\hat{Y}-Y)^2}{n}} \quad (2)$$

In both equations, Y-hat represents the individual-predicted adalimumab concentration, Y represents the observed adalimumab concentration, and n is the number of observations.

Additionally, a Predicted-Corrected Visual Predictive Check (pcVPC) for the reference and the final model was performed to evaluate predictive performance. Graphical evaluation, e.g. residual vs. predicted, observed vs. predicted and NPDE, was also evaluated.

A bootstrap of the data was performed to compare statistical significance of the differences between bias and imprecision of the different models.

### 2.6. Model Validation

A numerical Predictive Check (NPC) was performed as an internal validation of the model adequacy of each model. NPC quantitatively compares the cumulative observed adalimumab concentrations that correspond to the model-simulated percentiles with their expected concentrations that represent the 50th percentile of the observed concentrations, as well as the 95% confidence interval (CI) for the 50th percentile of the predicted concentrations.

The accuracy and robustness of parameter estimates were evaluated using a bootstrap with 500 replicates constructed by sampling individuals with replacements from the original dataset. Model parameters were estimated for each bootstrap replicate and were used to estimate the mean and 95% CI from the individual replicates.

These databases generated with the bootstrap were also used to validate predictive performance by calculating the mean and 95% CI of bias and imprecision of each model for each of the 500 replicates.

### 2.7. Clinical Impact

The evaluation of the clinical impact of PopPK models was performed by calculating the true positives and false positives of the predictions of the last TSC for each model compared to the last observed TSC. It is worthwhile to mention again that the last TSCs were left out to calculate the EBEs of the PK parameters for each model. Three different scenarios were considered to calculate true and false positives, assuming three concentration ranges: below the target; within the target; and above the target. The last observed TSC was considered the standard reference for each concentration range. True and false positives were calculated by comparing the coincidences and discrepancies with the predicted TSC with each PopPK model, corresponding to such last observed TSC. The target interval of the TSC that was considered in this study was within 8–12 mg/L for clinical response or remission [6,15].

The 95% CI of true and false positives in each scenario for each model was calculated with the bootstrap.

### 2.8. Software

The software used for model development was Monolix 2023R1® [24]. The statistical analysis, data visualization and validation were performed using R software v4.2.2 [25], implemented in RStudio 2022.07.2 + 576 [26].

## 3. Results

### 3.1. Patient Characteristics

The resulting dataset comprised 54 IBD patients in treatment with adalimumab with at least two TSCs. Approximately 85% of the patients were diagnosed with Crohn's disease and 15% with ulcerative colitis. The summary of the characteristics of the studied population compared to the population of the reference model is listed in Table 1.

As an induction phase, 43 patients were treated subcutaneously with 160/80 mg and 2 patients with 80/40 mg at weeks 0/2. The information regarding the induction phase of the other nine patients was not available in their medical histories. Following this phase, all patients were treated with 40 mg of adalimumab every other week. A total of 148 TSC, 19 of them in the induction phase, were available for analysis. 68.2% of TSC were below 8 mg/L, 16.2% between 8 and 12 mg/L and 15.6% over 12 mg/L. AAA were detected in nine patients (17%). 22 patients were on a concomitant immunomodulator (6-

mercaptopurine, aminosalicylate, azathioprine, corticosteroids, methotrexate or combined). 39 patients were treated with adalimumab originator (HUMIRA®), and 15 patients were treated with biosimilars (10 patients with HYRIMOZ® and 5 patients with IDACIO®).

