Universidad de Cantabria **2025**

Programa de Doctorado en Medicina y Ciencias de la Salud

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Tesis doctoral

EFICACIA Y SEGURIDAD DE LOS TRATAMIENTOS BIOLÓGICOS EN ENFERMEDAD DE CROHN REFRACTARIA AL TRATAMIENTO CON ANTAGONISTAS DEL FACTOR DE NECROSIS TUMORAL

PhD Thesis

EFFECTIVENESS AND SAFETY OF BIOLOGICAL THERAPY IN CROHN'S DISEASE AFTER FAILURE OF TUMOR NECROSIS FACTOR ANTAGONISTS

UC | Escuela de **Doctorado**

Javier Crespo García, Profesor Titular del Departamento de Medicina y Psiquiatría de la Universidad de Cantabria.

CERTIFICO: Que Dña. María José García García ha realizado bajo mi dirección el trabajo que lleva por título: **"Eficacia y seguridad de tratamientos biológicos en enfermedad de Crohn refractaria al tratamiento con antagonistas del factor de necrosis tumoral".**

Considero que dicho trabajo se encuentra terminado y reúne los requisitos necesarios para su presentación como memoria de Doctorado y así poder optar al grado de Doctor por la Universidad de Cantabria.

Fdo. Javier Crespo García

Montserrat Rivero Tirado, doctora en Medicina y Cirugía por la Universidad de Cantabria.

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Fdo. Montserrat Rivero Tirado

AGRADECIMIENTOS

Quisiera agradecer a mi director de tesis, Javier, por la confianza que ha depositado en mi para poder dedicarme a la enfermedad inflamatoria intestinal. Gracias por servir como ejemplo con tu enorme capacidad de trabajo, innovación y búsqueda de la excelencia.

Gracias Montse, por acompañarme en este camino, por tu apoyo personal y profesional y por acogerme con entusiasmo en la unidad de enfermedad inflamatoria intestinal. Por confiar en mí desde el principio y haberme hecho conseguir logros que me parecían inimaginables cuando comencé este camino.

Quiero agradecer a mis compañeras de la unidad de enfermedad inflamatoria intestinal, Bea, Coral y Marisol, por animarme en momentos de flaqueza y apoyarme en mi proyecto.

Mi gratitud a todo el Servicio de Aparato Digestivo del Hospital Universitario Marqués de Valdecilla, por todo su apoyo durante la realización de esta tesis y compartir los momentos difíciles, especialmente a Marta, por ser mi guía durante el proceso de depósito.

Quiero agradecer especialmente este trabajo a Javier y María que me han enseñado y me siguen enseñando de forma totalmente altruista a realizar proyectos de investigación. Su entusiasmo y pasión por la ciencia han sido una gran fuente de inspiración. Gracias por permitirme ser parte de su equipo.

No quisiera olvidarme de dar las gracias a mi familia, especialmente a mis padres, por animarme siempre a progresar, por todo vuestro esfuerzo que me ha permitido poder conseguir todas mis metas y por acompañarme siempre en cada paso, desde el más pequeño hasta el más grande

Por último, gracias a mi marido Mario, por su apoyo, cariño y paciencia, y por apoyarme en todas mis decisiones.

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ABREVIATURAS

ADA: Adalimumab

CDAI: Índice de actividad clínica de la enfermedad de Crohn

CU: Colitis ulcerosa

EII: Enfermedad inflamatoria intestinal

ev: Endovenoso

EC: Enfermedad de Crohn

HLA: Antígeno leucocitario humano

IC: Intervalo de confianza

IFN: Interferón

IFX: Infliximab

Ig: Inmunoglobulina

IL: Interleucina

JAK: Janus quinasas

MAdCAM-1: Moléculas de adhesión celular de la adresina mucosa 1

mg/kg: Miligramo por kilogramo

NF-κB: Factor nuclear kappa B

NK: Natural killer

NOD: Receptores intracelulares por dominio de oligomerización por unión de nucleótidos

OR: Odds ratio

sc: Subcutáneo

SES-CD: Índice endoscópico simple para enfermedad de Crohn

S1PR: Moduladores de los receptores de esfingosina 1 fosfato

TGFβ: Factor de crecimiento transformante beta

TLR: Toll-like receptors

TNFα: Factor de necrosis tumoral alfa

UST: Ustekinumab

VEDO: Vedolizumab

vs.: Versus

Abreviaturas de los artículos:

AEG: Asociación Española de Gastroenterología

BMI: Body mass index

CD: Crohn's disease

CI: Confidence interval

CRP: C-reactive protein

ECCO: European Crohn's and Colitis Organisation

EMA: European Medicines Agency

GDPR: European General Data Protection Regulation

GETECCU: The Spanish Working Group on Crohn's Disease and Ulcerative Colitis

HBI: Harvey-Bradshaw index

IBD: Inflammatory bowel disease

IL: Interleukin

IPTW: Inverse probability weighting

IQR: Interquartile range

OR: Odds ratio

REDCap: Research Electronic Data Capture

SD: Standard deviation

TNF: Tumor necrosis factor

UC: Ulcerative colitis

1. INTRODUCCIÓN

1.1. Antecedentes históricos de la enfermedad de Crohn

Desde el año 1612 se habían publicado numerosos casos clínicos de pacientes jóvenes con dolor abdominal crónico, persistente, acompañando de fiebre que producía el fallecimiento de esos pacientes. Las autopsias revelaban inflamación intestinal y ulceraciones en la mucosa intestinal y perforación.[1–4] En 1830, Abraham Colles describió la afectación de la enfermedad perianal y fistulizante consistente en fístulas rectovaginales y rectovesicales en niños de Dublín. [5] Sin embargo, no se diferenció como una entidad propia hasta este 1859, donde Samuel Wilks describió el término colitis ulcerosa para describir una paciente con diarrea crónica, fiebre y afectación transmural en la autopsia.[6] Posteriormente, esta enfermedad se identificó como enfermedad de Crohn.[7]

La enfermedad de Crohn se describió en 1932 por tres médicos, Burrill Bernard Crohn, Leon Ginzberg y Gordon D. Oppenheimer.[8] El cuadro clínico se componía de dolor abdominal, diarrea fiebre y pérdida de peso. Hasta ese momento, cualquier cuadro inflamatorio a nivel intestinal era catalogado como tuberculosis intestinal. Con la publicación de su serie 14 pacientes operados por el Dr. A. A. Berg, denominaron por primera vez a esta enfermedad como ileítis regional, conformando una entidad diferente de la tuberculosis intestinal, pero con hallazgos de granulomas benignos. Cuatro años más tarde, en 1936, el mismo grupo publicó una serie de casos consistente en 9 pacientes que por primera vez tenían afectación de íleon y colon derecho, definiéndose con los años el espectro clínico que presenta esta enfermedad.[9]

Entre las diferentes etiologías postuladas en ese momento y hasta su mejor caracterización, se encontraban bacterias (incluyendo la tuberculosis debido a la formación de granulomas que se observaban en las piezas quirúrgicas y necrológicas), virus, reacciones alérgicas (debido a la cantidad de eosinófilos), obstrucción linfática e incluso la contaminación fecal. Actualmente, aunque la etiología está algo más definida, sigue sin saberse con precisión cuál es el detonante o los mecanismos etiopatogénicos que desencadenan el desarrollo de esta enfermedad de forma fehaciente.[10–12]

1.2 Etiopatogenia y vías inmunológicas de la enfermedad de Crohn

La enfermedad de Crohn tiene una etiología multifactorial. Se han involucrado diferentes factores entre los que se encuentra una posible predisposición genética a la que se asocian factores ambientales multifactoriales que actúan como desencadenantes de la enfermedad. Esta situación provoca una alteración en la homeostasis del sistema inmune originando una respuesta inmune del individuo a nivel intestinal con cambios en la permeabilidad de la barrera mucosa, traslocación de antígenos o/y bacterias intestinales, y activación de múltiples vías inflamatorias. A continuación, describiremos brevemente algunos de los factores involucrados en la etiopatogenia de la enfermedad:

- Factores genéticos: En familias con múltiples miembros afectos se observa una elevada concordancia en el fenotipo de la enfermedad.[13] Por otra parte, se ha observado que los gemelos monocigóticos presentan un diagnóstico de enfermedad de Crohn en un 35%, mayor que en gemelos dicigóticos (4%).[14] Además, estudios de GWAS han demostrado más de 200 variantes genéticas que podrían estar asociados a una mayor predisposición para enfermedad de Crohn [15]

- Diferencias en la dieta: La dieta tiene un papel determinante en la enfermedad y es un aspecto muy preguntado por los pacientes con esta enfermedad, pudiendo estar involucrada en la disbiosis intestinal. En población pediátrica, la nutrición enteral ha demostrado ser un tratamiento eficaz en la inducción de la remisión clínica.[16] Además, recientemente se ha postulado que una dieta de exclusión en estos pacientes podría mejorar los brotes de esta enfermedad, aunque los resultados de los estudios no permiten establecer claramente un tipo de dieta.[17]

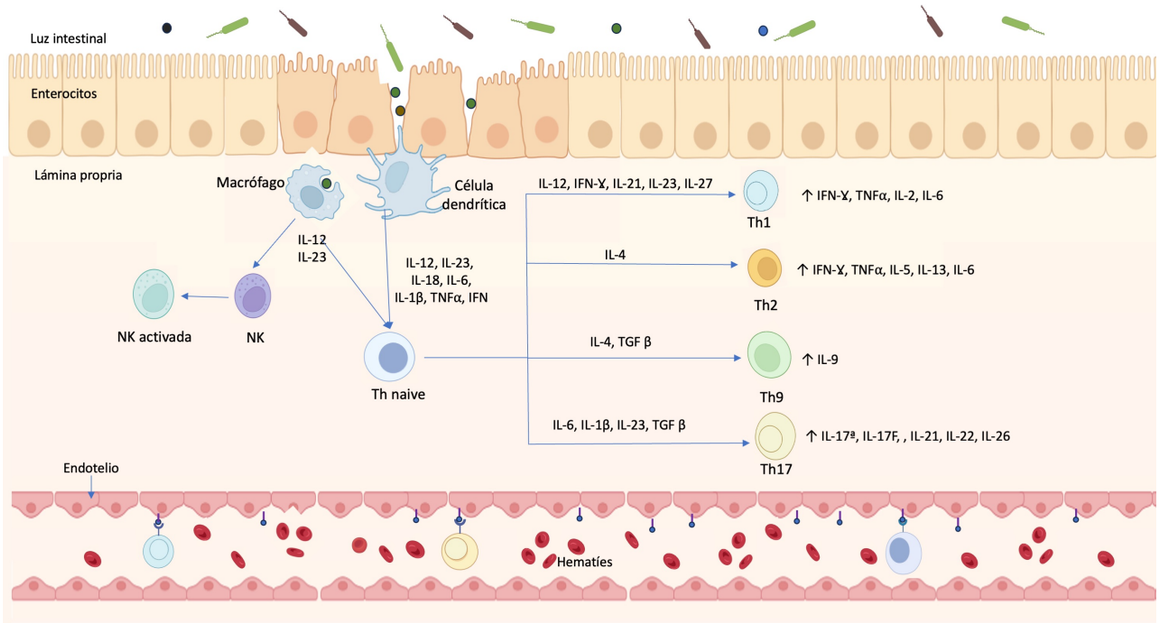
- Alteración en la microbiota: entre los principales cambios observados en la microbiota intestinal incluyen una disminución de la biodiversidad, fundamentalmente de los grupos Firmicutes y Bacteroidetes, una menor estabilidad y una sobreexpresión o infrarrepresentación de ciertas especies que conlleva disbiosis, alteración en la

metabolómica y alteraciones en la regulación del sistema inmune.[18] Entre la enfermedad inflamatoria intestinal se observa una disminución de la producción bacteriana de ácidos grasos de cadena corta, butirato, la producción de sulfuro de hidrógeno y de succinato entre otros metabolitos.[19]

- Otros factores: existen múltiples factores ambientales que se han relacionado con la enfermedad de Crohn entre los que se pueden incluir el tabaco, la actividad física, infecciones y otras condiciones sociosanitarias.[20] Además, hay que destacar que el uso de antibióticos durante la infancia también se ha relacionado con un mayor riesgo de desarrollar enfermedad inflamatoria intestinal.[21]

Estos factores pueden contribuir en mayor o menor medida a ocasional una alteración en la hemostasis del intestino y provocar una alteración inmunológica. A nivel inmunológico existen alteraciones tanto a nivel de la inmunidad innata como de la inmunidad adaptativa. Respecto a la inmunidad innata, se produce una alteración en la barrera epitelial y un aumento de permeabilidad intestinal que facilita la traslocación de antígenos a las células presentadoras de antígenos, principalmente células dendríticas y macrófagos.[22] La activación de los toll-like receptors (TLR) y los receptores intracelulares por dominio de oligomerización por unión de nucleótidos (NOD) que perpetúan la respuesta inflamatoria mediante la activación de las vías de señalización intracelulares como el factor nuclear kappa B (NF-κB). Estas células promueven la respuesta inmune adaptativa, activando principalmente la respuesta Th1 y Th17 en la enfermedad de Crohn. Posteriormente se producen citocinas proinflamatorias como el factor de necrosis tumoral alfa (TNFα), la interleucina (IL) 6, IL-12 e IL-23. En la figura 1 se describe brevemente los mecanismos inmunológicos implicados en la enfermedad de Crohn.

Figura 1. Vías inmunológicas proinflamatorias activadas en la enfermedad de Crohn.



Fuente: elaboración de la autora. Realizado en Biorender.com

Abreviaturas: IL: interleucina, NK: natural killer, TNF: factor necrosis tumoral, IFN: interferón, TGF β: factor de crecimiento transformante beta

1.3. Diagnóstico de la enfermedad de Crohn

No existen unos criterios únicos que permitan realizar el diagnóstico de la enfermedad de Crohn. El diagnóstico se establece de acuerdo con una combinación de criterios clínicos, bioquímicos, fecales, endoscópicos, histológicos y microbiológicos.[23] En pacientes sin un diagnóstico establecido pero sospecha clínica alta se debe realizar una evaluación de intestino delgado mediante pruebas radiológicas o cápsula endoscópica, siempre considerando el potencial riesgo de la cápsula endoscópica si se sospecha la existencia de estenosis en estos tramos.[24] En pacientes diagnosticados de enfermedad de Crohn, es importante valorar radiológicamente el intestino delgado para excluir afectación de tramos proximales que no se pueden valorar en la endoscopia, y además, en población pediátrica es importante visualizar el tracto digestivo alto mediante una gastroscopia.[25] Para poder diagnosticar una enfermedad de Crohn se deben excluir otras causas de colitis y/o diarrea.[26,27] El diagnóstico diferencial se detalla en la Tabla 1.

Tabla 1. Diagnóstico diferencial de enfermedad de Crohn.

Infecciones	*Yersinia spp, Shigella spp, Salmonella spp, Campylobacter spp, Escherichia coli, Mycobacterium tuberculosis,* micobacterias atípicas, *Chlamydia trachomatis*, Entoamoeba histolytica, Giardia lamblia, Citomegalovirus, Histoplasma capsulatum, *Neisseria gonorrhoeae*, Isospora belli, Strongyloides stercoralis, Criptosporidium spp, Treponema palidum, virus del herpes simple, espiroquetosis intestinal, *Clostridioides difficile*

Enfermedades inmunomediadas o inmunodeficiencias	Hidradenitis supurativa, enfermedad de Bechet, sarcoidosis, vasculitis de pequeño vaso, síndromes autoinflamatorios, síndrome Hermansky-Pudlak, inmunodeficiencia común variable.
Enfermedades ginecológicas	Endometriosis
Enfermedades digestivas	Diverticulitis, colitis asociada a divertículos, enfermedad celiaca, colitis isquémica, úlcera rectal solitaria, cáncer colorrectal
Otros	Enteritis rádica, antiinflamatorios no esteroideos, linfoma intestinal

Por otra parte, se debe realizar un diagnóstico diferencial entre la enfermedad de Crohn y la colitis ulcerosa. Sin embargo, el 10-15% de los pacientes serán diagnosticados de enfermedad inflamatoria intestinal no clasificada al no tener criterios definidos para una de las dos enfermedades o presentar rasgos de ambas.[28] A nivel histológico, la inflamación focal o parcheada (presencia de linfocitos y células plasmática), la preservación de mucina en los sitios activo, los granulomas y la alteración focal en la arquitectura de las criptas son características histológicas relacionadas con la enfermedad de Crohn.[29] Se debe recordar que estos criterios pueden variar en pacientes tratados por lo que es importante realizar un diagnóstico diferencial adecuado antes de iniciar tratamiento para esta enfermedad. En la Tabla 2 se indican los criterios más específicos para cada una de las enfermedades.

Tabla 2. Características diferenciales de la enfermedad de Crohn y la colitis ulcerosa.

	Enfermedad de Crohn	Colitis ulcerosa
Localización de la inflamación - Íleon - Colon - Recto	Todo el tracto Frecuentemente afectado Mayor en tramos proximales Preservado	Especialmente en colon y recto No excepto ileítis por reflujo Mayor en tramos distales Afectado
Distribución de úlceras Tipo de úlceras	Segmentarias Aftoides, confluyentes, lineales	Difusas y continuas Superficiales
Pseudopólipos	Poco frecuentes	Frecuentes
Patrón en empedrado	Frecuente	Ausente
Fisuras Fístulas	Frecuente Frecuente	Ausente Ausente
Atrofia mucosa	Mínima	Frecuente
Grosor de la pared	Aumentado	Normal
Envoltura grasa del mesenterio	Presente	Ausente
Estenosis	Presente	Excepcional
Irregularidad criptas	Focal y discontinuo	Continua
Inflamación aguda Inflamación crónica	Focal y discontinua Focal y discontinuo	Difusa, continua Continua, menor en tramos proximales
Afectación parcheada	Frecuente	Excepcional
Localización	Transmural	Superficial, mucosa, en ocasiones submucosa

Serositis	Presente	Ausente
Agregados linfoides	Común, transmurales	En mucosa, a veces submucosa colitis
Granulomas	Presentes	Ausentes excepto si rotura de criptas Frecuente
Polimorfismos epiteliales en criptas Abscesos crípticos	Focal y discontinua Excepcional	 Frecuente Frecuente
Disminución mucina	Excepcional y leve	Excepcional
Hiperplasia neuronal	Frecuente	Ausente
Hipertrofia muscular	Presente	Presente
Metaplasia células de Paneth Metaplasia en glándulas pilóricas	Excepcional Presente	Excepcional

1.4 Tratamiento médico de la enfermedad de Crohn

Afortunadamente, el tratamiento de la enfermedad ha evolucionado a lo largo del tiempo. Inicialmente el único tratamiento factible era la cirugía. Posteriormente, se descubrió que el tratamiento con corticoides suponía una mejoría en los parámetros clínicos, analíticos, y en la evolución de la enfermedad.[30] Sin embargo, no se recomienda el tratamiento a largo plazo debido a los efectos adversos graves de estos fármacos.[31,32] Por ello eran necesarios otros tratamientos que pudieran controlar la inflamación a largo plazo con un perfil de seguridad adecuado.