**Table 1.** Summary of the characteristics of the included patients in the reference and the final model.

| Characteristics | Population of the reference model | Population of the final model |
|---|---|---|
| Patients | 65 | 54 |
| Age (yr) † | 37 (17–61) | 43.5 (11–89) |
| Sex, male, n (%) | 16 (25%) | 30 (55.6%) |
| Weight (kg) † | 68 (43–109) | 66.5 (34.8–94.0) |
| Body mass index (kg/m$^2$) † | NA | 22.84 (14.1–32.03) |
| Albumin (g/dL) † | NA | 3.86 (1.97–4.96) |
| Prealbumin (mg/dL) † | NA | 24.2 (9.0–37.0) |
| CRP (mg/L) † | NA | 0.770 (0.0575–6.680) |
| FCP (mg/kg) † | NA | 513 (25–3600) |
| IBD type, CD, n (%) | 65 (100%) | 46 (85.2%) |
| Adalimumab originator (Humira®), n (%) | NA | 38 (70.4%) |
| Prior treatment with infliximab | NA | 35 (64.8%) |
| Concomitant immunomodulator, n (%) | NA | 22 (40.7%) |
| 6-Mercaptopurine | NA | 1 (4.6%) |
| Aminosalicylate | NA | 3 (13.6%) |
| Azathioprine | NA | 6 (27.3%) |
| Corticosteroids | NA | 5 (22.7%) |
| Methotrexate | NA | 2 (9.1%) |
| Combined | NA | 5 (22.7%) |
| Adalimumab serum samples | 341 | 148 |
| Adalimumab serum concentrations (mg/L) † | NA | 4.90 (0.10–27.4) |
| AAA positive, n (%) | 9 (13.8%) | 9 (16.7%) |
| AAA serum concentrations (mg/L) †,‡ | NA | 115 (15–459) |

*NA = not available; CRP: C-reactive protein; FCP: fecal calprotectin; IBD: inflammatory bowel disease; CD: Crohn's disease; AAA: antibodies against adalimumab. † Median and range of population used to develop the reference model and the final model. ‡ Median and range of patients with presence of antibodies against adalimumab.*

### 3.2. Model Development, Covariate Analysis and Evaluation

Due to the lack of serum concentrations in the absorption phase in the dataset and the small number of AAA-positive patients, ka and the covariate of AAA on CL/F were fixed to the values of the reference model, 0.00625 1/h and 4.5, respectively.

In the first step, all the parameters were estimated, keeping the model structure of the reference model.

Figure 1 shows the relationship between EBEs of CL/F and albumin with a statistically significant slope ($p < 0.001$). In the forward inclusion step of the covariate modeling, only albumin was found to be a significant covariate influencing CL/F, with an improvement in the Objective Function Value (OFV) of 12 ($p < 0.001$).

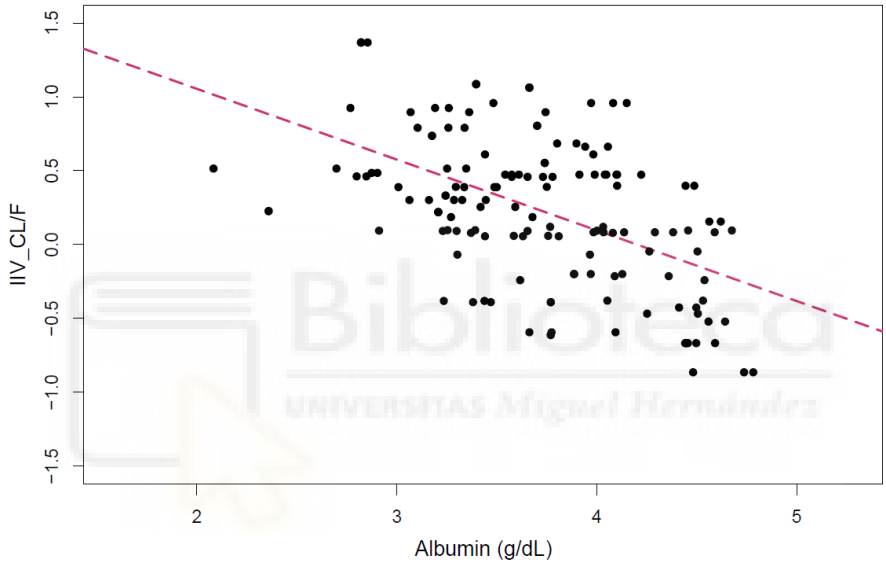


**Figure 1.** Interindividual variability of apparent clearance versus albumin.

$$\mathrm{CL/F} = \mathrm{CL_{pop}} \cdot (1 + \mathrm{AAA} \cdot \mathrm{cov_{AAA-CL/F}}) \cdot \left(\frac{\mathrm{ALB}}{\mathrm{mALB}}\right)^{\mathrm{cov_{ALB-CL/F}}} \qquad (3)$$

CL/F is defined according to Equation (3), where AAA is a categorical covariate representing the absence and presence of AAA, and albumin is a continuous covariate weighted to the mean value (3.77 g/dL) in the studied population (mALB). In addition, the inclusion of albumin as a covariate on CL/F resulted in better performance in terms of bias and imprecision. Model structure and code have been added as a Supplementary File (Figure S1).

In the second step, the use of priors in different parameters was evaluated. The inclusion of informative priors in the IIV of CL/F and the IIV of V/F resulted in a substantial reduction in RSE, not only on these parameters but also in the parameters estimated without priors. The resulting RSE using priors decreased from 30.6% to 3.4% for the IIV of CL/F and from 114.5% to 1.4% for the IIV of V/F, compared to the model where all parameters

were estimated. For the remaining parameters, the inclusion of priors did not improve the fit, neither in terms of RSE nor predictive performance. Additionally, residual unexplained variability was modeled using a proportional error model due to the high RSE of the additive error (83.8%). This model would be considered the final model.

The final model shows a considerable reduction in bias compared to the reference model and a similar dispersion of Individual Residuals (IRES), as is shown in Figure 2. Table 2 shows bias and imprecision for the reference and the final model and the differences between them. The final model behaves better in terms of bias and imprecision. The 95% CI of the differences, calculated with the bootstrap, shows statistical differences in bias but not in imprecision.

The pcVPC for the reference and the final model, represented in Figure 3, shows that the final model performs better than the reference model. The same results are observed in Observed vs. Predicted (Figure S2) and NPDE (Figure S3) plots, available in the Supplementary File.

The values of each parameter of the final model compared to the reference model are listed in Table 3.

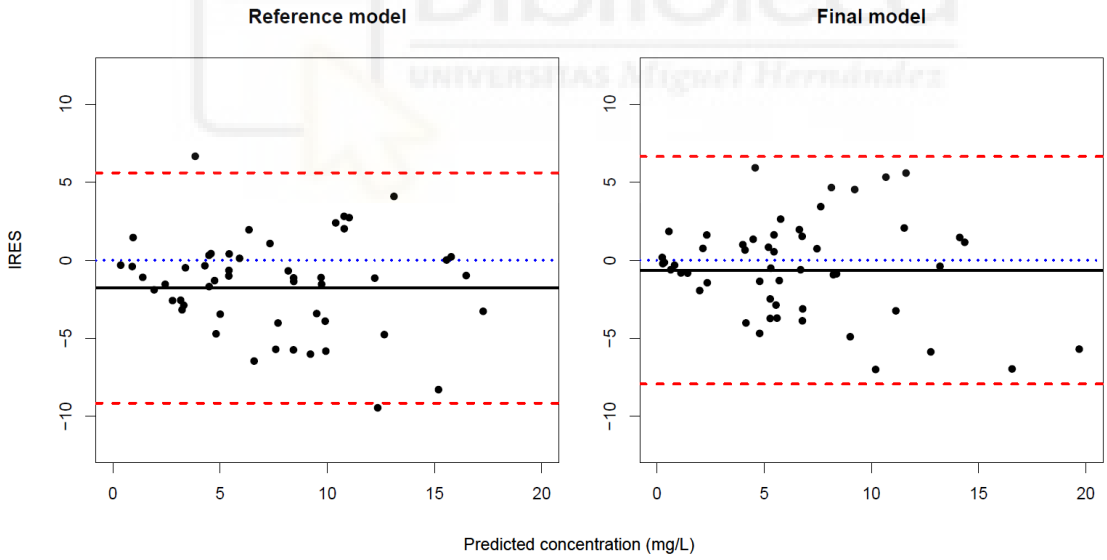


**Figure 2.** Individual residual (IRES) versus the individual predicted of the last observed trough serum concentrations (TSC) for the reference and the final model. The mean IRES (black solid line) represents the bias of each model; red dashed line represents the 5th and 95th percentile for IRES; blue dotted line the line corresponding to 0.

**Table 2.** Bias and imprecision with the 95% confidence interval for the reference and the final model.

| | Models | | Bootstrap Results (n=500) | |
|---|---|---|---|---|
| **Model** | **Bias (95% CI)** | **Imprecision (95% CI)** | **Bias (95% CI)** | **Imprecision (95% CI)** |
| **Reference Model** | −1.79 (−2.82 : −0.793) | 4.14 (3.11 : 5.09) | −1.78 (−2.76 : −0.804) | 4.10 (3.12 : 5.09) |
| **Final Model** | −0.849 (−1.86 : 0.160) | 3.99 (2.43 : 5.33) | −0.854 (−1.87 : 0.160) | 3.90 (2.52 : 5.28) |
| **Difference** | −0.939 | 0.150 | 0.927 (0.353 : 1.46) | 0.200 (−0.670 : 1.08) |

*CI: Confidence Interval.*

### 3.3. Model Validation

The NPC of the reference and the final model are represented in Figure 3. The final model shows a better performance compared to the reference model.