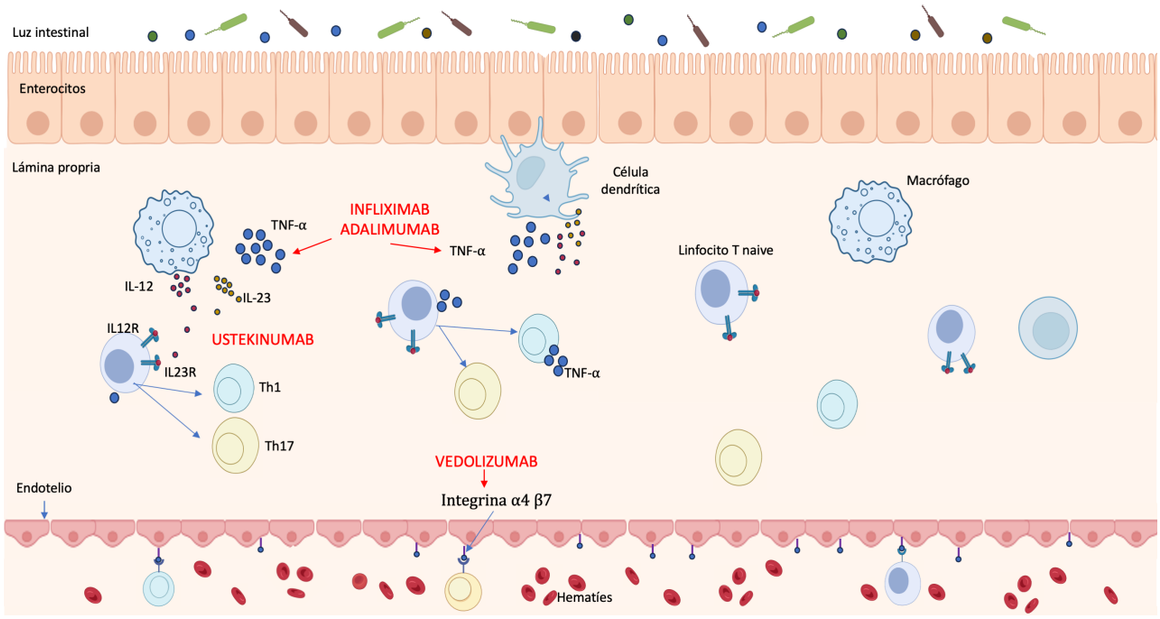
Los fármacos inmunosupresores, como la azatioprina, la mercaptopurina y el metotrexato, son eficaces para controlar la enfermedad en determinados casos.[33,34] Tras descubrir su potencial uso en la enfermedad de Crohn, se posicionaron como un tratamiento habitual a falta de otros tratamientos más eficaces.

A partir de los años 90, se inició la era de los fármacos biológicos. Estos fármacos han supuesto una auténtica revolución en el tratamiento de la enfermedad de Crohn con mejoría del control inflamatorio y de la calidad de vida de los pacientes. Esto ha permitido que los objetivos terapéuticos sean más exigentes, posicionándose a largo plazo la curación mucosa, normalización de la calidad de vida y la ausencia de discapacidad.[35] Existen diferentes fármacos biológicos que han sido aprobados con diferentes mecanismos de acción.

Estos fármacos actúan en dianas inflamatorias involucradas en la respuesta inmune en la enfermedad inflamatoria intestinal.[36] Aunque cada vez se conoce más sobre la inmunología y los mecanismos proinflamatorios que provocan la inflamación intestinal, hay una gran complejidad entre los diferentes vías inflamatorias y una interacción entre estas vías que perpetúa la respuesta inflamatoria. Los principales fármacos biológicos se dirigen contra proteínas proinflamatorias como el TNFα, las integrinas y la subunidad p40 de la IL 12 y 23.[37,38] La inhibición de estas proteínas disminuye la activación de las vías inflamatorias y la síntesis de genes proinflamatorios en las

células. En la figura 2 se exponen algunas vías inmunológicas utilizadas como diana terapéutica sobre la que actúan los fármacos biológicos hasta la aprobación de ustekinumab.

Figura 2. Vías inmunológicas y dianas terapéuticas de los fármacos biológicos en la enfermedad de Crohn.



Fuente: elaboración de la autora. Realizado en Biorender.com

Abreviaturas: IL: interleucina, TNFα: factor de necrosis tumoral alfa

1.4.1 Fármacos contra el factor de necrosis tumoral

1.4.1.1 Infliximab

Los fármacos anti-TNF transformaron radicalmente el manejo de la enfermedad inflamatoria intestinal. Los familia de los TNF incluyen 19 ligandos y múltiples receptores con propiedades proinflamatorias, apoptóticas y reguladoras de la respuesta inmune entre otras.[39] El término TNF se utilizó por primera vez en 1962, donde se observó en muestras sanguíneas de ratones con sarcoma, una actividad necrotizante tumoral tras administrar polisacárido de *Serratia marcercens*.[40] Por otra parte, en 1975, investigadores americanos describieron un factor citotóxico producido por macrófagos al que llamaron TNF [41] Finalmente, en

1984, se consiguió aislar los dos factores citotóxicos diferenciales: la α proveniente de los macrófagos y el beta (β) producido por linfocitos. [42]

La síntesis de TNFα se produce principalmente por macrófagos, linfocitos T, células endoteliales, adipocitos y fibroblastos. El antagonista de esta molécula empezó a estudiarse en ensayos clínicos como tratamiento anticancerígeno, pero el estudio en esta patología desapareció debido escasa eficacia y la toxicidad observada.[43] El creciente interés de la comunidad científica motivó su estudio en otras patologías, observando que los niveles de TNF α estaban aumentados en los procesos sépticos mediado por la producción en los macrófagos. Por ello, se evaluó la administración de anticuerpos TNF tras inducir de forma experimental shock bacteriano. Su administración protegía contra éste, la disfunción de órganos vitales y el fallecimiento, demostrando que el TNF era un mediador del shock bacteriano.[44] En 1992, se describió por primera vez la elevación en heces de TNF en pacientes con actividad de la enfermedad inflamatoria intestinal, permitiendo el desarrollo posterior de este fármaco en esta patología.[45]

<u>Eficacia de infliximab en ensayos clínicos y vida real en pacientes con enfermedad de Crohn</u>

En 1993, se publicó se desarrolló y caracterizó el tratamiento con inmunoglobulina (Ig) G anti-TNF quimérico de ratón y ese mismo año se publicó el primer caso clínico en vida real de eficacia de infliximab en un paciente con enfermedad de Crohn.[46,47]. En 1995 se presentaron por primera vez los datos de vida real de una serie de 10 pacientes con enfermedad de Crohn en la que se administró una dosis única de infliximab a dosis de 10 ó 20 miligramos por kilogramo (mg/kg) con mejoría en los índices de actividad clínica de la enfermedad de Crohn (CDAI) de 8 pacientes.[48] En 1997 se publicó el primer ensayo clínico

multicéntrico, aleatorizado y doble ciego para pacientes con enfermedad de Crohn moderada grave en la que se administró una única dosis de infliximab. Posteriormente, estos resultados se corroboraron en el ensayo clínico ACCENT I donde se valoraba en un número mayor de pacientes el mantenimiento con infliximab [49] Los ensayos clínicos que describen la eficacia y seguridad infliximab se describen en la tabla 3. Finalmente, la Agencia Europea del Medicamento aprobó su uso para enfermedad de Crohn en 1998.

Infliximab es ampliamente usado para la enfermedad de Crohn desde su aprobación en 1998. El uso de este medicamento ha supuesto un cambio sustancial en el tratamiento de los pacientes con enfermedad de Crohn con mejoría en la calidad de vida, disminución de síntomas como la fatiga, la ansiedad y depresión de nuestros pacientes.[50] Existe una amplia experiencia con este fármaco que ha demostrado su eficacia en esta patología con un buen perfil de seguridad.[51] Respecto a la eficacia, los fármacos anti-TNF han demostrado disminuir significativamente la hospitalización (Odds ratio (OR) 0,46; intervalo de confianza (IC) 95 %: 0,36-0,6) y las tasas de cirugía (OR 0,23; IC 95 %: 0,13–0,42) cuando se compara con placebo.[52] En el registro observacional prospectivo TREAT se incluyó 3440 pacientes tratados con infliximab (20.971 pacientes-año) comparado tratamiento convencional (n=2.833, 14.806 pacientes-año) demostrando demostró una mayor tasa de efectos adversos en el grupo tratado con infliximab respecto a tratamiento convencional con corticoides y/o inmunosupresores [2,15 por 100 pacientes por año versus (vs.) 0,86 por 100 pacientes-año].[53]

Desde 2016 se han comercializado los fármacos biosimilares de infliximab lo que ha permitido una reducción importante del gasto sanitario con un perfil de eficacia y seguridad similar al fármaco original.[54] Por otra parte, en 2018 la Agencia

Europea del Medicamento aprobó el uso de infliximab subcutáneo, una opción que parece disminuir la pérdida de respuesta al proporcionar mayor biodisponibilidad y aumentar los niveles sanguíneos de infliximab independientemente del uso de fármacos inmunosupresores asociados.[55,56]

Como hemos podido corroborar, infliximab sigue siendo una muy buena opción terapéutica para los pacientes con enfermedad de Crohn. Este medicamento está evolucionando a formas de presentación novedosas que probablemente mejorarán la persistencia del fármaco y disminuirá la pérdida de respuesta.

Tabla 3. Ensayos clínicos que evaluaron la eficacia y seguridad de infliximab en enfermedad de Crohn.

	Tipo de ensayo clínico	Ramas de tratamiento	Eficacia	Seguridad
Targan SR et al.[57]	Multicéntrico, aleatorizado, doble ciego Inducción	Placebo IFX 5 mg/kg ev IFX 10 mg/kg ev IFX 20 mg/kg ev Dosis extra de 10 mg/kg ev en no respondedores a semana 4.	Disminución 70% CDAI: - Placebo: 17% - IFX 5 mg/kg: 81% (5mg) * -IFX 10 mg/kg: 50%* -IFX 20 mg/kg: 64%*	Dosis única: no diferencias con placebo Segunda dosis: 7% reacción infusional
Rutgeers P et al.[58]	Multicéntrico, aleatorizado, doble ciego Mantenimiento en respondedores de ensayo previo	Placebo IFX 10 mg/kg ev cada 8 semanas	Respuesta clínica semana 44: - IFX 62% vs. placebo 37%, p=0,16 Remisión clínica semana 44: - IFX 52.9% vs. 20% placebo, p=0,013	No diferencias entre IFX y placebo

Present, DH et al.[59]	Multicéntrico, aleatorizado, doble ciego. Fistulas perianales y abdominales.	Placebo IFX 5 mg/kg ev en semana 0, 2 y 6 IFX 10 mg/kg ev en semana 0, 2, y 6	Redución 50% número de orificios: - Placebo 26% - IFX 5 mg/kg 68%* - IFX 10 mg/kg 53%*	No diferencias entre IFX y placebo
Regueiro M et al.[60]	Multicéntrico, aleatorizado, doble ciego Recurrencia postquirúrgica	Placebo IFX 5 mg/kg ev cada 4 semanas	Recurrencia endoscópica: - Placebo: 85% - IFX: 9%* Remisión clínica: - Placebo: 53% - IFX: 80%	Similar entre los grupos - Placebo: 84% - IFX: 73%

Abreviaturas: IFX: infliximab, mg: miligramo, kg: kilogramo, ev: endovenoso *Valor p<0,05 respecto a placebo

1.4.1.2 Adalimumab

El desarrollo de adalimumab tiene sus raíces en una técnica revolucionaria desarrollada por George Smith en 1985, conocida como "phage display" o expresión de fagos.[61] Esta técnica permite la selección de anticuerpos con alta afinidad por antígenos específicos, como el TNF α, al exponer fragmentos de proteínas en la superficie de bacteriófagos. Smith utilizó fagos modificados genéticamente para exhibir diversas proteínas, facilitando así la identificación de aquellas con la mayor afinidad y especificidad para un objetivo particular. Por esta innovadora contribución, Smith recibió el Premio Nobel de Química en 2018.

En el desarrollo de adalimumab, se utilizaron técnicas de expresión de fagos para seleccionar las secuencias de ADN que codifican las regiones variables de los anticuerpos humanos. Estas secuencias fueron clonadas y optimizadas para crear un anticuerpo monoclonal IgG humano, dirigido específicamente contra el TNF α. El resultado fue el desarrollo del primer anticuerpo monoclonal completamente humanizado, denominado adalimumab.[62]

<u>Eficacia de adalimumab en ensayos clínicos y vida real en pacientes con enfermedad de Crohn</u>

En 2004 se publica el primer caso clínico de adalimumab en enfermedad de Crohn en un paciente con reacción alérgica a infliximab con curación mucosa.[63] Los primeros casos clínicos se describen pacientes que no pueden ser tratados con infliximab por efectos adversos.[64] Sin embargo, su eficacia se demostró con las publicaciones de los ensayos clínicos como el CLASSIC I donde se valoraba la eficacia tras la inducción (tabla 4). Finalmente, adalimumab fue aprobado por la Agencia Europea del Medicamento en 2007.

Desde entonces, adalimumab ha demostrado su eficacia y seguridad en la práctica clínica en pacientes con enfermedad de Crohn. PYRAMID fue el registro prospectivo que se inició tras la aprobación de adalimumab en vida real.[65] Este registro incluyó 2057 pacientes naive con un seguimiento de 6 años. La proporción de pacientes en remisión clínica, valorada mediante el índice de Harvey-Bradshaw, aumento significativamente del 29% al 68% tras un año de tratamiento. Los efectos secundarios se observaron en 40 por cada 100 pacientes-año. Otro estudio prospectivo analizó la eficacia y seguridad de este fármaco encontrando una tasa de efectos adversos de 13% a un año de seguimiento.[66]

Al igual que sucedió con infliximab, en 2017 se aprobó por la Agencia Europea del Medicamento el primer biosimilar de adalimumab, conocido como Amjevita. Para su aprobación, los biosimilares precisan demostrar un riguroso proceso de calidad, en fases preclínicas en relación a su función química y funcional sin diferencias en inmunogenicidad.[67] Posteriormente se han aprobado numerosos biosimilares de diferentes compañías farmacéuticas que han permitido el tratamiento de los pacientes con un menor coste para el sistema sanitario.[68] Estos fármacos han demostrado ser comparables al fármaco original lo que ha permitido el cambio generalizado en nuestro sistema sanitario.[69]

Tabla 4. Ensayos clínicos que evaluaron la eficacia y seguridad de adalimumab en enfermedad de Crohn.

	Tipo de ensayo clínico	Ramas de tratamiento	Eficacia	Seguridad
Hanauer S et al.[70]	Multicéntrico, aleatorizado, doble ciego Inducción	Placebo Grupo 1: ADA 40 mg sc semana 0, 20 mg semana 2 Grupo 2: ADA 80 mg sc semana 0, 40 mg sc semana 2 Grupo 3: ADA 160 mg sc semana 0, 80 mg semana 2	Remisión clínica semana 4: - Placebo: 12% - Grupo 1: 18% - Grupo 2: 24%* - Grupo 3: 36%*	No diferencias respecto al placebo - Placebo: 74% - Grupo 1: 68% - Grupo 2: 68% - Grupo 3: 75%
Sandborn WJ et al.[71]	Multicéntrico, aleatorizado, doble ciego. Mantenimiento tras el ensayo previo	Placebo ADA 40 mg sc cada 2 semanas ADA 40 mg sc semanal	Remisión semana 52: - Placebo 44% - ADA 40 mg cada 2 semanas: 67%* - ADA 40 semanal: 88%*	No diferencias entre las ramas - Placebo 100% - ADA 40 mg cada 2 semanas: 79% - ADA 40 mg semanal: 78%
Colombel JF et al.[71]	Multicéntrico, aleatorizado, doble ciego. Inducción y mantenimiento	Inducción: 80 mg sc semana 0, 40 mg sc semana 2 Mantenimiento:	Remisión semana 26 / 56: - Placebo 17% / 12% - ADA cada 2 semanas 40% / 36%*	No se observaron diferencias - Placebo: 85% - ADA cada 2 semanas: 89%

		- Placebo - ADA 40 mg sc cada 2 semanas - ADA 40 mg sc semanal	- ADA semanal 47% / 41%*	- ADA semanal: 86%
Pannaccione R et al.[72]	Multicéntrico, aleatorizado, doble ciego Mantenimiento del previo.	- Placebo durante el estudio previo - ADA 40 mg sc cada 2 semanas - ADA 40 mg sc semanal	Remisión clínica semana 116 - Placebo: 37% - ADA cada 2 semanas: 42% - ADA semanal: 50%	Efectos adversos: 94% Ingresos: - Placebo: 6,5% - ADA cada 2 semanas: 8,8% - ADA semanal: 13%
Rutgeerts P et al.	Multicéntrico, aleatorizado, doble ciego Inducción y multicéntrico	Inducción ADA 160 mg sc semana 0 y 80 mg sc semana 2. Mantenimiento: - Placebo - ADA 40 mg sc cada 2 semanas	Curación mucosa semana 52: - Placebo: 24% vs. ADA 24% p<0,001 Remisión clínica semana 52: - Placebo 3% vs. ADA 18%, p=0,001	No diferencias - Placebo: 84% - ADA: 95%

Abreviaturas: ADA: adalimumab, sc subcutáneo *Valor p <0,05 respecto a placebo

1.4.1.3 Motivos de suspensión de anti-TNF

Los anti-TNF son fármacos muy eficaces en enfermedad de Crohn. Si embargo, aproximadamente el 30% de los pacientes suspenderán estos fármacos por diversos motivos pese a persistir actividad inflamatoria intestinal.[73] A continuación se detallan los principales motivos de suspensión de estos fármacos.