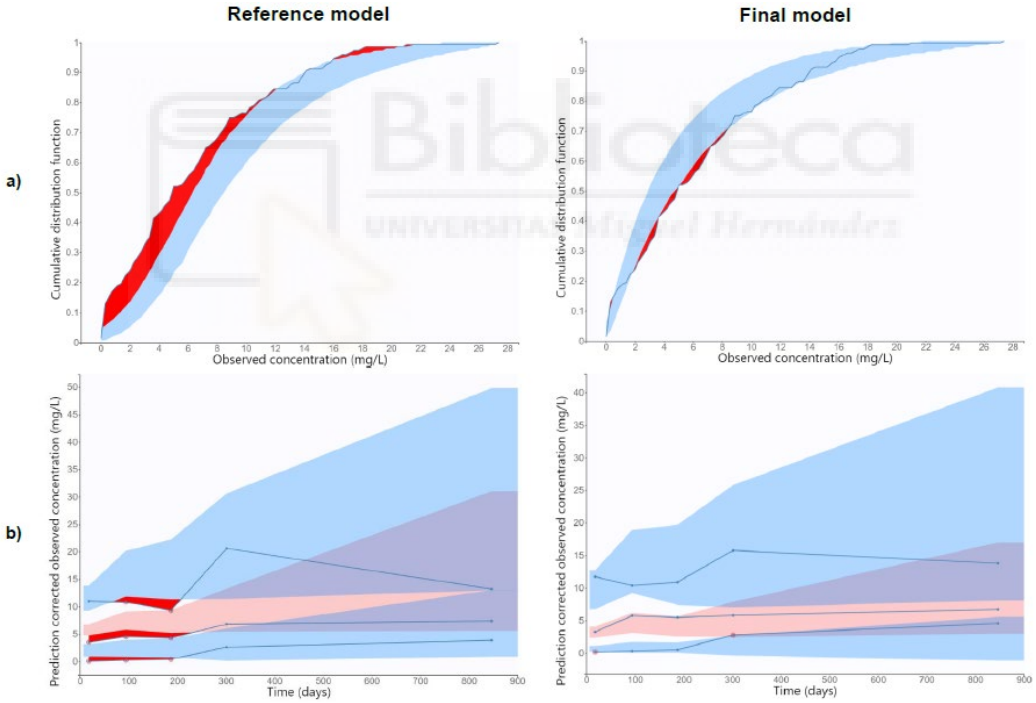


**Figure 3.** (**a**) NPC of the reference and the final model. Blue solid line depicts the empirical distribution. Blue shaded area represents the 95% confidence interval for the median of the predictions, and the red shaded areas represent the outliers. (**b**) pcVPC of the reference and the final model. Blue solid lines represent the 5th, 50th and 95th percentiles of the observed concentrations; Blue shaded areas represent the 95% confidence interval of the 5th and 95th percentiles of the predictions; pink shaded area represents the 95% confidence interval for the 50th percentile of the predictions, and red shaded areas represent the outliers.

The RSE of the estimated PK parameters in the final model was below 50% in the bootstrap analysis. No significant differences were observed between the mean values of the PK parameters in the bootstrap analysis of the final model. Moreover, estimated PK parameters were within the 95% CI of the parameters obtained in the bootstrap.

**Table 3.** Population pharmacokinetic parameters of the reference model and the final model.

| | **Reference model** | **Final Model** | | **Bootstrap Results (n=500)** | |
|---|---|---|---|---|---|
| | **Estimate (%RSE)** | **Estimate (%RSE)** | **95% CI** | **Mean Value (%RSE)** | **95% CI** |
| CL/F (L/h) | 0.0175 (9%) | 0.0312 (10.9%) | 0.0246 : 0.0378 | 0.0314 (12.4%) | 0.0234 : 0.0391 |
| ALB_CL/F | - | −2.33 (2.8%) | −2.46 : −2.21 | −2.36 (43.8%) | −4.39 : −0.335 |
| V/F (L) | 13.5 (10%) | 7.76 (24.1%) | 4.09 : 11.42 | 7.70 (19.9%) | 4.69 : 10.7 |
| IIV_CL/F | 0.65 (10%) | 0.667 (15.5%) | 0.464 : 0.869 | 0.666 (3.4%) | 0.623 : 0.710 |
| IIV_V/F | 0.48 (19%) | 0.477 (33.9%) | 0.160 : 0.794 | 0.474 (1.4%) | 0.460 : 0.487 |
| Proportional error | 0.15 (16%) | 0.547 (8.4%) | 0.458 : 0.637 | 0.543 (8.7%) | 0.451 : 0.636 |
| Additive error (mg/L) | 1.8 (8%) | - | - | - | - |

*%RSE, relative standard error; CI: confidence interval; CL/F: apparent clearance; V/F: apparent volume; ALB: albumin; IIV: interindividual variability.*

### 3.4. Clinical Impact

Figure 4 shows true and false positives of the individual predictions of the last observed TSC of the final model for each scenario. Among all the last observed TSCs in the dataset, 36 TSCs fell below target, 8 TSCs fell within the target, and 10 TSCs fell above target. Table 4 shows true and false positives of the predictions of the last TSC and the differences between the reference and the final model for each scenario. In all cases, the final model performs better than the reference model in terms of true positives and false positives.

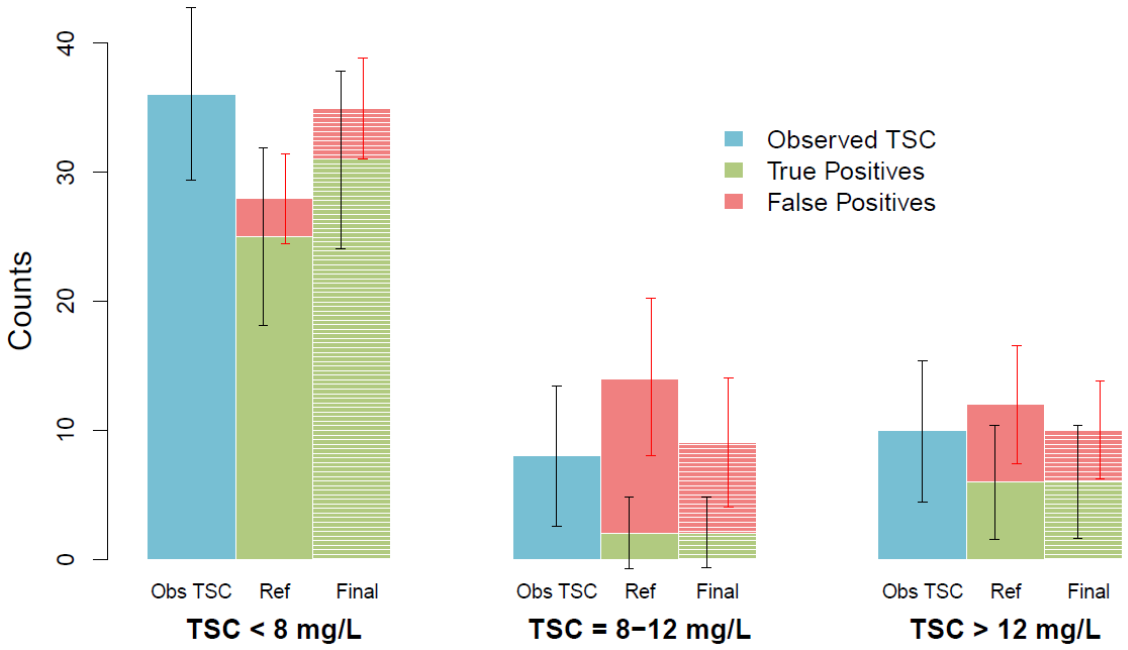


**Figure 4.** Clinical impact of the reference (Ref) and the final model (Final) predictions compared to the last observed trough serum concentrations (Obs TSC) in the different scenarios. Black arrows represent the 95% CI of the last observed TSC and the true positives of the last TSC predictions, and red arrows represent the 95% CI of the false positives of the last TSC predictions.