- Fallo de respuesta primaria: aproximadamente el 10-40% de los pacientes no responden a la inducción con anti-TNF, lo que se denomina fallo de respuesta primaria.[74,75]. Aunque un segundo anti-TNF es eficaz en pacientes con fracaso a otro anti-TNF previo, el porcentaje de remisión disminuye al 30% en caso de ausencia de respuesta primaria.[76]

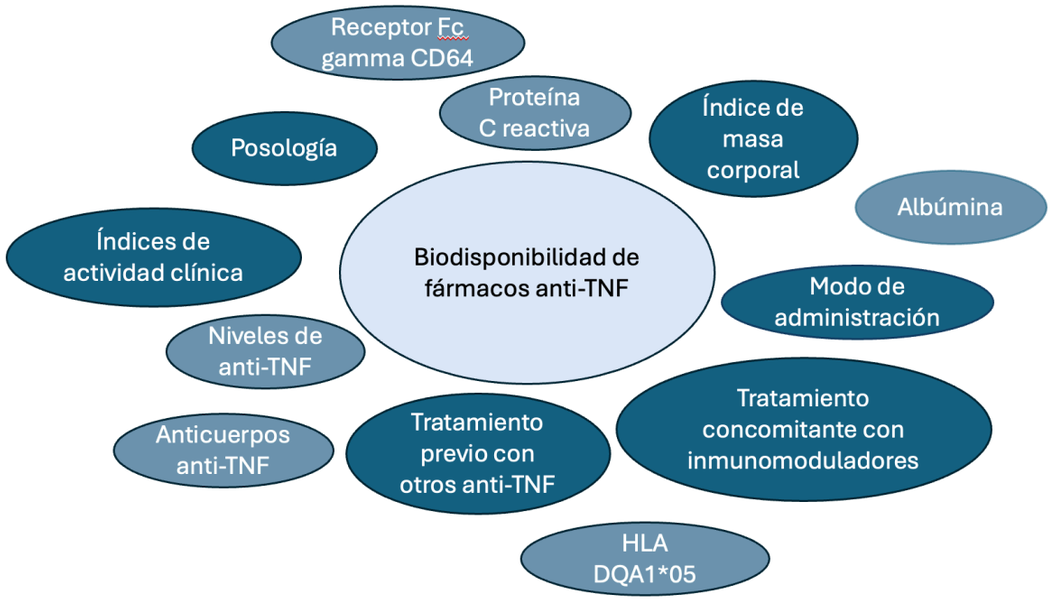
- Pérdida de respuesta secundaria: los anti-TNF son eficaces para inducir la remisión. Sin embargo, el 30% de los pacientes tratados con infliximab o adalimumab perderá respuesta durante el año siguiente tras el inicio del tratamiento, precisando ajustes de la dosis del fármaco e incluso cambiar el tratamiento.[77]

- Efectos adversos: entre el 20-25% de los pacientes suspenden el tratamiento por esos efectos secundarios. Hay numerosos artículos publicados evaluando la seguridad de los anti-TNF, pero el principal motivo de suspensión en estos casos son las infecciones.[78] El riesgo de éstas es mayor en pacientes tratados con un tratamiento inmunosupresor concomitante.[79]

- Otras causas: entre otras se encuentra la decisión del paciente, la falta de adherencia, enfermedad oncológica activa e incluso el embarazo cuando no existía evidencia científica sobre la seguridad de estos fármacos en estas situaciones.

Hay diversos mecanismos que se han involucrado tanto en el fallo de respuesta primaria como en la pérdida de respuesta a los fármacos anti-TNF. En la figura 3 se detallan algunos de los factores involucrados en la biodisponibilidad de estos fármacos.[80–82]

Figura 3. Factores involucrados en la respuesta a fármacos anti-TNF.



Fuente: elaboración de la autora

Abreviaturas: HLA: antígeno leucocitario humano, TNF: factor de necrosis tumoral

1.4.2 Vedolizumab

Vedolizumab es un anticuerpo monoclonal totalmente humanizado que se dirige de forma específica contra la integrina α4β7. Esta integrina permite la interacción de los linfocitos con las moléculas de adhesión celular de la adresina mucosa 1 (MAdCAM-1), cuya expresión predominante se localizada en las células endoteliales colónicas.[83] Su unión facilita la migración de células inmunogénicas desde la sangre a la mucosa digestiva en el proceso de inflamación.

Vedolizumab bloquea la integrina α4β7 y cambia el patrón de migración linfocitaria a la mucosa intestinal. En su desarrollo preclínico se evaluó su afinidad in vitro y en modelos animales para posteriormente iniciar los ensayos clínicos en enfermedad inflamatoria intestinal.[84] El desarrollo de esta molécula permitió el tratamiento de pacientes que presentaban un comportamiento refractario o eran intolerantes a fármacos anti-TNF, hito importante ya que en ese momento el tratamiento de estos pacientes seguía siendo limitado.

Eficacia en ensayos clínicos y vida real

En 2011 se publican los resultados de los ensayos clínicos de fase II y en 2013 los de fase III en pacientes con colitis ulcerosa. Vedolizumab demostró ser eficaz para esta enfermedad aprobándose por la Agencia Europea del Medicamento en 2014 como tratamiento de pacientes con colitis ulcerosa. Sin embargo, habría que esperar 4 años para su aprobación con indicación de enfermedad de Crohn. En la tabla 5 se describen los ensayos clínicos que han demostrado la eficacia y seguridad de vedolizumab en enfermedad de Crohn y que permitieron su aprobación.

En 2022, se publicaron los primeros resultados del ensayo clínico VISIBLE 2 sobre la eficacia de vedolizumab subcutáneo en enfermedad de Crohn.[85] Esta modalidad de posología ofrece mayor comodidad al paciente disminuyendo las visitas al centro hospitalario manteniendo una eficacia y seguridad similar.[86]

Tabla 5. Ensayos clínicos que evaluaron la eficacia y seguridad de vedolizumab en enfermedad de Crohn.

	Tipo de ensayo clínico	Ramas de tratamiento	Eficacia	Seguridad
Sandbord WJ et al. [87]	Multicéntrico, aleatorizado, doble ciego Inducción y mantenimiento Fase 3	Inducción: - VEDO 300 mg ev semana 0 y 2 - Placebo semana 0 y 2 Mantenimiento si respuesta a semana 6: - VEDO 300 mg ev cada 4 semanas - VEDO 300 mg ev cada 8 semanas - Placebo	Inducción, remisión semana 6 - VEDO 14.5% vs. placebo 6.8%, p=0,02 Mantenimiento, remisión semana 52 - VEDO 36% vs. placebo 21,6% (p=0,004) - VEDO 39% vs. placebo 21,6% (p=0,001)	No diferencias estadísticas significativas, aunque hubo mayor número de infecciones y infecciones graves en el grupo de vedolizumab.
Sands BE et al.[88]	Multicéntrico, aleatorizado, doble ciego, inducción tras refractariedad a anti-TNF	Inducción: - VEDO 300 mg ev semana 0, 2 y 6 - Placebo semana 0,2 y 6	VEDO 15% vs. 12%, p=ns	No diferencias entre los grupos

	Fase 3			
Danese S et al.[89]	Ensayo abierto, multicéntrico, remisión endoscópica Fase 3b	VEDO 300 mg sc semana 0, 2 y 6. Posteriormente cada 8 semanas	Remisión endoscópica: - Semana 26: 12% - Semana 52 de 18% Remisión radiológica: - Semana 26: 22% - Semana 52: 38% Respuesta histológica: - Semana 26: 26% -Semana 52: 26,5%	9% efectos adversos graves a semana 26, 7% a semana 52
Lowëmberg M et al.[90]	Ensayo abierto, multicéntrico, remisión endoscópica e histológica Fase 4	VEDO 300 mg sc semana 0, 2 y 6. Dosis extra la semana 10. Posteriormente cada 8 semanas	Remisión endoscópica: - Semana 26: 33 - Semana 52: 36% Remisión histológica: - Semana 26: 64%	5% de efectos adversos, 2% graves

Loftus EV Jr et al.[91]	Ensayo abierto, multicéntrico, seguridad Fase 4	VEDO 300 mg ev cada 4 semanas	Remisión clínica tras 7,7 años: 28%	Efectos adversos graves: 41% Suspensión por efectos adversos: 17%

Abreviaturas: VEDO: vedolizumab, TNF: factor necrosis tumoral, ev: endovenoso, sc: subcutáneo

1.4.3 Ustekinumab

Ustekinumab es un anticuerpo monoclonal totalmente humanizado que se dirige contra la subunidad p40 presente en las IL 12 y 23.[92] Estas dos proteínas se producen en las células dendríticas y macrófagos en respuesta a señales inflamatorias. La IL 12 promueve la diferenciación de linfocitos indiferenciados hacia linfocitos Th1, implicadas en la producción de citocinas proinflamatorias, incluyendo interferón gamma (IFNγ) y TNFα.[93] Por otra parte, la IL 23 promueve la diferenciación de linfocitos indiferenciados hacia linfocitos Th17, promoviendo la expresión de citocinas proinflamatorias como TNFα, IL-1β e IL-6.[94] Ustekinumab se une a la subunidad p40 que comparten la IL 12 y la IL 23 inhibiendo la unión de éstas al receptor IL-12Rβ1, que se expresa en la superficie de los linfocitos T y, por tanto, no se produce la liberación de las citocinas proinflamatorias.

<u>Eficacia en ensayos clínicos y vida real</u>

Este fármaco es ampliamente conocido por sus propiedades anti-inflamatorias utilizadas y demostradas en otras enfermedades autoinmunes, especialmente en la psoriasis cutánea. Sin embargo, hasta 2008 no se publicó el primer ensayo clínico en la enfermedad de Crohn. En la tabla 6 se describen los ensayos clínicos realizados en esta enfermedad. Este fármaco supuso una mejoría importante en el manejo de los pacientes al incluirse dentro de las opciones terapéuticas en enfermedad refractaria a otros tratamientos biológicos.

El primer caso descrito en vida real fue en 2011 en un paciente con enfermedad de Crohn y psoriasis inducida por anti-TNF.[95] Posteriormente, se han publicado numerosos estudios de vida real sobre la eficacia de ustekinumab en pacientes con enfermedad de Crohn.[96,97]

Tabla 6. Ensayos clínicos que evaluaron la eficacia y seguridad de ustekinumab en enfermedad de Crohn.

	Tipo de ensayo clínico	Ramas de tratamiento	Eficacia	Seguridad
Sandbord WJ et al. [98]	Doble ciego, aleatorizado Fase 2a	Población 1: - Placebo sc semana 0 y 3 -> UST 90 mg sc semana 8 y 11 - UST 90 mg sc semana 0 y 3-> placebo sc semana 8 y 11 - Placebo ev semana 0-> UST 4,5 mg/kg mg ev semana 8 - UST 4,5 mg/kg ev semana 0 -> placebo ev semana 8. Población 2: abierto - UST sc 90 mg - UST iv 4,5 mg/kg	Población 1: respuesta clínica a semana 8 - Placebo sc-> UST: 50% - UST sc-> placebo: 48% - Placebo ev-> UST: 30% - UST ev-> placebo: 50% Población 2: respuesta clínica a semana 8 - UST sc: 43% - UST ev: 54%	No diferencias entre los grupos

Sandbord WJ et al.[99]	Multicéntrico, aleatorizado, doble ciego Inducción y mantenimiento, fracaso previo a TNF Fase 2b	Inducción: - UST 1 mg/kg ev dosis única - UST 3 mg/kg ev dosis única - UST 6 mg/kg ev dosis única - Placebo Mantenimiento: - UST 90 mg sc semana 8 y 16 - Placebo	Inducción, respuesta clínica semana 6 vs. placebo (disminución CDAI 100 puntos) - UST 1 mg/kg: 37% vs. 24% (p=0,02) - UST 3 mg/kg: 34% vs. 24% (p=0,06) - UST 6 mg/kg: 40% vs. 24% (p=0,005) Mantenimiento semana 22: - UST 42% vs 27% placebo, p=0,03	No diferencias estadísticas significativas entre efectos adversos y efectos adversos graves entre los grupos
Feagan BG et al.[100]	Multicéntrico, aleatorizado, doble ciego Inducción y mantenimiento Fase 3	Inducción - UST 130 mg ev dosis única - UST 6 mg/kg ev dosis única - Placebo Mantenimiento: - UST 90 mg sc cada 8 semanas	Inducción, respuesta clínica semana 6 (disminución CDAI 100 puntos) - Expuestos TNF: UST 130 mg 34% vs. 6 mg/kg 34% 130 vs 22% placebo (p<0,003) - No expuestos TNF:	Efectos adversos similares entre grupos

		- UST 90 mg sc cada 12 semanas - Placebo	*UST 130 mg 52% vs. UST 6mg/kg 56% vs. 29% placebo (p<0,001) *p<0,003 para ambas comparaciones contra placebo Mantenimiento: remisión semana 44 - UST cada 8 semanas 52% vs. UST cada 12 semanas 49% vs. 36% placebo (p=0,005)	
Danese S et al.[101]	Aleatorizado, multicéntrico, abierto Tratamiento por objetivos (TO) vs. tratamiento estándar (TE) durante mantenimiento Fase 3b	TO: optimización según SES-CD, CDAI y biomarcadores TE: optimización según criterios clínicos del investigador	Resultados de semana 48: - Repuesta clínica (disminución al menos del 50% en el SES-CD): TO 68% vs. TE 78%, p=0,02 - Remisión semana 48: TO 62% vs. TE 70%, p=0,07	No diferencias en seguridad

			- Respuesta endoscópica: TO 38% vs. TE 30%, p=0,09 - Remisión endoscópica: TO 11% vs. TE 15%, p=0,5 - Curación mucosa: TO 14% vs. TE 17%, p=0,07)	

Abreviaturas: TNF: factor de necrosis tumoral; UST: ustekinumab; ev: endovenoso; sc: subcutáneo; CDAI: índice de actividad en enfermedad de Crohn; SES-CD: índice endoscópico simple para enfermedad de Crohn

1.5 Estado actual del tema: posicionamiento de los fármacos en el tratamiento de la enfermedad de Crohn

Gracias a los avances en el conocimiento de las vías inmunológicas y la síntesis de nuevos fármacos, disponemos de varias alternativas de tratamiento médico útiles en la enfermedad de Crohn. La complejidad de esta enfermedad se manifiesta con diferentes escenarios clínicos, con variabilidad en la localización de la inflamación, formas fistulizantes, estenosantes, perianales y manifestaciones extraintestinales entre otras. Esto, añadido a las diferentes opciones terapéuticas, ocasiona que el posicionamiento de los diferentes tratamientos cobre especial relevancia. Para ello, se necesitan estudios que comparen los diferentes fármacos en esta enfermedad.

En el momento del desarrollo de los trabajos que compendian esta tesis, sólo se había publicado un ensayo clínico en pacientes naive con enfermedad de Crohn donde se comparaba adalimumab y ustekinumab.[102] Sin embargo, no existían estudios comparativos en pacientes con fracaso previo a anti-TNF. Por este motivo surgen los estudios clínicos comparativos entre fármacos. En la tabla 7 se muestran los estudios publicados que comparan vedolizumab y ustekinumab en pacientes con fracaso previo a anti-TNF previo a nuestro estudio.

Tabla 7. Estudios que comparan vedolizumab y ustekinumab en pacientes con enfermedad de Crohn con fracaso previo a anti-TNF previos a nuestro estudio.

Estudio	**Tipo de estudio**	**Número de pacientes por tratamiento**	**Eficacia (ustekinumab vs. vedolizumab)**
Biemans, V.B.C. et al[103]	Registro prospectivo	28 ustekinumab 128 vedolizumab	• Remisión clínica (semana 52): 46% vs. 26%; p < 0,004

			• Remisión bioquímica (semana 8): 35% vs. 19%; p < 0,002
Alric, H. et al[104]	Retrospectivo	107 ustekinumab 132 vedolizumab	• Remisión clínica (semana 48): 45% vs. 34%; p < 0,13 • Remisión bioquímica (semana 48): 29% vs. 22%; p < 0,25
Townsend, T. et al[105]	Retrospectivo	45 ustekinumab 85 vedolizumab	• Remisión clínica (mes 12): 42% vs 26%; p < 0,057
Manlay, L et al[106]	Retrospectivo	224 ustekinumab 88 vedolizumab	• Remisión clínica (semana 52): 49% vs 41%, p = 0,04
Onali, S et al[107]	Retrospectivo	239 ustekinumab 231 vedolizumab	• Remisión clínica (semana 52): 43% vs 56%, p = 0,01

Abreviaturas: vs.: versus

Por otra parte, es importante considerar la seguridad de los fármacos en el algoritmo de posicionamiento terapéutico. En la tabla 8 se resumen algunos de los estudios publicados sobre el efecto de los diferentes fármacos biológicos y las complicaciones postoperatorias previos al estudio POSTSURG.

Tabla 8. Relación entre la exposición durante el periodo preoperatorio y las complicaciones postoperatorias de los fármacos biológicos.

	No relación			Evidencia de relación		
	EII	CU	EC	EII	CU	EC
Anti-TNF	Cohen 2019[108]	Billioud 2013[109] Cohen 2019[108]	Cohen 2019[108]	Billoud 2013[109] Narula 2013[110]	Kulaylat 2017[111] Xu 2019[112]	Yamamoto 2019[113]
Vedolizumab	Novello 2020[114] Yamada 2017[114]	Ferrante 2017[115] Yamada 2017[116] Kim 2020[117]	Lightner 2017[118] Yamada 2017[114]	Lightner 2018[119]	Lightner 2017[118]	Novello 2020[114]
Ustekinumab	Novello 2019[120]		Novello 2019[120]			Lightner 2019[121]

Abreviaturas: TNF: factor de necrosis tumoral, EII: enfermedad inflamatoria intestinal, CU: colitis ulcerosa, EC: enfermedad de Crohn

1.6 Justificación del proyecto

La aprobación de los fármacos ocurre tras la publicación de los ensayos clínicos que demuestran la eficacia y seguridad de los fármacos. Sin embargo, los ensayos clínicos tienen ciertas limitaciones actualmente. Entre ellas podemos encontrar la ausencia de comparación con los fármacos de referencia, el desconocimiento en enfermedad refractaria, de edad avanzada, o con determinadas manifestaciones clínicas como las fístulas abdominales y la enfermedad perianal, un número de pacientes incluidos limitado que reduce la aparición de efectos adversos de baja frecuencia o la evaluación de la seguridad en vida real o en el periodo preoperatorio.

Además, no existen ensayos clínicos comparativos que evalúen la eficacia de vedolizumab y ustekinumab en pacientes con enfermedad de Crohn refractarios a anti-TNF y el seguimiento de los estudios de práctica clínica real publicados es de un año. Por ello, se necesitan estudios que evalúen la eficacia y seguridad de estos fármacos en diferentes escenarios:

- Evaluar la eficacia y seguridad de vedolizumab y ustekinumab en enfermedad de Crohn refractaria a tratamiento anti-TNF.
- Evaluar la seguridad de los fármacos durante el periodo postoperatorio y el riesgo de complicaciones según su exposición durante el periodo preoperatorio.

2. HIPÓTESIS DEL ESTUDIO Y OBJETIVOS

2.1 Hipótesis

Las hipótesis de nuestros estudios son:

- Ustekinumab es más eficaz que vedolizumab en pacientes con enfermedad de Crohn refractaria a tratamiento anti-TNF
- El tratamiento preoperatorio con fármacos biológicos no se asocia a un mayor riesgo de complicaciones postoperatorias.

2.2 Objetivos

Para evaluar las hipótesis previamente comentadas se han desarrollado dos estudios de investigación. El primero de ellos es el estudio VERSUS donde se comparó vedolizumab y ustekinumab en pacientes con enfermedad de Crohn refractaria a anti-TNF. El segundo trabajo es el estudio POSTSURG donde se evaluó la seguridad de los fármacos durante el periodo preoperatorio. Por ello, los objetivos que se exponen se diferencian según el tipo de estudio realizado.