**Table 4.** True and false positives of the predictions of the last TSC and the differences between the reference and the final model for each scenario.

| | TSC < 8 mg/L | | TSC = 8-12 mg/L | | TSC > 12 mg/L | |
|---|---|---|---|---|---|---|
| | **True Positives** | **False positives** | **True Positives** | **False positives** | **True Positives** | **False positives** |
| **Reference model** | 25.0 (18.1 : 31.9) | 2.95 (−0.50 : 6.41) | 2.04 (−0.71 : 4.80) | 12.1 (5.95 : 18.1) | 5.93 (1.53 : 10.3) | 6.04 (1.47 : 10.6) |
| **Final model** | 30.9 (24.0 : 37.8) | 3.99 (0.0720 : 7.90) | 2.07 (−0.676 : 4.81) | 7.00 (1.99 : 12.0) | 6.01 (1.62 : 10.4) | 3.99 (0.189 : 7.80) |
| **Difference** | 5.90 (1.50 : 10.4) | 1.04 (−0.836 : 2.90) | 0.0300 (−2.80 : 2.85) | −5.05 (−10.0 : −0.102) | −0.0800 (−2.71 : 2.87) | −2.04 (−4.74 : 0.660) |

*TSC: trough serum concentrations.*

## 4. Discussion

The MIPD approach can be a useful tool to optimize the dose of drugs with high pharmacokinetic variability. To apply this methodology in the clinical routine, it is common to use PopPK models found in the literature due to the difficulties of building in-house PopPK models with the available data in hospitals.

The model reference was based on 341 adalimumab serum concentrations derived from 65 patients during a follow-up of 500 days, although only Crohn's disease patients were included in this study. Regarding the analytical assay, ELISA and Double-antigen ELISA were used to measure adalimumab TSCs and AAA, respectively. However, it is not specified which limit of titers was used to consider the patients as AAA positives. The value of this limit is crucial in the estimation of the proportion of positives and, therefore, its quantitative effect on CL/F. Moreover, biochemical covariates such as albumin, C-reactive protein or fecal calprotectin were not available.

The inclusion of AAA and albumin in the final model as covariates of CL/F was found to statistically improve the OFV and also reduce the interindividual variability in CL/F. The association between the presence of AAA and the increase in adalimumab CL/F, leading to lower adalimumab concentrations, has been reported in numerous studies [8–13]. In our study, the presence of AAA was found to be a determinant covariate. However, the estimation of the effect of AAA on CL/F was not possible due to the small number of patients' positives for AAA and, therefore, it was fixed to the reference model value.

The results of this study suggest that patients with lower albumin have a higher CL/F. In addition, CL/F increases 12-fold as albumin rises from the lowest value (1.97 g/dl) to the highest value (4.96 g/dl). Therefore, patients with lower albumin require higher doses to reach the desired target; otherwise, plasma concentration would fall into the infratherapeutic range. Several studies demonstrated the correlation of higher albumin levels with higher response rates to infliximab and adalimumab [27–34]. In fact, albumin was a significant covariate on CL in a considerable number of previously published PK models of infliximab for IBD [35]. In contrast, other studies that developed PopPK models of adalimumab in Crohn's disease [19,21] or IBD patients [22] observed that higher albumin levels were associated with lower adalimumab CL/F and higher serum levels, considering albumin as an influential inflammatory marker of adalimumab clearance, although, finally, they did not include it as a covariate in the PopPK model. However, albumin is also a well-known surrogate marker of disease that could exacerbate with an increase in CL. Therefore, further studies are necessary to establish whether albumin has a direct impact on CL or the change in CL and, consequently, the change in plasma concentration of Adalimumab has an impact on the albumin.

Several studies have shown that fecal calprotectin and C-reactive protein are reliable markers of endoscopic activity and therapeutic response in IBD patients [36–38]. In fact, C-reactive protein and fecal calprotectin showed a positive influence on adalimumab CL/F in a PopPK model of adalimumab developed for IBD that included the latter as a

continuous covariate [22]. However, the association of TSC and C-reactive protein or fecal calprotectin was not found in our data.

Body weight was included as a covariate on CL/F in four PopPK models of adalimumab in Crohn's disease [1,19,21] or IBD patients [22] and on V/F in one of them [19]. However, body weight, lean body weight and body mass index did not show a significant relationship with any PK parameter of adalimumab in our population.

A priori information could be used to stabilize the estimation of the model parameters when the data available are sparse. Several studies showed that the use of priors allowed a better fit to the new data than fixing the parameters [39–42]. Moreover, the model built with priors in our study was more stable, provided a better fit of the data and reduced IIV. In this line, other authors also obtained similar results [43].

In order to mimic the real-world conditions, predictive performance was calculated with TSCs that were left out for the calculation of EBEs of the PK parameters. The results of predictive performance in terms of bias and imprecision were −1.79 and 4.14 for the reference model and −0.849 and 3.99 for the final model, respectively. The bootstrap analysis of predictive performance showed statistically significant differences in terms of bias.