2.2.1 Estudio VERSUS

Objetivo primario:

- Evaluar y comparar la persistencia de vedolizumab y ustekinumab en pacientes con enfermedad de Crohn que recibieron anti-TNF en la práctica clínica.

Objetivos secundarios:

- Comparar la eficacia a corto plazo de vedolizumab y ustekinumab (en las semanas 4, 8 y 16).
- Comparar la eficacia a largo plazo de vedolizumab y ustekinumab.
- Identificar los factores predictores de respuesta a corto y largo plazo.
- Evaluar la remisión clínica sin esteroides al final de la inducción y durante el tratamiento de mantenimiento.
- Describir las tasas quirúrgicas en pacientes tratados con ustekinumab o vedolizumab.
- Comparar la seguridad de vedolizumab y ustekinumab en la práctica clínica.

2.2.2 Estudio POSTSURG

Objetivo primario:

- Comparar el riesgo de complicaciones postoperatorias inmediatas en los pacientes con enfermedad inflamatoria intestinal que recibieron tratamiento biológico en el periodo preoperatorio respecto a los pacientes no expuestos a estos fármacos.

Objetivos secundarios:

- Identificar los factores asociados al riesgo de aparición de complicaciones postoperatorias en relación con aspectos clínicos, procedimientos quirúrgicos y tratamientos perioperatorios diferentes a los fármacos no biológicos
- Describir la prevalencia de las distintas complicaciones postoperatorias inmediatas

3. PUBLICACIONES QUE COMPENDIAN LA TESIS DOCTORAL

3. Publicaciones que compendian la tesis doctoral

Las publicaciones que compendian este trabajo de tesis doctoral son las siguientes:

- Artículo 1: Comparative study of the effectiveness of vedolizumab versus ustekinumab after anti-TNF failure in Crohn's disease (VERSUS-CD): data from ENEIDA registry.
- Artículo 2: Impact of biological agents on postsurgical complications in inflammatory bowel disease: a multicentre study of GETECCU

El artículo 1 constituyó el primer paso para la consecución del primer objetivo de la presente tesis doctoral. Este artículo permitió identificar y evaluar los pacientes con enfermedad de Crohn que habían recibido vedolizumab y ustekinumab en práctica clínica, dos fármacos de reciente aparición en ese momento. Con este estudio se alcanzó el objetivo principal de esta tesis, evaluar la eficacia de estos tratamientos en la práctica clínica. Por otra parte, los efectos secundarios producidos por estos fármacos de cualquier índole también fueron analizados permitiendo conseguir uno de los objetivos secundarios. Para este artículo, se utilizó el registro nacional ENEIDA del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). Este registro ha facilitado la realización estudios a partir de un gran número de pacientes procedentes de diferentes centros de España. Desde su creación en 2006, se han publicado más de 50 artículos que han contribuido sustancialmente al conocimiento de esta enfermedad, entre los que se encuentra el artículo mencionado.

Finalmente, el segundo artículo permitió conocer la seguridad inmediata de estos fármacos durante el periodo postoperatorio cuando se administran durante el periodo preoperatorio. El objetivo de este estudio fue mucho más ambicioso, puesto que se analizó la seguridad en pacientes con enfermedad de Crohn incluyendo una cohorte de pacientes con colitis ulcerosa. Además, se

compararon diferentes fármacos incluyendo los fármacos anti-TNF. Ambos artículos completan perfectamente el análisis de la seguridad en dos situaciones muy frecuentes en la enfermedad de Crohn: durante el tratamiento médico y durante el tratamiento quirúrgico.

3.1 Artículo 1

- **Título:** Comparative study of the effectiveness of vedolizumab versus ustekinumab after anti-TNF failure in Crohn's disease (VERSUS-CD): data from ENEIDA registry

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- **Revista:** J Crohns Colitis. 2024 Jan 27;18(1):65-74. doi: 10.1093/ecco-jcc/jjad124. PMID: 37522878.

- **Factor de impacto en 2023:** 8,3
    - Cuartil en Aparato Digestivo: D1, posición 14/143, percentil 90,6%

COMPARATIVE STUDY OF THE EFFECTIVENESS OF VEDOLIZUMAB VERSUS USTEKINUMAB AFTER ANTI-TNF FAILURE IN CROHN'S DISEASE (VERSUS-CD): DATA FROM ENEIDA REGISTRY

Short title: Vedolizumab vs. ustekinumab after anti-TNF failure in Crohn's disease.

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MJ García, M Chaparro and JP Gisbert: study design, data collection, data interpretation, manuscript writing and final version approval. MJ García analysed the data. The rest of authors contributed to patient inclusion and data collection. All the authors discussed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

María José García has received financial support for travelling and educational activities from Janssen, Pfizer, AbbVie, Takeda, Kern Pharma, Faes Farma and Ferring.

Montserrat Rivero has served as a speaker, a consultant and advisory member for AbbVie, MSD, Pfizer, Takeda and Janssen.

Agnès Fernández-Clotet has served as a speaker, or has received education funding from Dr.Falk, Janssen, Takeda, Chiesi and Pfizer.

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Francisco Mesonero has served as a speaker, or has received research or education funding from Janssen, Takeda, MSD, AbbVie, Pfizer, Kern Pharma, Ferring, Galapagos, Chiesi, Faes Pharma, and Dr. Falk Pharma.

Federico Bertoletti has served as a speaker for Pfizer and has received financial support for travelling and educational activities from AbbVie, Dr. Falk Pharma, Ferring, Janssen, Kern Pharma, MSD, Norgine, Pfizer, Takeda and Tillots Pharma.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be shared upon reasonable request to the corresponding author.

FUNDING

The authors report assistance from Equipo3datos for the statistical analysis; this support was funded by the Spanish Working Group in Crohn's Disease and Ulcerative Colitis (GETECCU). The ENEIDA registry of GETECCU is supported by Pfizer, Takeda, Biogen, AbbVie and Galapagos.

ABBREVIATIONS

CD: Crohn's disease

CI: confidence intervals

CRP: C-reactive protein

GETECCU: The Spanish Working Group on Crohn's Disease and Ulcerative Colitis

GDPR: European General Data Protection Regulation

IBD: inflammatory bowel disease

IL: interleukin

IPTW: inverse probability weighting

IQR: interquartile range

HBI: Harvey-Bradshaw index

TNF: tumour necrosis factor

SD: standard deviation

ABSTRACT

Background: Both vedolizumab and ustekinumab are approved for the management of Crohn's disease (CD). Data on which one would be the most beneficial option when anti-TNF agents fail are limited.

Aims: To compare the durability, effectiveness and safety of vedolizumab and ustekinumab after anti-TNF failure or intolerance in CD.

Methods: CD patients from ENEIDA registry who received vedolizumab or ustekinumab after anti-TNF failure or intolerance were included. Durability and effectiveness were evaluated both in the short and the long term. Effectiveness was defined according to Harvey-Bradshaw index (HBI). Safety profile was compared between both treatments. The propensity score was calculated by the inverse probability weighting method to balance confounder factors.

Results: A total of 835 patients from 30 centres were included, 207 treated with vedolizumab and 628 with ustekinumab. Dose intensification was performed in 295 patients. Vedolizumab (vs. ustekinumab) was associated with higher risk of treatment discontinuation [Hazard ratio (HR) 2.55, 95%CI:2-02-3.21], adjusted by corticosteroids at baseline (HR 1.27; 95%CI:1.00-1.62), moderate-severe activity in HBI (HR 1.79; 95%CI:1.20-2.48) and high levels of C-reactive protein at baseline (HR 1.06; 95%CI:1.02-1.10). The inverse probability weighting method confirmed these results. Clinical response, remission and corticosteroid-free clinical remission were higher with ustekinumab than vedolizumab. Both drugs had low risk of adverse events with no differences between them.

Conclusion: In CD patients who have failed to anti-TNF agents, ustekinumab seems to be superior to vedolizumab in terms of durability and effectiveness in clinical practice. The safety profile is good and similar for both treatments.

Key-words: Crohn's Disease, ustekinumab, vedolizumab, durability, effectiveness

INTRODUCTION

Crohn's disease (CD) causes chronic inflammation of the bowel, leading to organ damage and impaired quality of life. Since the introduction of anti-tumour necrosis factor alpha (TNF) therapy, the natural history of CD has changed; nevertheless, there still remains a considerable percentage of patients who either do not respond to this therapy or lose response over time[1–3]. In addition, although generally safe, anti-TNF drugs are associated with the occurrence of adverse effects leading to therapy discontinuation[4–6].

In this respect, vedolizumab and ustekinumab were approved by the US Food and Drug Administration and by the European Medicines Agency in 2014 and 2016, respectively, for moderate-severe CD. These therapies reduce inflammation and improve quality of life in CD[7–10]. In case of anti-TNF failure, both vedolizumab and ustekinumab have demonstrated their effectiveness for induction and maintenance in CD in clinical trials and real-life studies[11–13]. No criteria have been established as to which therapy is the best option for a particular patient[14]. Moreover, both treatments have not been compared in randomized head-to-head clinical trials with anti-TNF failure CD patients and only in a few real-life studies. Hence, real-life studies are needed to compare vedolizumab and ustekinumab in those patients, and to identify prognostic factors of response to allow positioning these current drugs into the CD therapeutic algorithm.

For the above mentioned reasons, the main aim of our study was to compare the durability of vedolizumab and ustekinumab in clinical practice. Additionally, we aimed

to compare their short-term and the long-term effectiveness, to identify the predictive factors of clinical response and remission, and to compare the safety profile of both therapies.

METHODS

Study design

We designed a multicentre study selecting CD patients included in the ENEIDA registry. The ENEIDA registry is a prospectively maintained nationwide database supported by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU)[15]. The database is regularly updated by all participants to ensure the quality of information. Our study group was comprised by patients included in ENEIDA registry from January 1, 2012 to December 30, 2020. The study was carried out according to the STROBE statement[16].

Study population

CD patients older than 18 years who had been treated with vedolizumab or ustekinumab after anti-TNF failure or intolerance were eligible, including primary non-response, loss of response or intolerance to anti-TNF. Vedolizumab or ustekinumab therapy had to have been prescribed for luminal activity including postoperative recurrence, perianal disease or intolerance to anti-TNF. An interval of less than 6 months between the last dose of anti-TNF and the first dose of vedolizumab or ustekinumab was required to consider the sequential therapy after anti-TNF failure or intolerance eligible for this study. Patients who had previously received anti-interleukin (IL) 12, IL-23, or anti-integrins for CD or other immune-mediated diseases, those receiving the drugs as prophylaxis of postoperative recurrence or to treat other diseases than CD were excluded from the study. Vedolizumab was initiated with an intravenous infusion of 300 mg at 0, 2 and 6 weeks as induction and thereafter every 8 weeks. An extra dose of 300

mg at week 10 was allowed. Ustekinumab induction therapy consisted in an intravenous dose according to patient weight (6 mg/kg) followed by subcutaneous administration of 90 mg every 8 or 12 weeks according to investigator criteria. Patients were followed-up until the last dose of vedolizumab or ustekinumab; or until therapy discontinuation, whichever came first.

Data collection

Demographic and clinical characteristics were obtained from the ENEIDA registry; including location, behaviour, perianal disease and extraintestinal diseases. CD was categorized according to the Montreal classification. Clinical activity and treatment response was assessed by the Harvey-Bradshaw index (HBI). Effectiveness was evaluated at weeks 8 and 16 during the induction period and every 6 months during the maintenance phase. Clinicians were asked to provide objective parameters of inflammation such as C-reactive protein (CRP), haemoglobin, faecal calprotectin and/or endoscopic activity when available. Endoscopic activity was graded as quiescent, mild, moderate and severe according to the investigators' criteria. Side effects, reason of discontinuation and clinical approach after therapy discontinuation were also recorded.

Definitions

- Follow-up time: from the first dose administration to the date of the analysis.

- Time of exposure: time that the patient was under the treatment.

- Active disease at vedolizumab or ustekinumab initiation: Active disease was defined as a score ≥5 points in HBI.

- Response to therapy: To elucidate whether the patients responded to the therapy or not, HBI was calculated at baseline and at week 16 after treatment initiation. During the maintenance period, HBI was also measured every 6 months until the last dose of vedolizumab or ustekinumab; or until therapy discontinuation, whichever came first. The response to therapy was evaluated only when HBI was >4 before ustekinumab or vedolizumab initiation. Clinical remission was defined as an HBI <5. Corticosteroid-free clinical remission was defined as an HBI <5 alongside no corticosteroid administration in a certain visit. Clinical response was defined as a reduction in HBI ≥3 points from baseline alongside clinical remission criteria.

- Dosage intensification: In patients treated with vedolizumab it was defined as a dose interval reduction from 8 to 6 weeks or to 4 weeks in the maintenance period. In the ustekinumab cohort, intensification was defined as a dose interval reduction from 12 to 8 weeks, from 8 to 4 weeks; or when an intravenous dose was administered in the maintenance period.

- Loss of response: it was defined as a worsening in patient's symptoms (HBI>4) leading to dose escalation, addition of another medication, change to another drug or surgery.

Ethical considerations

The ENEIDA registry was approved by the ethics committees of each participant centre. Informed consent was signed by all the participants before inclusion in the registry and each subject was issued with a personal code number to ensure that patient identity remains unknown to the sponsor. This study was conducted in accordance with the Declaration of Helsinki principles, the European General Data Protection Regulation (GDPR) 2016/679 and the Spanish Data Protection Organic Law 3/2018. The protocol

was reviewed by the investigation committee of GETECCU before retrieving the stored data from the ENEIDA registry.

Statistical analysis

Percentages and 95% confidence intervals (CI) were calculated for categorical variables. The mean and standard deviation (SD), or the median and interquartile range (IQR) —depending on whether they were normally distributed or not— was used to describe quantitative variables. Chi-square test or Fisher's exact test was used to compare categorical variables while Mann-Whitney U test or *t*-Test compared the differences between quantitative variables depending on data distribution. Using a logistic regression model, variables associated at induction and maintenance period with the likelihood of clinical response, clinical remission and corticosteroid-free clinical remission were identified in the multivariate analysis. The selected model was based on Akaike information criterion (AIC), Bayesian information criterion (BIC) and clinical significance.

The Kaplan-Meier method evaluated the long-term durability of vedolizumab or ustekinumab, and any differences between survival curves were evaluated with the log-rank test. Patients who discontinued the treatment for any reason were considered as treatment failure, while patients who maintained the therapy at the end of the study were considered as censored cases. Stepwise multivariate analysis using the Cox model was used to identify factors associated with treatment discontinuation. Missing data in the short term were imputed as non-response while the last observation carried forward method was used for imputation in the evaluation of long-term effectiveness. In the log-

rank test and in the multivariate analysis, statistical significance was considered when p <0.05. All statistical analyses were performed with STATA Statistical Software: Release 14. StataCorp LP.

Sample size

Percentages of treatment durability in real-life studies for anti-TNF-exposed patients at week 16 and also one year after vedolizumab and ustekinumab initation were considered to calculate the sample size of the study[17,18]. A two-sided α level of 0.05 and a power of 80% was established. Considering differences of 20% at week 16, and 30% at week 52, 150 patients per group were requiered to evalute treatment durability.

Sensitivity analysis

Inverse probability weighting (IPTW) and propensity matching score analysis were performed to adjust both cohorts for baseline differences and factors. All the potential confounding factors were meticulously evaluated and discussed by the investigators. The final selection of the variables was based on their clinical relevance or their statistical significance by *t*-test, Mann-Whitney U-test and Chi-square test depending on whether the variable was quantitative or qualitative. The included variables were sex, smoking habit, location and behaviour of the disease, perianal disease, extraintestinal manifestations, prior IBD surgery, use of concomitant immunomodulators and corticosteroids, cause of anti-TNF discontinuation, number of previous anti-TNFs, and activity parameters including HBI, CRP and haemoglobin. Those variables were evaluated graphically before and after the IPTW score to ascertain the balance of the

confounding factors. The sensitivity analysis was used to confirm the differences in the main outcome (treatment durability).

RESULTS

Baseline characteristics

A total of 835 patients from 30 centres were included, 25% (n=207) treated with vedolizumab and 75% (n=628) with ustekinumab. The main characteristics of all patients are described in Supplementary table 1. The proportion of patients among different centres are detailed in Supplementary table 2.

When both treatments were compared, the prevalence of ileal location was higher in the ustekinumab group than in the vedolizumab group [48% (n=301) vs. 38% (n=79), p<0.05]. The distribution of disease was similar between both cohorts. Patients treated with vedolizumab had undergone IBD surgery before treatment initiation more frequently [54% (n=111) vs. 43% (n=268), p<0.005] and they had received at least 2 anti-TNF therapies also more frequently than those patients treated with ustekinumab [65% (n=134) vs. 45% (n=285), p<0.001]. Regarding baseline activity, the vedolizumab group showed higher use of concomitant corticosteroids [39% (n=80) vs. 23% (n=144), p<0.001], increased levels of CRP (2.0 mg/dL, SD 2.7 vs. 1.5 mg/dL, SD 2.2; p<0.005) and lower levels of haemoglobin (12.7 g/dL, SD 1.8 vs. 13.3 g/dL, SD 1.8, p<0.001) compared with patients treated with ustekinumab. After propensity matching score, all the baseline characteristics were balanced, and no statistical differences were observed between both groups (Supplementary figure 1). Differences in baseline characteristics are detailed in table 1.

Survival rate of vedolizumab and ustekinumab

The median time of follow-up (from the initiation of the therapy to database lock) was 4.7 years (IQR 3.2-5.5) for patients treated with vedolizumab and 2.8 years (IQR 2.0-3.6) for ustekinumab, while the median of therapy exposition was similar between both groups (1.0 years, IQR 0.4-2.1 and 1.5 years IQR 0.7-2.6, respectively). The durability of ustekinumab was superior than that of vedolizumab (figure 1). The discontinuation ratio was 49 per 100 person-years for vedolizumab and 19 for ustekinumab ($p<0.001$). The highest rates of discontinuation occurred during the first year after therapy initiation; 62 per 100 person-years during the first year vs. 43 during the second year in patients treated with vedolizumab and 23 vs. 17 per 100 person-years in the ustekinumab cohort. Vedolizumab (vs. ustekinumab) therapy was associated with higher risk of treatment discontinuation in multivariate analysis (HR 2.55, 95% CI:2-02-3.21) adjusted by corticosteroids at baseline (HR 1.27; 95%CI: 1.00-1.62), moderate-severe activity based on the HBI (HR 1.79; 95% CI: 1.20-2.48) and levels of C-reactive protein at baseline (HR 1.06; 95% CI: 1.02-1.10). With the IPTW method to control confounding factors the results remained similar: the risk of treatment discontinuation was higher with vedolizumab (compared with ustekinumab) (HR 2.11; 95% CI: 1.50-2.99).

A total of 350 patients discontinued the treatment at the last visit of the study, 71% (95% CI: 65.3-77.6) (n=148) in the vedolizumab group and 32% (95% CI: 28.5-35.8) (n=202) in the ustekinumab. The main cause of treatment discontinuation was primary non-response followed by secondary non-response (table 2). Treatment discontinuation led to initiation of other biological therapy or small molecule therapies in 62% (n=217), surgery 28% (n= 97), immunomodulators 3% (n=12), no treatment in 3% (n=11) and corticosteroids 2% (n=7).

Short-term effectiveness

The effectiveness was evaluated in 597 patients —who had active disease at the start of treatment defined by an HBI>4 points—, 152 in the vedolizumab group and 445 in the ustekinumab group. The treatment was discontinued in 13 patients during the induction phase: one in the vedolizumab and 12 in the ustekinumab group. Clinical response, clinical remission and corticosteroid-free remission rates were statistically higher in patients treated with ustekinumab (figure 2).

Multivariate analysis confirmed that ustekinumab (vs. vedolizumab) was associated with higher likelihood of clinical response (OR 1.84; 95% CI:1.27-3.18), clinical remission (OR 2.01; 95% CI:1.27-3.18) and corticosteroid-free clinical remission (OR 1.84; 95% CI:1.12-3.03) in the short term (week 16). Variables associated with clinical response and remission for each therapy are detailed in table 3.

Long-term effectiveness

A total of 584 patients were followed-up at least for six months. The multivariate analysis showed that ustekinumab was superior to vedolizumab in sustaining clinical response, clinical remission and corticosteroid-free clinical remission during the first two years after therapy initiation ($p<0.05$), whereas no significant differences were observed afterwards (figure 2).

In the multivariate analysis, the likelihoods of achieving clinical response (OR 1.80, 95% CI:1.17-2.79), clinical remission (OR 1.73, 95% CI:1.10-2.70) and corticosteroid-free

clinical remission (OR 1.69, 95% CI:1.07-2.68) at one year were significantly higher in patients treated with ustekinumab (vs. vedolizumab). The factors associated with clinical remission at one year are detailed in Supplementary table 3.

Loss of response and therapy discontinuation

Overall, 770 patients reached remission at week 16, and 514 lost response over time, 74% (n=154) in the vedolizumab group and 57% (n=360) in the ustekinumab group (p<0.001). After losing response, 295 patients (57%) intensified the dosage, 140 (27%) switched to other biological agent, 63 (12%) underwent surgery, 13 (2.5%) initiated steroids, and 3 (0.6%) added immunomodulator therapy.

During the maintenance phase, 293 patients required dose intensification; 34% (n=61) were treated with vedolizumab and 39% (n=232) with ustekinumab (p=0.2). In the vedolizumab group, 48 patients reduced their dose interval to once every 4 weeks and 13 patients to once every 6 weeks. The intensification strategy in the ustekinumab group was switching to intravenous dose in 25 patients and reducing the dose intervals in 207 patients to once every 4 weeks. Clinical response to intensification at investigators' criteria was achieved by 34% (n=21) of patients in the vedolizumab group and 65% (n=143) in the ustekinumab group (p=0.001).

Safety

Overall, 11.6% (n=97) of patients suffered at least one adverse event, 3.6% (n=30) in the vedolizumab group and 8% (n=67) in the ustekinumab group (p=0.1). The incidence rate of adverse events was 6.6 and 5.3 per 100 person-years in patients treated with

vedolizumab and ustekinumab, respectively. Infections were the most frequent adverse event, reported in 65 patients (1.6%), followed by arthralgia in 13 patients (0.3%), and skin disorders in 11 patients (0.3%). Serious adverse events were observed in 22 patients: 9 (1.1%) in the vedolizumab group and 13 (1.6%) in the ustekinumab group ($p>0.05$). Adverse events led to therapy discontinuation in 30 patients: 13 (1.6%) in vedolizumab and 17 (2%) in the ustekinumab group, $p>0.05$. One patient died in the vedolizumab group due to an infectious arthritis complicated with septic shock. The safety profile according to the treatment is detailed in table 4.

DISCUSSION

To our knowledge, to date this is the largest cohort comparing the durability of vedolizumab and ustekinumab treatment in CD patients in clinical practice. Our study demonstrates that the durability of ustekinumab therapy is superior to vedolizumab in CD patients after anti-TNF failure.

Results on vedolizumab and ustekinumab comparison have been published in 7 reports to date[19]. Biemans et al. described discontinuation rates similar to those of our study: 52% and 34% respectively at one year after therapy initiation[18]. Comparable results were obtained in another cohort study of 322 patients who were followed for 16.5 months[20]. When adalimumab, infliximab, vedolizumab and ustekinumab were evaluated, lower discontinuation rates with ustekinumab were found in another population-based cohort study[21]. However, phenotype of CD, intolerance or loss of response to other medical therapies was not evaluated in the last-mentioned cohort and therefore, biological positioning in real life remains an unmet need. In contrast to the aforementioned studies, only one report showed similar treatment persistence for vedolizumab and ustekinumab in yet another large UK cohort study; therefore, more data are necessary to clarify the difference between this outcome and the above mentioned results [22].

The most frequent cause of therapy discontinuation was primary non-response followed by secondary non-response. The discontinuation rate was highest during the induction period in both groups. This rate gradually decreased over time during the maintenance

phase, in which both treatments were usually maintained[23,24]. Dosage optimization improved treatment persistence in patients with secondary loss of response to ustekinumab so the differences between both survival curves might be influenced by this strategy[25]. Treatment intensification has been gradually implemented in clinical practice and therefore, our results are consistent with real-life experiences[26–28].

We also compared the short-term effectiveness of vedolizumab and ustekinumab after anti-TNF failure, as this aspect is crucial when choosing between drugs in clinical practice. We observed that the highest clinical benefit was achieved with ustekinumab compared with vedolizumab, suggesting higher effectiveness of ustekinumab in CD in clinical practice —the remission rate at week 16 was higher with ustekinumab than with vedolizumab (39% vs. 24%, $p<0.05$). In this respect, other studies have reported conflicting results, although they had limited sample size to address this comparison[18,29,30]. In our cohort, we overcame this limitation with a representative large population of patients and thus, our results provide accurate information on the effectiveness of these drugs on this scenario.

Regarding long term effectiveness, higher rates of clinical remission for ustekinumab were observed when it was compared with vedolizumab at one year (48% vs. 32%). Previous reports analysed effectiveness only at one year after therapy initiation while long-term data after that time have not been described[31]. The multivariable analysis in our study showed that these results were maintained 2.5 years after therapy initiation, whereas similar rates between both drugs were obtained afterwards. The reduction in

the sample size after this time probably limits the power of the study for obtaining reliable differences between both groups.

An adequate safety profile, with no differences between both drugs, was observed in the present study. Long-term clinical trials and real-life studies of vedolizumab reported an incidence rate of 11-15 per 100 person-years of serious adverse events[32,33]. Regarding the safety profile of ustekinumab, the incidence rate of adverse events and serious adverse events previously reported in clinical practice were similar to our results[34,35]. These results are consistent with safety data of clinical trials also reporting infections as the most frequent adverse event, followed by arthralgia and headache[36,37]. Hence, both vedolizumab and ustekinumab are safe even in susceptible populations[38,39].

Our study has some limitations. Of note, although ENEIDA is a prospectively maintained database, some parameters such as CRP, haemoglobin, calprotectin or HBI are not routinely included in the registry; however, they were available in most patients as they are part of the routine monitoring of disease activity in clinical practice. For that reason, medical history was reviewed, and activity data were included by each investigator. In addition, mucosal healing was not determined in all patients; however, this fact reflects what happens in clinical practice, where only patients with suboptimal response are usually assessed for the persistence of mucosal inflammation. More parameters of severe disease were observed in the vedolizumab group such as the existence of prior IBD surgery, number of failed anti-TNF agents, concomitant corticosteroids at baseline, higher levels of CRP and lower levels of haemoglobin. This study is a clinical practice study, hence the extra dose of vedolizumab was not administered to all patients. Also,

phatophysiological mechanisms were not studied and therefore, differences among both treatments could no be explained. Despite these limitations, IPTW score confirmed that ustekinumab durability was higher than vedolizumab.

Despite these limitations, our study has important strengths. Firstly, this study is the largest cohort published to date comparing the durability of vedolizumab and ustekinumab in real life. Secondly, the time of follow-up is the longest ever recorded, with a median of 4.7 years for vedolizumab and 2.8 for ustekinumab. Moreover, IPTW score balanced the differences in baseline characteristics and avoided their influence on the results. Another strength is the inclusion of patients who required intensification dosage during the follow-up. In routine practice, treatment intensification is frequently initiated after loss of response so the durability of both therapies revealed the durability of vedolizumab and ustekinumab in real clinical practice.

In conclusion, the durability of ustekinumab was higher than that of vedolizumab in CD patients after anti-TNF failure or intolerance. Both treatments were effective in this setting, with higher rates of clinical remission for those patients under ustekinumab therapy during the first two years after treatment initiation. A relevant proportion of patients lost response over time, although the intensification strategy was able to increase the treatment durability of both drugs. Finally, the safety profile of vedolizumab and ustekinumab was good, with no differences between both treatments.

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TABLES

Table 1. Baseline characteristics of patients under vedolizumab or ustekinumab treatment in our cohort of Crohn's disease patients with previous failure to anti-TNF.

	Vedolizumab (n= 207)	Ustekinumab (n=628)	p-value (overall)
Male, n (%)	103 (50)	317 (50)	0.9
Tobacco, n (%)			0.2
- Current smoker	47 (25)	158 (27)	
- Former smoker	33 (18)	129 (22)	
- Non-smoker	108 (58)	292 (50)	
Age at vedolizumab or ustekinumab initiation (years) (mean, SD)	45.7 (16)	45.6 (15)	1
Age at diagnosis (mean, SD)	33.0 (16)	33.3 (16)	0.8
CD duration (years) (mean, SD)	12.7 (9.8)	12.4 (9.6)	0.6
Location, n (%)			<0.05*
- Ileal (L1)	79 (38)	301 (48)	
- Colonic (L2)	30 (15)	75 (12)	
- Ileocolonic (L3)	98 (47)	252 (40)	
- Upper disease (L4)	24 (12)	63 (10)	0.5
Behaviour, n (%)			0.6
- Inflammatory (B1)	107 (52)	317 (51)	
- Stricturing (B2)	53 (26)	148 (24)	
- Penetrating (B3)	47 (23)	163 (26)	
Perianal disease, n (%)	76 (37)	208 (33)	0.3
Presence of extraintestinal manifestations, n (%)	78 (38)	212 (34)	0.3
Extraintestinal manifestation, n (%)			
- Axial arthropathy	13 (6.3)	41 (6.5)	0.9
- Peripheral arthropathy	38 (18)	89 (14)	0.1
- Cutaneous	23 (11)	76 (12)	0.7
- Ocular	8 (3.9)	29 (4.6)	0.6
- Primary sclerosing cholangitis	0 (0)	5 (0.8)	0.2
Previous surgery for IBD, n (%)	111 (54)	268 (43)	<0.05*
Number of failed anti-TNF agents, n (%)			<0.001*
- 1 anti-TNF	73 (35)	343 (55)	
- ≥ 2 anti-TNF	134 (65)	285 (45)	
Previous anti-TNF agents, n (%)			
- Infliximab	172 (83)	414 (66)	<0.001*
- Adalimumab	169 (82)	494 (79)	0.4
- Certolizumab	7 (3.4)	17 (2.7)	0.6
- Golimumab	1 (0.5)	5 (0.8)	0.6
- Others	0 (0)	2 (0.3)	0.4
Cause of anti-TNF discontinuation, n (%)			<0.001*
- Secondary non-response	109 (53)	375 (60)	
- Primary non-response	72 (35)	141 (23)	

- Intolerance	26 (13)	112 (18)	
Concomitant immunomodulator, n (%)	76 (37)	197 (31)	0.2
Immunomodulator agent, n (%) - Azathioprine - Methotrexate - 6-Mercaptopurine	 52 (68) 20 (26) 4 (5.3)	 139 (71) 49 (25) 9 (4.6)	0.9
Concomitant corticosteroids, n (%)	77 (37)	139 (22)	<0.001*
Harvey-Bradshaw index (points) (mean, SD)	6.4 (3.2)	6.0 (3.2)	0.2
Biochemical parameters (mean, SD) - C-Reactive protein (mg/dL) - Haemoglobin (g/dL) - Faecal calprotectin (μg/g)	 2.0 (2.7) 12.7 (1.8) 740.9 (973)	 1.5 (2.2) 13.3 (1.8) 639.3 (814)	 <0.05* <0.001* 0.4
Colonoscopy, n (%)	71 (34.3)	208 (33.1)	0.8
Endoscopic activity, n (%) - Quiescent - Mild - Moderate - Severe	 4 (5.6) 7 (9.9) 31 (44) 29 (41)	 8 (3.9) 19 (9.1) 115 (55) 66 (32)	0.4

SD: standard deviation; CD: Crohn's disease; TNF: tumor necrosis factor; n: number of patients; *p<0.05

Table 2. Causes of treatment discontinuation.

	Overall (n=350)	Vedolizumab (n= 148)	Ustekinumab (n=202)
Primary non-response, n (%)	198 (57)	80 (54)	118 (58)
Secondary non-response, n (%)	96 (27)	49 (33)	47 (23)
Adverse events n (%)	21 (6.0)	10 (7.4)	11 (6.4)
Other, n (%)	13 (3.7)	4 (2.7)	9 (4.5)
No response of other immune-mediated diseases, n (%)	13 (3.7)	3 (2.0)	10 (5.0)
Tumours, n (%)	6 (1.7)	2 (1.4)	4 (2.0)
Pregnancy, n (%)	3 (0.9)	1 (0.7)	2 (1.0)

n: number of patients

Table 3. Factors associated with clinical response, clinical remission and corticosteroid-free clinical remission at week 16.

			Ajusted odds ratio	95% confidence interval
Overall cohort	Clinical response	Ustekinumab (vs. vedolizumab)	1.84	1.24-2.74
		No prior CD surgery	1.42	1.02-2.00
	Clinical remission	Ustekinumab (vs. vedolizumab)	2.01	1.27-3.18
		Mild activity in HBI (vs. moderate-severe)	3.22	2.18-4.77
	Corticosteroid-free clinical remission	Ustekinumab (vs. vedolizumab)	1.84	1.12-3.03
		Mild activity in HBI (vs. moderate-severe)	2.57	1.70-3.88
		No prior CD surgery	1.84	1.24-2.72
		No corticosteroids at baseline	1.98	1.25-3.15

CD: Crohn's disease, vs.: versus, HBI: Harvey-Bradshaw index

Table 4. Adverse events of vedolizumab and ustekinumab.

	Vedolizumab (n=207)			Ustekinumab (n= 628)			p-value
	AE n (%)	SAE n (%)	Therapy discontinuation n (%)	AE n (%)	SAE n (%)	Therapy discontinuation n (%)	
Infection	15 (7.2)	6 (2.9)	3 (1.4)	50 (8.0)	12 (1.9)	7 (1.1)	0.9
Arthralgia	3 (1.4)	2 (1.0)	2 (1.0)	10 (1.6)	1 (0.2)	3 (0.5)	0.6
Infusion reactions	3 (1.4)	0 (0)	1 (0.5)	1 (0.2)	0 (0)	1 (0.2)	<0.05
Deterioration of other IMIDs	4 (1.9)	0 (0)	4 (1.9)	5 (0.8)	0 (0)	3 (0.5)	0.2
Headache	1 (0.5)	0 (0)	0 (0)	7 (1.1)	0 (0)	1 (0.2)	0.9
Skin lesions	2 (1.0)	0 (0)	0 (0)	9 (1.4)	0 (0)	9 (1.4)	0.4
Others	6 (2.9)	1 (0.5)	3 (1.4)	12 (1.9)	4 (0.6)	4 (0.6)	0.2

AE: adverse events, SAE: serious adverse events, IMIDs: immune-mediated diseases

Figure 1. Comparison of vedolizumab and ustekinumab survival rates over time.