Regarding the clinical impact, the final model obtained 15% more true positives (39 vs. 33) than the reference model. Similarly, the final model obtained 30% less false positives than the final model. Therefore, the final model better predicts the need for dose modification.

One of the main limitations of this study is its retrospective design, where patients were selected for MIPD based on the clinical decision of the physician, which implies a potential bias related to the disease severity. This potential bias could lead to an underestimation of the mean values and variance of albumin, C-reactive protein and fecal calprotectin in the IBD population. Another limitation inherent to the clinical setting is that only TSCs were available since data were obtained from the clinical setting; therefore, there is a lack of serum concentrations in the absorption phase and, consequently, ka could not be estimated, so it was fixed to the value of the reference model.

In conclusion, the developed PopPK model, using informative priors in IIV of CL/F and IIV of V/F based on the reference model, adequately characterized adalimumab PK in the studied population and performed better than the reference model in terms of predictive performance. The main structural difference between both models was the inclusion of albumin as a meaningful covariate on CL/F. To our knowledge, this is the

first PopPK model of adalimumab in IBD that identified albumin as a covariate on CL/F. Additionally, the final model significantly improves the clinical impact on the target population and could allow a more accurate dose optimization and an improvement of adalimumab treatment efficacy.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines11102822/s1.

**Author Contributions:** Conceptualization, R.N.-M., A.R.-L. and P.M.-S.; data curation, A.R.-L. and P.M.-S.; formal analysis, S.M.-M. and R.N.-M.; investigation, S.M.-M. and R.N.-M.; methodology, S.M.-M., R.N.-M. and A.R.-L.; supervision, A.R.-L.; writing—original draft, S.M.-M. and R.N.-M.; writing—review and editing, A.R.-L. and P.M.-S. All authors have read and agreed to the published version of the manuscript.

**Funding:** S.M.-M. received a predoctoral fellowship from Miguel Hernandez University ("Ayudas a la contratación de personal investigador en formación 2021").

**Institutional Review Board Statement:** This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Alicante University General Hospital.

**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of this study.

**Data Availability Statement:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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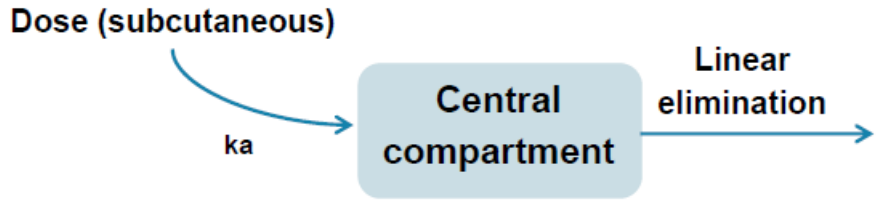
*Supplementary material*

# Population pharmacokinetic model of adalimumab based on prior information using real world data

**Figure S1.** Structural model and Monolix code of the final model.

**Figure S2.** Goodness of fit plot for the reference and the final model.

**Figure S3.** NPDE of the reference and the final model.




**DESCRIPTION:**
The administration is extravascular with a first order absorption (rate constant ka). The PK model has one compartment (volume V) and a linear elimination (clearance Cl).

**[LONGITUDINAL]**
input = {ka, V, Cl, beta1, AAA, beta2, ALB}
AAA={use=regressor}
ALB={use=regressor}

**EQUATION:**
```
if AAA==0
                ClwithAAA=Cl
elseif AAA==1
                ClwithAAA= Cl * (1+ beta1)
end
                ClwithALB= (ALB/3.77)^beta2
```