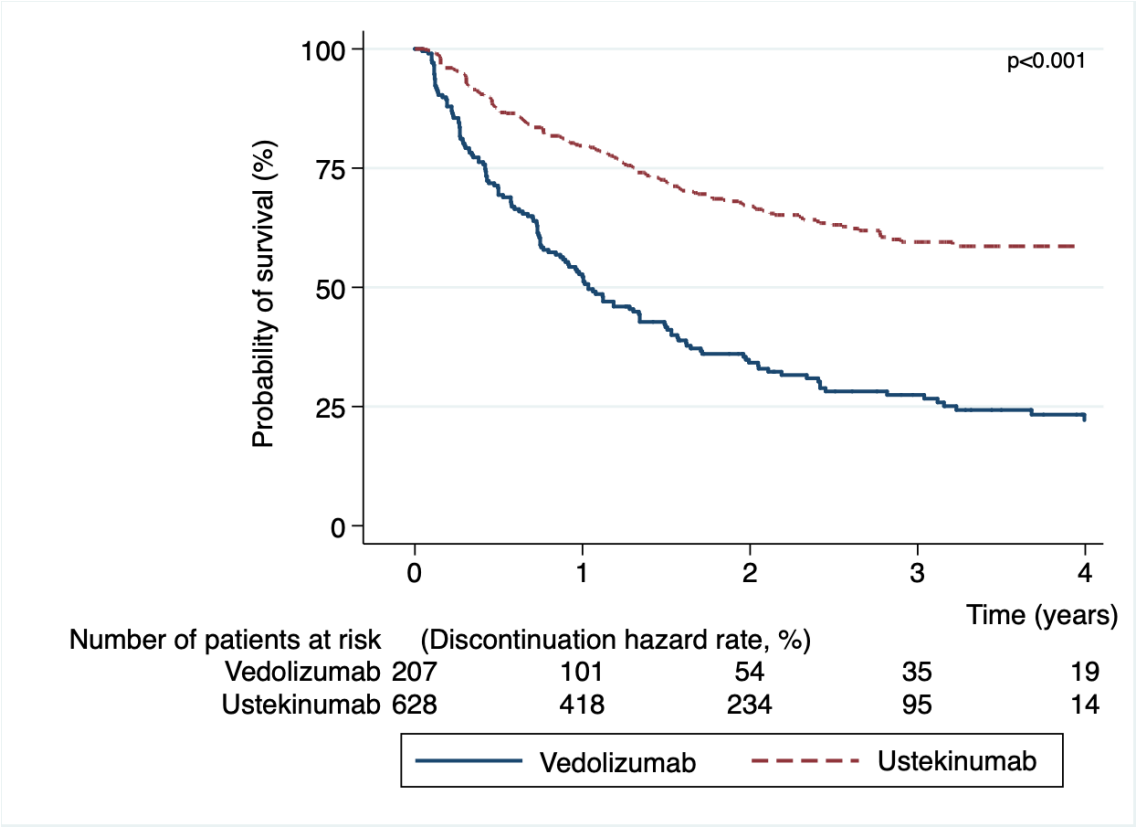
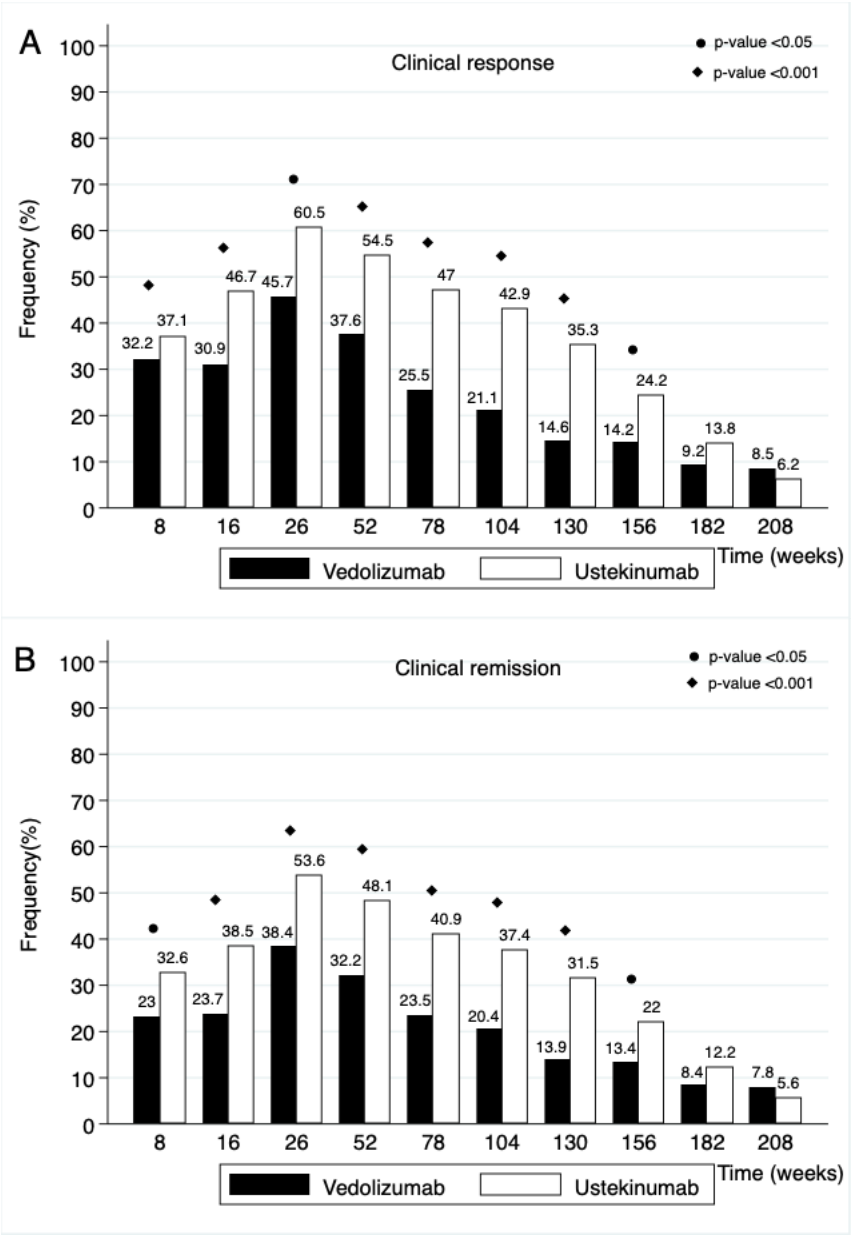
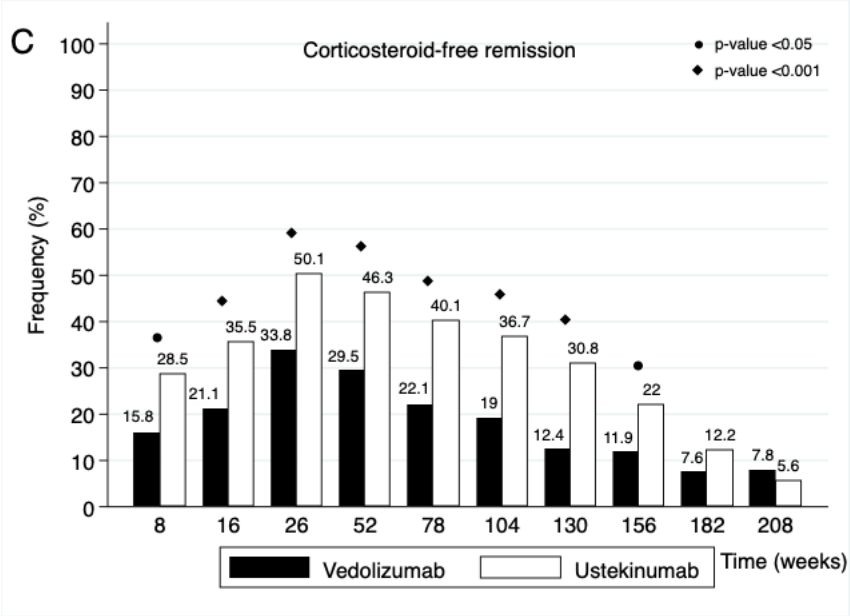


Figure 2. Short-term and long-term clinical response, clinical remission and corticosteroid-free remission in patients treated with vedolizumab and ustekinumab. Parameters of short- and long-term response to vedolizumab and ustekinumab. A, clinical response. B, clinical remission. C, corticosteroid-free remission




C
Corticosteroid-free remission
p-value <0.05
p-value <0.001
Frequency (%)
100
90
80
70
60
50
40
30
20
10
0
15.8
28.5
21.1
35.5
33.8
50.1
29.5
46.3
22.1
40.1
19
36.7
12.4
30.8
11.9
22
7.6
12.2
7.8
5.6
8
16
26
52
78
104
130
156
182
208
Vedolizumab
Ustekinumab
Time (weeks)

3.2 Artículo 2

- **Título:** Impact of biological agents on postsurgical complications in inflammatory bowel disease: a multicentre study of GETECCU

- **Autores:** María José García, Montserrat Rivero, José Miranda-Bautista, Iria Bastón-Rey, Francisco Mesonero, Eduardo Leo-Carnerero, Diego Casas-Deza, Carmen Cagigas Fernández, Albert Martin-Cardona, Ismael ElHajra, Nerea Hernández-Aretxabaleta, Isabel Pérez-Martínez, Esteban Fuentes-Valenzuela, Nuria Jiménez, Cristina Rubín de Célix, Ana Gutiérrez, Cristina Suárez Ferrer, José María Huguet, Agnes Fernández-Clotet, María González-Vivó, Blanca Del Val, Jesús Castro-Poceiro, Luigi Melcarne, Carmen Dueñas, Marta Izquierdo, David Monfort, Abdel Bouhmidi, Patricia Ramírez De la Piscina, Eva Romero, Gema Molina, Jaime Zorrilla, Cristina Calvino-Suárez, Eugenia Sánchez, Andrea Nuñez, Olivia Sierra, Beatriz Castro, Yamile Zabana, Irene González-Partida, Saioa De la Maza, Andrés Castaño, Rodrigo Nájera-Muñoz, Luis Sánchez-Guillén, Micaela Riat Castro, José Luis Rueda, José Manuel Benítez, Pedro Delgado-Guillena, Carlos Tardillo, Elena Peña, Santiago Frago-Larramona, María Carmen Rodríguez-Grau, Rocío Plaza, Pablo Pérez-Galindo, Jesús Martínez-Cadilla, Luis Menchén, Manuel Barreiro-De Acosta, Rubén Sánchez-Aldehuelo, María Dolores De la Cruz, Luis Javier Lamuela, Ignacio Marín, Laura Nieto-García, Antonio López-San Román, José Manuel Herrera, MaríaChaparro, Javier P.Gisbert.

- **Revista**: J Clin Med. 2021 Sep 26;10(19):4402. doi: 10.3390/jcm10194402. PMID: 34640421; PMCID: PMC8509475.

- **Factor de impacto en 2020:** 4,24
    - Cuartil en categoría Medicina Interna: Q1, posición 39/167, porcentaje 76,95%

Journal of
Clinical Medicine

MDPI

Article

Impact of Biological Agents on Postsurgical Complications in Inflammatory Bowel Disease: A Multicentre Study of Geteccu

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Citation: García, M.J.; Rivero, M.; Miranda-Bautista, J.; Bastón-Rey, I.; Mesonero, F.; Leo-Carnerero, E.; Casas-Deza, D.; Cagigas Fernández, C.; Martin-Cardona, A.; El Hajra, I.; et al. Impact of Biological Agents on Postsurgical Complications in Inflammatory Bowel Disease: A Multicentre Study of Geteccu. *J. Clin. Med.* **2021**, *10*, 4402. https://doi.org/10.3390/jcm10194402

Academic Editor: Jose E. Mesonero

Received: 7 September 2021
Accepted: 24 September 2021
Published: 26 September 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: Background: The impact of biologics on the risk of postoperative complications (PC) in inflammatory bowel disease (IBD) is still an ongoing debate. This lack of evidence is more relevant for ustekinumab and vedolizumab. Aims: To evaluate the impact of biologics on the risk of PC. Methods: A retrospective study was performed in 37 centres. Patients treated with biologics within 12 weeks before surgery were considered "exposed". The impact of the exposure on the risk of 30-day PC and the risk of infections was assessed by logistic regression and propensity score-matched analysis. Results: A total of 1535 surgeries were performed on 1370 patients. Of them, 711 surgeries were conducted in the exposed cohort (584 anti-TNF, 58 vedolizumab and 69 ustekinumab). In the multivariate analysis, male gender (OR: 1.5; 95% CI: 1.2–2.0), urgent surgery (OR: 1.6; 95% CI: 1.2–2.2), laparotomy approach (OR: 1.5; 95% CI: 1.1–1.9) and severe anaemia (OR: 1.8; 95% CI: 1.3–2.6) had higher risk of PC, while academic hospitals had significantly lower risk. Exposure to biologics (either anti-TNF, vedolizumab or ustekinumab) did not increase the risk of PC (OR: 1.2; 95% CI: 0.97–1.58), although it could be a risk factor for postoperative infections (OR 1.5; 95% CI: 1.03–2.27). Conclusion:

Preoperative administration of biologics does not seem to be a risk factor for overall PC, although it may be so for postoperative infections.

Keywords: inflammatory bowel disease; Crohn's disease; ulcerative colitis; anti-TNF; ustekinumab; vedolizumab; postoperative complications; surgery; preoperative therapy

1. Introduction

Inflammatory bowel disease (IBD) management completely changed after the approval by the European Medicines Agency (EMA) of the first anti-tumor necrosis factor (TNF) in 1999 [1]. Since then, biologics have increased the therapeutic armamentarium previously based on corticosteroids, immunomodulators and surgery. The development of these therapies exerted a positive impact on the natural history of IBD and an improvement in the control of inflammation [2]. However, only a proportion of patients respond to medical therapy and surgery still has a fundamental role in the management of IBD [3]. For this reason, 50% of the patients affected by Crohn's disease (CD) and 10–20% of ulcerative colitis (UC) patients require surgery within 10 years after diagnosis [4,5]. Furthermore, 15–20% of those surgeries suffer from postoperative complications, thus preventing these side effects is highly relevant [6,7].

Several risk factors related to postoperative complications have been identified, such as preoperative corticosteroid administration, malnutrition, hypoalbuminemia or other factors associated to the surgical procedure, such as the experience of the surgeon or the surgery approach [8–10]. Regarding preoperative treatment, the preoperative administration of thiopurines or methotrexate does not seem to be associated with a higher risk of postoperative complications [11].

Several studies have evaluated the risk of postoperative complications in patients treated with biologics, mainly anti-TNF, obtaining conflicting results [12,13]. Furthermore, safety data about more recently approved biologics, such as vedolizumab and ustekinumab, in this setting are limited [14,15]. Therefore, the safety of preoperative biological therapy within the preoperative period remains unclear. A high proportion of patients who undergo surgery are using biological agents and, therefore, knowing whether this treatment poses a higher risk of complications is of utmost importance in determining whether to schedule surgery.

Therefore, our aim was to evaluate the impact of preoperative biological therapy (not only anti-TNF but also vedolizumab and ustekinumab) on the risk of postsurgical complications (mainly focused on infections). In addition, we aimed to identify clinical characteristics, surgical procedures and any treatment administered during the preoperative period that might impact on patients' outcomes. Thus, our study will contribute to improve the knowledge of the safety of these treatments during the postoperative period.

2. Materials and Methods

2.1. Study Design and Population

We designed a multicentre retrospective study of patients who required abdominal surgery as treatment for IBD. Patients above 18 years old who required surgery between 1 January 2009 and 31 December 2019 were included. This period was chosen after considering the approval date of IBD biological therapy to establish a homogeneous management of these diseases in Spain. Pregnant women, patients on immunosuppressants for diseases other than IBD, patients on biologicals for diseases other than IBD or patients who underwent surgeries for perianal disease were excluded. In order to establish the risk of these patients, we compared two groups: the exposed cohort, which was comprised of patients whose last dose of biological therapy had been administered at any point during 12 weeks before the date of surgery, and the non-exposed cohort, which was comprised of patients who had not been subjected to any biological therapy in the same period. Once

the surgeries were assigned to each group, the clinical characteristics of both categories were studied and their differences concerning clinical features, biochemical parameters, preoperative treatments and surgical procedures were analysed. Surgeries with and without complications were compared according to the presence of biological therapy during the preoperative period. Postsurgical infections were also separately analysed because they are especially relevant complications.

The study was conducted by the Young Group of the Spanish Working Group of Crohn's disease and Ulcerative Colitis (GETECCU). The study was carried out in accordance to the European General Data Protection Regulation (GDPR) 2016/679 and the Spanish Data Protection Organic Law 3/2018. The protocol was approved by the Research Ethics Committees of each centre and the Spanish Agency of Medicines and Medical Devices (code MJG-VED-2019-01).

2.2. Data Collection

All patients diagnosed with IBD were distributed into three categories, namely CD, UC and IBD-unclassified, according to the recommendations set by the European Crohn and Colitis Organisation (ECCO). The location and the severity of IBD at the time of surgery was recorded according to the Montreal Classification. Data collection included demographic characteristics such as sex, date of birth, IBD diagnosis date, smoking habit at the time of surgery and anthropometric measurements. The Harvey-Bradshaw index and partial Mayo score as well as laboratory parameters including nutritional status were recorded two weeks before the date of surgery. The parameter closer to the date of surgery was chosen when more than one were found in the medical records. Data of corticosteroid, immunomodulator administration previous to the date of surgery were also collected. The biologic agents included during the preoperatory period were infliximab, adalimumab, golimumab, vedolizumab and ustekinumab. Regarding the surgical procedure, indication, whether surgery was urgent or elective, type of surgery, postoperative complications, length of hospital stay, 30-day hospital readmission, 30-day surgical requirements to control complications and 90-day death rate were recorded. Clavien-Dindo classification was used to assess the severity of complications [16]. The centres involved in the study were categorized in 5 levels, according to parameters such as number of hospital beds, local population assigned, the existence of university teaching and available diagnostic tests such as on-site nuclear or radiological techniques, with 5 being the maximum score for these parameters.

Study data were collected by an electronic data capture tool (Research Electronic Data Capture (REDCap), which is hosted by Asociación Española de Gastroenterología (AEG; www.aegastro.es) [17]. AEG provided this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap is a secure, web-based application designed that supports data capture for research studies and provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for importing data from external sources.

2.3. Definitions

- Postoperative complications: the presence of superficial wound infection, intraabdominal infection, urinary tract infection, bacteraemia, respiratory infection, fever above 38 °C of unknown origin, anastomosis leak, mechanical obstruction, postoperative ileus, bleeding, thrombosis, fistula or evisceration during the 30 days after the date of surgery.
- Anaemia: haemoglobin level under 12 g/dL for women and under 13 g/dL for men at any point during the two weeks prior to surgery [18]. Severe anaemia was considered when haemoglobin level was under 10 g/dL regardless of the sex [19].
- Low albumin levels: albumin levels lower than 3 g/dL at any point during the two weeks before the date of surgery [20].

- Low cholesterol levels: serum cholesterol level below 160 mg/dL at any point during the two weeks prior to surgery [10].
- Smoking habit: current smokers included individuals who actively smoked more than seven cigarettes per week, former smokers included individuals who quit smoking more than six months ago and non-smokers included those patients who had never smoked before [21].
- Nutritional risk: a weight loss >10% within six months or body mass index (BMI) <18.5 kg/m^2 [22].

2.4. Statistical Analysis

Quantitative variables are expressed as mean and standard deviation or median and interquartile range, depending on whether they have a normal distribution or not. Qualitative variables are expressed as percentages and 95% confidence intervals (CI). Chi-square test or the Fisher exact test were used to compare qualitative variables, while differences of quantitative variables between the two groups were analysed by the Student *t*-test or the Wilcoxon-rank sum test depending on data distribution. A significant result was considered when the *p*-value was ≤ 0.05 for the overall comparison of both groups (exposed to biological therapy or non-exposed to these drugs). The analysis was performed separately for each variable. Afterwards, a multivariate analysis through binary logistic regression was carried out to compare the risk of every variable with respect to the risk of postoperative complications as well as the risk of postoperative infections. Two models were evaluated: the first model included the perioperative administration of biological therapy as a binary variable, while the second model evaluated the biological therapy in 3 categories (anti-TNF, ustekinumab and vedolizumab). All the variables with a univariate $p < 0.20$ and those that were clinically relevant were evaluated in the multivariate analysis as independent variables while the presence of postoperative complications was considered as the dependent variable. All statistical analyses were performed with STATA Statistical Software: Release 14. StataCorp LP.

A sensitivity analysis through propensity score was performed to evaluate baseline variables that could have an influence on the results. The variables included in the propensity score were those clinically or statistically significant through logistic regression, biological exposure being the dependent variable. The confounding factors included were carefully discussed, evaluated and selected before the data analysis. Surgeries were matched one-to-one through the genetic matching method and the covariates were balanced for both groups [23]. To evaluate the balance of each variable, a graphic representing the means of each covariate compared to the estimated propensity score was made after matching by exposure.

3. Results

3.1. Patient Population

A total of 1535 IBD surgeries in 1370 patients from 37 hospitals were performed. Baseline characteristics of both groups are detailed in Table 1. Overall, in 584 surgery patients had been exposed to anti-TNF before surgery, 58 to vedolizumab and 69 to ustekinumab. In thirty-five percent of the surgeries there was no previous exposure to biological therapy at any point during the disease course, while patients had been treated with one biological treatment in 40% of the surgeries, with two biological treatments in 16.9% and with three or more in 8.3% of the surgeries. Regarding the type of intervention, small bowel surgery was the most frequent in 48.8% of the cases, followed by colonic surgery (26.6%), ileocolonic surgery (19.0%) and restorative surgery (5.6%).

Table 1. Clinical characteristics of the surgeries according to prior exposition to biological therapy. *p*-values were calculated by Chi-square test, *t*-test or Wilcoxon-rank sum.

	Exposed Cohort (*n* = 711)	Non-Exposed Cohort (*n* = 824)	*p*-Value
Gender: male	51.5 (363)	53.8 (443)	0.3
Median age at surgery (years) (mean, SD)	43.57 (13.48)	46.26 (15.36)	<0.001 *
Median age at IBD onset (years) (mean, SD)	33.43 (13.74)	37.40 (16.03)	<0.001 *
Mean duration of IBD until surgery (years) (mean, SD)	10.13 (8.56)	8.85 (9.05)	<0.05 *
Smoking habit (%, *n*) - Current smokers - Former smokers - Non smokers	 25.2 (170) 25.2 (170) 49.7 (336)	 31.6 (242) 18.8 (144) 49.5 (379)	<0.05 *
Type of disease (%, *n*) - Ulcerative colitis - Crohn's disease - IBD-unclassified	 18.76(132) 80.6 (573) 0.8 (6)	 18.1 (149) 80.7 (665) 1.2 (10)	0.76
Location of IBD (%, *n*) - Ulcerative proctitis (UC) - Left-side colitis (UC) -Extensive colitis (UC)	 3.6 (5) 23.2 (32) 73.2 (101)	 0.6 (1) 18.2 (29) 81.1 (129)	0.08
- Ileum (CD) - Colon (CD) - Ileocolonic (CD) - Upper disease (CD)	49.2 (282) 5.8 (33) 45.0 (258) 10.8 (62)	53.4 (355) 7.1 (47) 39.6 (263) 7.5 (50)	0.13
Behaviour of CD at surgery (%, *n*) - Inflammatory - Stricturing - Penetrating	 13.3 (76) 56.5 (324) 30.2 (173)	 16.5 (110) 46.3 (308) 37.1 (247)	<0.05 *
Perianal disease (yes) (%, *n*)	24.4 (140)	17.1 (14)	<0.05 *
Extraintestinal manifestations (yes) (%, *n*)	21.9 (156)	15.7 (129)	<0.05 *
Prior surgery for IBD (yes) (%, *n*)	31.1 (221)	35.8 (295)	0.05
Hospital admission within 3 months prior to surgery (yes) (%, *n*)	43.7 (310)	32.2 (265)	<0.001 *
Partial Mayo Score (mean, SD)	6.89 (2.27)	4.2 (3.04)	<0.001 *
Harvey-Bradshaw Index (mean, SD)	6.56 (3.59)	6.38 (3.28)	0.47
Weight at surgery (kg) (mean, SD)	64.18 (14.23)	65.99 (14.49)	0.08
Weight loss between 6 months and 2 weeks prior to surgery (kg) (mean, SD)	4.52 (8.73)	3.09 (7.18)	<0.05 *
BMI at surgery (mean, SD)	22.81 (4.53)	23.31 (4.48)	0.13
Haemoglobin (gr/dL) (mean, SD)	12.19 (1.98)	12.63 (2.11)	<0.001 *
Lymphocyte count (/mL) (mean, SD)	1895.51 (1096.27)	1702.5 (1013.08)	<0.001 *
C-reactive protein (mg/dL) (mean, SD)	4.53 (13.61)	5.05 (8.43)	0.47
Cholesterol (mg/dL) (mean, SD)	149.60 (43.40)	153.66 (43.52)	0.23
Prealbumin (mg/dL) (mean, SD)	21.84 (9.20)	21.41 (10.35)	0.76
Albumin (mg/dL) (mean, SD)	3.52 (0.70)	3.59 (0.78)	0.14
Malnutrition (yes) (%, *n*)	43.7 (151)	37.53 (158)	0.08
Blood transfusion (yes) (%, *n*)	13.5 (96)	6.9 (57)	<0.001 *
Intravenous iron treatment (yes) (%, *n*)	22.9 (163)	13.0 (107)	<0.001 *
Type of preoperative nutrition support (%, *n*) - No supplementary nutrition - Enteral - Parenteral - Enteral and parenteral	 61.6 (438) 20.4 (145) 9.3 (66) 8.7 (62)	 77.3 (637) 11.5 (95) 8.0 (66) 3.2 (26)	<0.001 *
Corticosteroids (yes) (%, *n*)	38.1 (271)	28.1 (231)	<0.001 *
Immunomodulators (yes) (%, *n*)	43.7 (311)	24.4 (201)	<0.001 *

SD = standard deviation; IBD = inflammatory bowel disease, UC = ulcerative colitis; CD = Crohn's disease; BMI = body mass index; * = statistical significance

3.2. Postoperative Complications

Postoperative complications were observed in 35.6% (95% CI: 33.2–38.1, n = 547) of the surgeries; 37.6% (95% CI: 34.0–41.2) in the exposed cohort and 34.0% (95% CI: 30.7–37.3) in the non-exposed cohort (p = 0.15). The most frequently found postoperative complications were infections, which occurred in 48.0% of the cases, followed by anastomosis leak in 15.6%, postoperative ileus in 12.4% and bleeding in 12.2% of the overall complications. Of surgeries with complications, 83.6% (n = 457) had one complication, 13.7% (n = 75) two complications, 2.2% (n = 12) three complications, and 0.6% (n = 3) more than three complications. According to exposure, 20.8% (n = 148) of postoperative infections were assigned to the exposed cohort and 19.3% (n = 159) to the non-exposed (p = 0.5). Using the Clavien-Dindo classification we grouped the complications according to severity levels; 55.2% (n = 302) of the cases required pharmacologic treatment without surgery, 35.1% (n = 192) needed endoscopic, radiological or surgical intervention and 9.7% (n = 53) of the surgeries presented a life-threating complication. Hospital readmission within 30 days after hospital discharge was needed in 7.2% (n = 110) of the patients and 1.9% (n = 29) required a new surgery. The 90-day mortality rate reached 0.7% (n = 11) of the surgeries. No significant differences in complication rates, Clavien-Dindo classification, type of complication, hospital readmission or the need for a new surgery were observed according to treatment exposure. Detailed data of this analysis is presented in Table 2.

Table 2. Effect of biological treatment on the incidence of postoperative complications calculated by Chi-square test.

	Exposed Cohort	Non-Exposed Cohort	*p*-Value
Overall complications (%, *n*)	37.6 (267)	34.0 (280)	0.15
Superficial wound infection (%, *n*)	7.7 (55)	7.5 (62)	0.8
Intraabdominal infection (%, *n*)	10.4 (74)	9.3 (77)	0.5
Other infections (%, *n*)	3.4 (24)	3.9 (32)	0.5
Anastomosis leak (%, *n*)	7.0 (50)	6.9 (57)	0.9
Bowel obstruction (%, *n*)	2.0 (14)	1.2 (10)	0.2
Postoperative ileus (%, *n*)	6.5 (46)	4.6 (38)	0.1
Bleeding (%, *n*)	5.2 (37)	5.2 (43)	0.9
Thrombosis (%, *n*)	0.4 (3)	0.7 (6)	0.4
Fistula (%, *n*)	0.8 (6)	1.0 (8)	0.8
Evisceration (%, *n*)	0.1 (1)	0.73 (6)	0.09

3.3. Postoperative Complications According to Exposure

When we grouped the cohort according to the exposure, 46.3% (95% CI: 43.8–48.9, n = 711) had received a biological treatment during the preoperative period and 53.7% (95% CI: 51.1–56.2, n = 824) of the surgeries had not. We found that the exposed cohort was composed of younger patients, with lower median age at the time of IBD surgery, higher proportion of stricturing behaviour, perianal disease and extraintestinal manifestations in comparison to the non-exposed cohort. Furthermore, more hospital admissions within three months before the date of surgery were registered in the exposed cohort (43.7% vs. 32.2%, p = 0.001), as well as higher Mayo scores (6.9 points vs. 4.2 points, $p \leq 0.0001$).

According to anthropometric and laboratory parameters, more weight loss within six months prior to surgery and lower levels of haemoglobin were observed in the exposed cohort resulting in an increased use of blood transfusions and intravenous iron in that group. Furthermore, more nutritional support was administered in that cohort, although no differences in cholesterol, albumin and prealbumin levels were observed between both groups (Table 1).

3.4. Predictive Factors Associated with the Appearance of Postoperative Complications

The factors associated with patients experiencing more postoperative complications as determined in the univariate analysis were male gender, age over 40 years at the time of surgery, a diagnosis of UC, severe anaemia, corticosteroid use, higher levels of C-reactive protein (CRP) and nutritional parameters such as low serum cholesterol and albumin levels during the preoperative period (Table 3). Surgical techniques were also analysed, finding higher risk in emergency surgeries, colonic surgeries, pouch surgeries and in those performed by laparotomy (Tables 3 and 4).

Table 3. Clinical and therapeutic features related to the presence of postoperative complications. *p*-values were calculated by Chi-square test, *t*-test or Wilcoxon-rank sum.

		Postoperative Complications (547 Surgeries)	Non-Complications (988 Surgeries)	*p*-Value
Gender (%, *n*)	Men	59.4 (325)	48.7 (481)	<0.001 *
Age at surgery (years) (%, *n*)	Younger than 40	34.9 (191)	44.3 (438)	<0.001 *
	Between 40 and 60	48.0 (262)	40.7 (402)	
	Older than 60	17.2 (94)	15.0 (148)	
Smoking habit (%, *n*)	Current smoker	27.8 (141)	29.0 (271)	0.84
	Former smoker	22.45(114)	21.4 (200)	
	Non smoker	49.7 (252)	49.6 (463)	
Type of disease (%, *n*)	Ulcerative colitis	21.6 (118)	16.5 (163)	<0.05 *
	Crohn's disease	76.6 (419)	82.9 (819)	
	IBD-unclassified	1.8 (10)	0.6 (6)	
Location at surgery (%, *n*)	Extensive colitis	83.0 (98)	74.2 (122)	0.21
	Left-side colitis	15.2 (18)	23.3 (38)	
	Proctitis	1.7 (2)	2.5 (4)	
	Ileal (L1)	44.4 (186)	55.1 (451)	<0.001 *
	Colic (L2)	47.3 (198)	39.4 (323)	
	Ileocolic (L3)	8.4 (35)	5.5 (45)	
	Upper (L4)	8.1 (34)	9.5 (78)	
Behaviour (only CD) (%, *n*)	Inflammatory	18.1 (76)	13.4 (110)	0.07
	Stricturing	48.0 (201)	52.6 (431)	
	Penetrating	33.9 (142)	33.9 (278)	
Perianal disease (%, *n*)	Yes	19.9 (109)	16.7 (165)	0.12
	No	80.1 (438)	83.3 (823)	
Prior IBD surgery (%, *n*)	Yes	35.3 (193)	32.7 (323)	0.3
	No	64.7 (355)	67.3 (665)	
Prior non-IBD surgery (%, *n*)	Yes	18.1 (99)	17.5 (173)	0.77
	No	81.9 (448)	82.5 (815)	
Extraintestinal manifestations (%, *n*)	Yes	19.9 (109)	17.8 (176)	0.3
	No	80.0 (438)	82.2 (812)	
Severe anaemia (%, *n*)	Yes	17.7 (81)	10.0 (81)	<0.001 *
	No	82.3 (376)	90.0 (732)	
Low albumin levels (%, *n*)	Yes	28.7 (93)	14.9 (84)	<0.001 *
	No	71.3 (231)	85.1 (479)	
Low cholesterol levels (%, *n*)	Yes	64.9 (163)	55.8 (235)	<0.05 *
	No	35.1 (88)	44.2. (186)	
Intravenous iron treatment (%, *n*)	Yes	21.4 (117)	15.5 (153)	<0.05 *
	No	78.6 (430)	84.5 (835)	
Blood transfusion (%, *n*)	Yes	15.2 (83)	7.1 (70)	<0.001 *
	No	84.8 (464)	92.9 (918)	
Type of nutritional support (%, *n*)	Enteral	41.4 (72)	58.7 (168)	<0.001 *
	Parenteral	33.3 (58)	25.9 (74)	
	Enteral and parenteral	25.3 (44)	15.4 (44)	
Glucocorticoids (%, *n*)	Yes	36.3 (198)	30.8 (304)	<0.05 *
	No	63.7 (347)	69.2 (683)	

Table 3. *Cont.*

		Postoperative Complications (547 Surgeries)	Non-Complications (988 Surgeries)	*p*-Value
Immunomodulator therapy (%, *n*)	Yes No	32.9 (180) 67.1 (367)	33.6 (332) 66.4 (656)	0.78
Biological therapy (%, *n*)	Yes No	48.8 (267) 51.2 (280)	44.9 (444) 55.1 (544)	0.15
Temporality of surgery (%, *n*)	Urgent Elective	23.8 (130) 76.2 (417)	15.3 (151) 84.7 (837)	<0.001 *
Surgical approach (%, *n*)	Laparotomy Laparoscopy	73.5 (402) 26.5 (145)	67.3 (665) 32.7 (323)	<0.05 *
Hospital level	2nd, 3rd or 4st category 5th Category	42.7 (234) 57.2 (313)	36.6 (362) 63.4 (626)	<0.05 *

IBD = inflammatory bowel disease; CD = Crohn's disease; * = statistical significance

Table 4. Univariate analysis of surgical procedures as risk factors for postsurgical complications calculated by logistic regression.

	Unadjusted Odds Ratio	95% Confidence Interval
Ileocecal resection	0.58	0.47–0.73
Bowel resection	0.90	0.63–1.27
Strictureplasty	1.68	0.70–4.03
Partial colonic resection	1.45	1.03–2.04
Subtotal colectomy	1.62	1.56–2.30
Total colectomy	1.72	1.06–2.79
Proctectomy	1.93	1.29–2.90
Pouch surgery	1.69	1.05–2.70

In the multivariate analysis, the factors that posed a risk for surgical complications were male gender, requirement of urgent surgery, need for laparotomy approach and haemoglobin levels under 10 gr/dL during the preoperative period. In contrast, being operated in centres whose category was 5 led to a reduction in the risk of postoperative complications (Table 5). Regarding the preoperative treatment for IBD, biological therapy was not associated with postoperative complications in the multivariate analysis (OR 1.24; 95% CI: 0.97–1.58).

Focusing on postoperative infections, the multivariate analysis showed that the patients that received biological therapy during the preoperative period were at increased risk of developing postoperative infections, with borderline statistical significance (OR 1.50; 95% CI: 1.03–2.17). Moreover, this result was confirmed in the propensity score, which showed a significant result for postoperative infections in patients exposed to biological therapy during the preoperative period. Other factors that influenced the risk of postoperative infections were high levels of CRP, hypoalbuminaemia, and the requirement of laparotomy (Table 5).

Table 5. Risk factors for postoperative complications and infections in the multivariate analysis calculated by logistic regression.

Postoperative Complications	Adjusted Odds Ratio	95% Confidence Interval
Exposure to biological therapy	1.24	0.97–1.58
Gender: male	1.54	1.21–1.95
Severe anaemia	1.83	1.30–2.57
Urgent surgery	1.61	1.21–2.16
Surgical approach: laparotomy	1.45	1.11–1.90
Hospital level: 5th category	0.69	0.54–0.88
Postoperative Infections	**Adjusted Odds Ratio**	**Confidence Interval 95%**
Exposure to biological therapy	1.50	1.03–2.17
C-reactive protein	1.04	1.01–1.06
Hypoalbuminemia	1.92	1.27–2.90
Surgical approach: laparotomy	2.15	1.39–3.32

3.5. Type of Biological Therapy during the Preoperative Period and Its Impact on Postoperative Complications

As previously mentioned, in the multivariate analysis the use of biological therapy during the preoperative period was not associated with suffering from overall postoperative complications. Furthermore, biological intensification during the preoperative period did not influence postsurgical complications ($p = 0.7$). The groups defined according to prior biological treatment were no biological therapy (584 surgeries), anti-TNF (261 exposed to adalimumab and 323 exposed to infliximab), vedolizumab (58) and ustekinumab (69). Regarding the type of IBD, for UC 101 cases had received anti-TNF, 28 vedolizumab, three ustekinumab and 149 no biological therapy, while for CD 477 had received anti-TNF, 30 vedolizumab, 66 ustekinumab and 665 no biological therapy. Results of the univariate analysis of association between preoperative biological treatment and postsurgical complication are shown in Figure 1 for IBD, UC and CD. In the multivariate analysis, no specific treatment was associated with postoperative complications or infections. Regarding other therapies, no statistically significant differences were found for corticosteroids or immunomodulators during the preoperative period.

3.6. Sensitivity Analysis

The estimation of the exposure to biological therapy during the preoperative period and its influence on postoperative complications and postoperative infections was confirmed in the propensity score matching analysis estimated with the following variables: mean age at surgery, age at IBD onset, average duration of IBD until surgery, extraintestinal manifestations, smoking habit, perianal disease, prior IBD surgery, need for nutritional support, haemoglobin level, and the need for transfusion. In the matched cohort, all standardised differences were below 10%. The means of each covariate compared to the estimated propensity score were represented in graphs, finding no significant differences (Figure 1, supplementary Figure S1). In the matched cohort ORs were 1.4 (95% CI: 0.85–2.33) for postoperative complications and 2.33 (95% CI: 1.12–4.07) for postoperative infections.

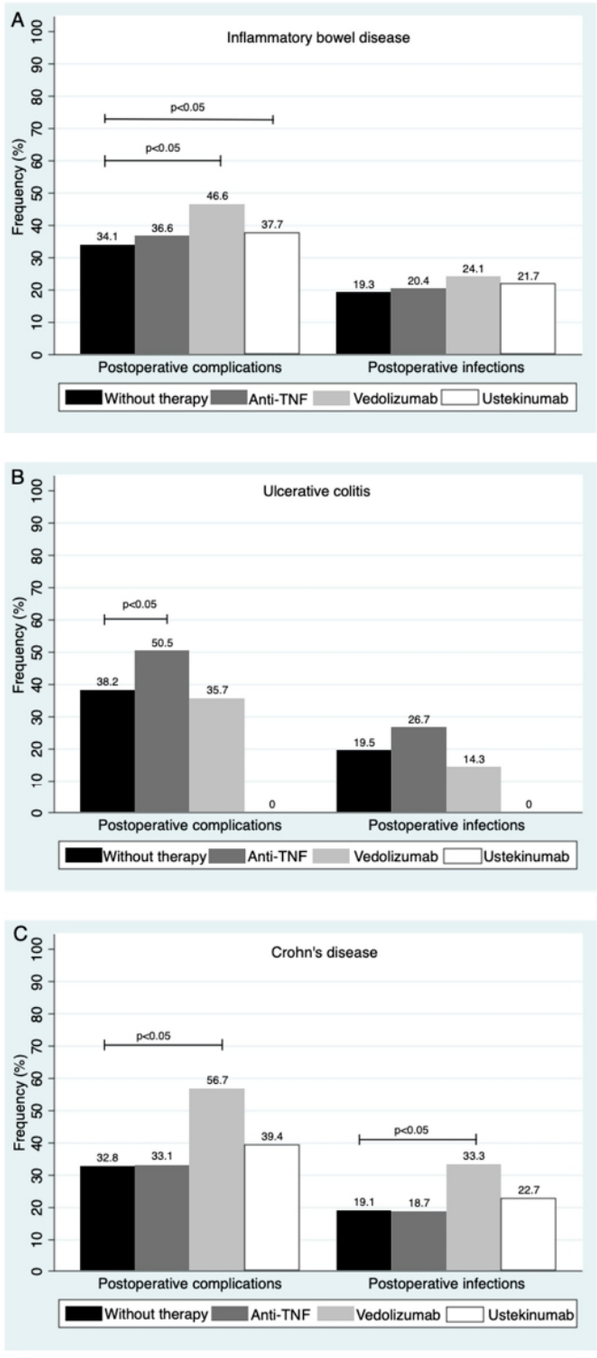

Figure 1. Effect of biological treatment during the preoperative period on frequency of postoperative complications and infections by Chi-square test. (**A**), Inflammatory bowel disease. (**B**), Ulcerative colitis. (**C**), Crohn's disease. Statistically significant differences ($p \leq 0.05$) are indicated in the graphic.