**PK:**
```
; PK model definition
Cc = pkmodel(ka, V, Cl=ClwithAAA*ClwithALB)
```

**OUTPUT:**
output = Cc



**Figure S1.** Structural model and Monolix code of the final model.

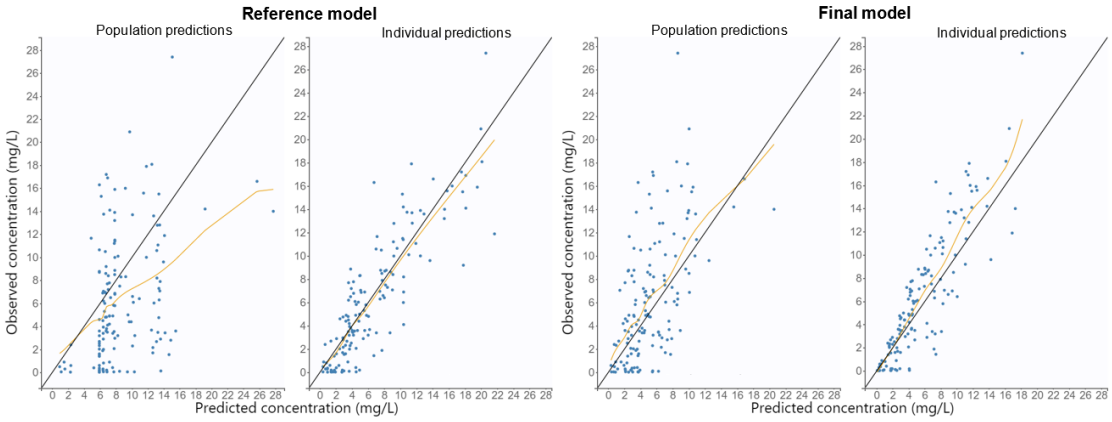



**Figure S2.** Goodness of fit plot for the reference and the final model.

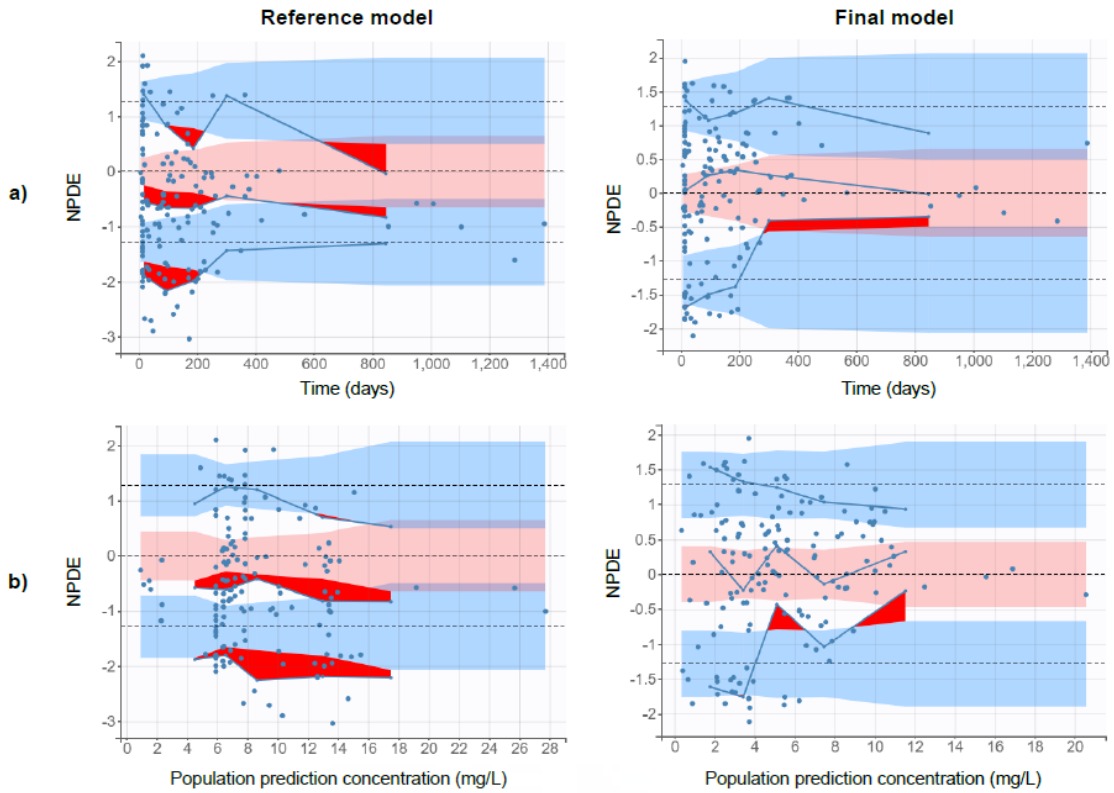



**Figure S3.** NPDE of the reference and the final model. (a) Plot of NPDE versus time. (b) Plot of NPDE versus population predicted concentration. Blue solid lines are the lines corresponding to 0, 5% and 95% critical values; black dashed lines, prediction intervals; blue-shaded area, 90% confi-dence interval (CI) of the 5% and 95% critical values; pink-shaded area, 90% CI of 0; red-shaded area, outliers of the bounds of the CI.