4. Discussion

To our knowledge, this is the largest cohort study that has evaluated the safety of preoperative anti-TNF, vedolizumab or ustekinumab treatments in IBD patients. Our results demonstrate that preoperative administration of biologics is not associated with overall postoperative complications in IBD patients, although it may be a risk factor for

postoperative infections. In the sensitivity analysis, the risk of postoperative complications was similar in the non-matched and the matched cohort so the differences in clinical characteristics do not affect the results of the study.

Although multiple studies have evaluated the risk of biological therapy during the preoperative term, its effect is still under debate. Similar incidences of postoperative complications in patients with or without this therapy was observed in our cohort. The preliminary data of several meta-analyses showed a higher risk of complications in IBD patients treated with anti-TNF, especially in those with CD [24,25]. In contrast to these data, the administration of preoperative infliximab was not related to the appearance of early postoperative complications in recent meta-analyses for CD [26,27]. Furthermore, the only two studies that evaluated this effect prospectively showed that neither anti-TNF administration nor anti-TNF drug levels during the preoperative period was associated with postoperative complications in IBD; therefore, the complete withdrawal of biological therapy during the preoperative period is not necessary to reduce the frequency of postoperative complications [28,29].

Data on recently approved treatments and their implications on the risk of postoperative complications are limited, as comparative studies have only been published since 2017. Our study is the first one analysing anti-TNF, vedolizumab, and ustekinumab, using a cohort of IBD patients with no preoperative biological therapy as control. In our study, no statistical differences were observed in the multivariate analysis between the different types of biological therapy. Only one study compared these treatments, exclusively for CD, and it had similar results [30]. Regarding vedolizumab, previous publications reported that this treatment was not an independent risk factor for developing postoperative complications compared to anti-TNF and ustekinumab [31,32]. However, more postoperative ileus was found after vedolizumab administration during the preoperative period compared to anti-TNF and no biological therapy [33].

Our cohort is also the largest reported to date analysing the preoperative administration of ustekinumab and its effect during the postoperative period. This therapy was recently approved for UC; accordingly, no information concerning its effect on this disease has ever been published. In our cohort only three UC patients were treated with ustekinumab, hence no conclusions could be established. Only two studies evaluated the association between previous ustekinumab administration and complications in CD [34,35]. Based on these preliminary data and according to previous publications, withdrawal of ustekinumab or vedolizumab before a surgical procedure does not seem to be required in routine practice to avoid postoperative complications.

Regarding postoperative infections, the exposure to biological therapy seemed to be an independent risk factor in our patient cohort, although the results only reached borderline statistical significance. A recent meta-analysis revealed a slightly higher incidence of infections in patients under anti-TNF therapy, although this effect was not observed for vedolizumab [36,37]. Discordance of results for anti-TNF agents could be influenced by therapeutic plasma concentrations of anti-TNF at the time of surgery [38]. Regarding vedolizumab and infection complications, only one study linked the preoperative administration of anti-integrins to a higher proportion of superficial wound infections, whereas no association was found in other studies [39–41]. Similarly, ustekinumab administration is not a risk factor for postoperative infections, even though its use was associated with intraabdominal sepsis after surgery in a single-centre study [34,42,43]. It is worth mentioning that, according to other studies, calcineurin inhibitors, thiopurines or methotrexate do not pose a risk for postoperative complications or infections [44,45].

Although one-third of all the patients in the current study had received corticosteroids before surgery, their effect was only detected in the univariate analysis, whereas hypoalbuminaemia was an independent risk factor for suffering from postoperative infections in the multivariate analysis. Corticosteroids are known to be one of the most important factors affecting the incidence of postoperative complications through their effect on wound healing and the bursting pressure of the healing [8,46]. Albumin and nutritional status are

also essential factors to evaluate during preoperatory management, despite the fact that a higher risk of complications has been observed in those patients with mixed or exclusive parenteral nutrition [47]. Of note, corticosteroids and hypoalbuminaemia are intimately associated with other factors involved in postoperative complications such as anaemia, the temporality of surgery or the surgical approach [48–50]. Regarding anaemia, only one study analysed the association between its severity and the risk of complications in IBD [51]. We report that suffering from anaemia before surgery is also a significant risk factor for postoperative complications. Its influence has been also recognized in other diseases such as colorectal cancer, hence the preoperative management of this condition is recommended in IBD [52,53]. Analysing the temporality of the surgery, we observed that urgent surgeries increased the rate of complications compared to elective ones; and the use of the laparotomy approach during surgery also increased complications, as described in previous reports [54–57]. Moreover, infections were linked to high CRP levels in our cohort [58]. For this reason, a balance of risk and benefit has to be assessed, trying to optimize the preoperative status of the patient by a multidisciplinary team, avoiding surgery delays, monitoring clinical condition and performing the surgery in referral centres when possible [59,60].

One of the limitations of our study is retrospective data collection. Also, the postoperative events included as complications depend on their definition in each study, thus their incidence could differ, thereby affecting the results between studies. However, the Clavien-Dindo classification, which has been used as an outcome in previous reports, was used to avoid this limitation by making an effort at standardising our data [61]. Nevertheless, neither patient comorbidity nor the risk associated with the anaesthetic procedure was collected. Another important aspect is the recent approval of vedolizumab or ustekinumab, which limits the number of patients treated with those drugs compared to anti-TNF therapy. On the other hand, a strength of our study is the application of the genetic matched score. The use of this method to compare cohorts improved the quality of our results in comparison to previous studies that did not utilize this analysis. Furthermore, our study is one of the largest cohorts for IBD patients encompassing both different hospital categories and various types of biological therapy. For that reason, our results show real-world postoperative complications and not only those from referral centres.

5. Conclusions

In conclusion, the preoperative administration of biological therapy does not seem to increase the risk for overall postoperative complications in IBD, although it may be a specific risk factor for postoperative infections. The need for urgent surgery, the laparotomy approach, severe anaemia as well as the type of hospital have to be considered as risk factors for developing postoperative complications. Finally, hypoalbuminaemia, the laparotomy approach and higher CPR levels increase the risk of developing postoperative infections.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10194402/s1. Figure S1: Relationship between means and propensity scores for different clinical variables. The blue line represents the non-exposed cohort and the yellow one the exposed cohort.

Author Contributions: M.J.G., M.C. and J.P.G.: study design, data collection, data interpretation, writing the manuscript and final version approval. M.J.G. analysed the data. The rest of authors contributed to patient inclusion and data collection. All the authors discussed the results and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The authors report assistance from Equipo 3datos for the statistical analysis; this support was funded by the Spanish Working Group in Crohn's Disease and Ulcerative Colitis (GETECCU).

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest: María José García has received financial support for travelling and educational activities from MSD, Janssen, Abbvie, Takeda and Ferring. Montserrat Rivero has served as a speaker and advisory member for Abbvie, MSD and Janssen. Manuel Barreiro-De Acosta has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Gillead, Celgene, Pfizer, Sandoz, Biogen, Fresenius, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, Gebro Pharma, Adacyte and Vifor Pharma. Eduardo Leo-Carnerero has served as speaker for and has received research funding from Abbvie, Takeda, Janssen, Ferring and Pfizer. Luis Menchén has served as a speaker or has received research or education funding from MSD, Abbvie, Pfizer, Takeda, Janssen, Ferring, Dr. Falk Pharma, Tillotts Pharma, General Electric, Fresenius, Sandoz and Medtronic. Diego Casas-Deza has received financial support for travelling and educational activities from MSD, Janssen, Ferring, Tillots, Takeda and Abbvie. Albert Martin-Cardona has received financial support for travelling and educational activities from Abbvie, Biogen, Ferring, Jannsen, MSD, Takeda, Dr. Falk Pharma and Tillotts. Yamile Zabana has received support for conference attendance, speaker fees, research support and consulting fees of Abvvie, Adacyte, Almirall, Amgen, Dr. Falk, FAES Pharma, Ferring, Jannsen, MSD, Otsuka, Pfizer, Shire, Takeda and Tillots. Ana Gutiérrez has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Tillotts Pharma, Chiesi and Otsuka Pharmaceutical. Cristina Suárez Ferrer has served as a speaker or has received education funding from MSD, Abbvie, Pfizer, Janssen, Takeda and Ferring. José María Huguet has served as a speaker, or has received research or education funding from MSD, Abbvie, Pfizer, Takeda, Janssen, Sandoz, Ferring and Faes Farma. Luigi Melcarne has served as a speaker has received financial support for educational activities from MSD, Janssen, Abbie, Takeda, Ferring, Dr. Falk, Pfizer, Sandoz, Tillotts Pharma Ferring. José Manuel Benítez has served as a speaker, consultant and advisory member for or has received financial support for educational activities from Dr. Falk Pharma, Faes Farma, Ferring, Shire Pharmaceuticals, MSD, Abbvie, Takeda and Janssen. María Chaparro has served as a speaker, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma. Javier P. Gisbert has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. José Miranda-Bautista, Iria Bastón-Rey, Francisco Mesonero, Carmen Cagigas Fernández, Ismael El Hajra, Nerea Hernández-Aretxabaleta, Isabel Pérez-Martínez, Esteban Fuentes-Valenzuela, Nuria Jiménez, Cristina Rubín de Célix, Agnes Fernández-Clotet, María González-Vivó, Blanca Del Val, Jesús Castro-Poceiro, Carmen Dueñas, Marta Izquierdo, David Monfort, Abdel Bouhmidi, Patricia Ramírez De la Piscina, Eva Romero, Gema Molina, Jaime Zorrilla, Cristina Calvino-Suárez, Eugenia Sánchez, Andrea Nuñez, Olivia Sierra, Beatriz Castro, Irene González-Partida, Saioa De la Maza, Andrés Castaño, Rodrigo Nájera-Muñoz, Luis Sánchez-Guillén, Micaela Riat Castro, José Luis Rueda, Pedro Delgado-Guillena, Carlos Tardillo, Elena Peña, Santiago Frago-Larramona, María Carmen Rodríguez-Grau, Rocío Plaza, Pablo Pérez-Galindo, Jesús Martínez-Cadilla, Rubén Sánchez-Aldehuelo, María Dolores De la Cruz, Ignacio Marín, Laura Nieto-García, Antonio López-San Román, José Manuel Herrera have no conflict of interest to declare.

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Supplementary Material

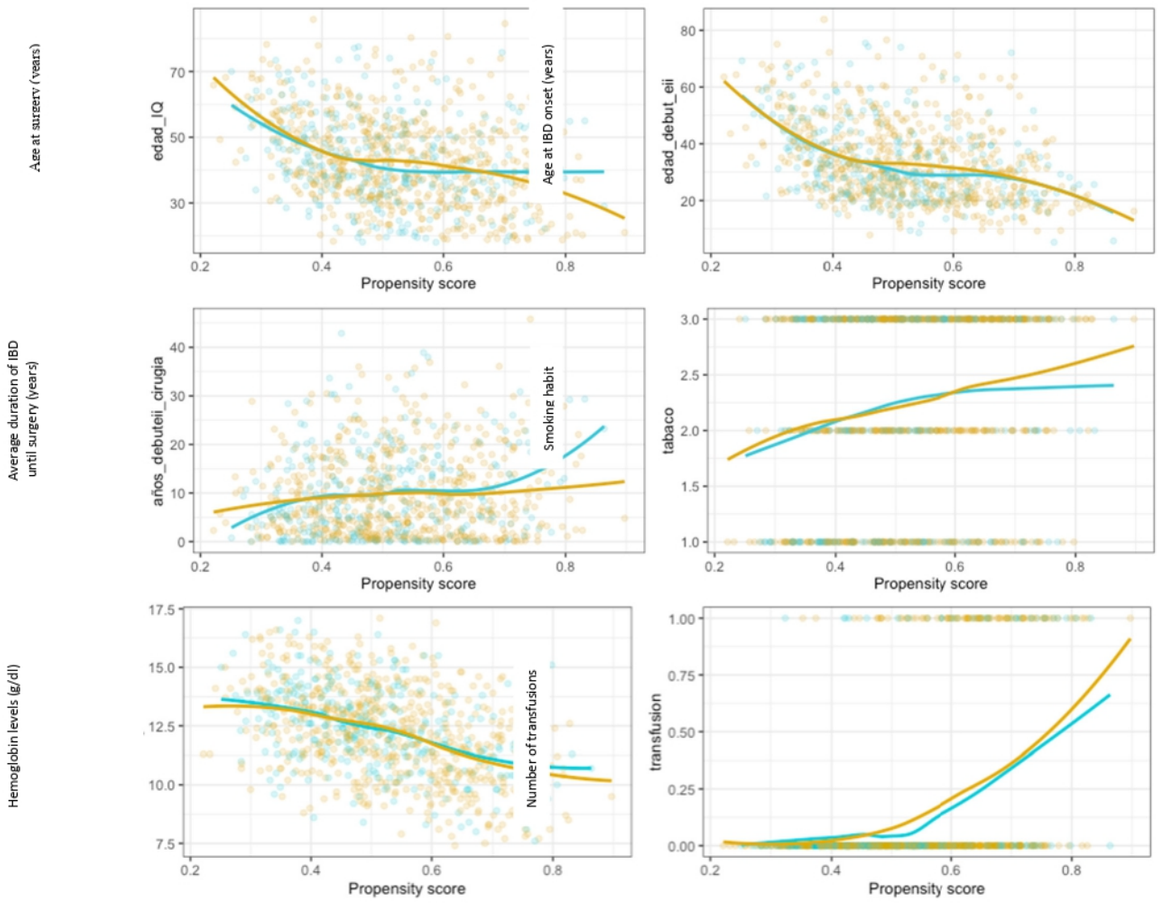


Figure S1. Relationship between means and propensity scores for different clinical variables. The blue line represents the non-exposed cohort and the yellow one the exposed cohort.

4. DISCUSIÓN GLOBAL

4.1 Durabilidad y eficacia del tratamiento: estudio VERSUS

El estudio VERSUS evaluó la eficacia y seguridad de vedolizumab y ustekinumab en pacientes con fracaso previo a anti-TNF, escenario habitual en la práctica clínica diaria. Este estudio agrupa el mayor número de pacientes hasta la fecha de su publicación.

Como objetivo primario, demuestra que ustekinumab tiene una mayor durabilidad después del fracaso de anti-TNF en estos pacientes cuando se compara con vedolizumab. El análisis de sensibilidad tras la realización de índices de propensión confirmó estos resultados. Estudios anteriores han mostrado resultados similares, con una menor suspensión en pacientes tratados con ustekinumab que con vedolizumab.[103,104] Además, otros estudios de cohortes han demostrado estos mismos resultados cuando se compara con otros tratamientos como infliximab y adalimumab de forma independiente, aunque estos resultados tienen que interpretarse con cautela al ser un estudio que no considera el número de línea y el fracaso a los tratamientos previos.[122]

Los motivos de suspensión fueron principalmente el fallo de respuesta primaria y la pérdida de respuesta secundaria, presentando de forma global mayor suspensión durante el periodo de inducción y disminuyendo progresivamente durante la fase de mantenimiento. La intensificación de los fármacos es una estrategia que se ha implementado paulatinamente en la práctica clínica como extrapolación de lo realizado con los fármacos anti-TNF.[123] Hasta la fecha de la publicación, sólo algunos estudios evaluaban la eficacia de la intensificación con los fármacos nuevos como vedolizumab y ustekinumab.[124,125] En nuestro estudio, la intensificación mejoró las tasas de persistencia del tratamiento en pacientes con pérdida secundaria, principalmente a ustekinumab.

Como objetivo secundario se analizó la eficacia en vida real, aspecto de suma importancia en la clínica. Ustekinumab demostró una mayor eficacia a corto plazo comparado con vedolizumab, con una tasa de remisión a las 16 semanas más alta (39% vs 24%). A un año, ustekinumab mantuvo tasas de remisión más altas que vedolizumab (48% vs 32%) y estos resultados se mantuvieron 2 años y medio después del inicio del tratamiento. Pese al corto tiempo de seguimiento a largo plazo de otros estudios publicados, Manlay et al. evaluaron este objetivo a 16 meses tras el inicio del tratamiento con resultados similares a los nuestros.[106] Hay que tener en cuenta que, en nuestros resultados, la reducción del tamaño muestral por pérdida de pacientes a lo largo del tiempo condiciona la detección de diferencias significativas después de estos 2 años y medio.

En conclusión, el tratamiento con ustekinumab es superior en términos de durabilidad y eficacia tanto a corto como a largo plazo en pacientes con enfermedad de Crohn después del fracaso de anti-TNF cuando se compara con vedolizumab.

4.2 Seguridad de tratamiento

La seguridad de los fármacos se evaluó en dos escenarios frecuentes en la práctica clínica diaria.

- Durante el tratamiento médico mediante el estudio VERSUS
- Durante el periodo postoperatorio mediante el estudio POSTSURG

4.2.1 Estudio VERSUS

En el estudio VERSUS se observó un buen perfil de seguridad para ambos fármacos, sin existir diferencias entre vedolizumab y ustekinumab. Los ensayos clínicos a largo plazo y los estudios en la vida real de vedolizumab objetivaron una tasa de eventos adversos de 11 por 100 años-persona.[91,126] En nuestro estudio estas tasas fueron menores con una incidencia de 6,6 por 100 años-persona en el caso de vedolizumab y de 5,3 por 100 años-persona en el caso de ustekinumab. En el caso de vedolizumab, los eventos adversos más frecuentes fueron las infecciones y el empeoramiento de otras enfermedades inmunomediadas, probablemente debido al mecanismo de acción selectivo de las integrinas y, por tanto, a la ausencia de eficacia en determinadas enfermedades extraintestinales y/o inmunomediadas.[127,128] En el caso de ustekinumab, los más frecuentes fueron las infecciones, las artralgias y la cefalea de forma similar a previas publicaciones.[129]

La mayoría de los estudios sólo evalúan la seguridad durante el tratamiento médico en diversas circunstancias y situaciones. Sin embargo, aunque bien es cierto que la seguridad no es la misma en todos los pacientes, variando en pacientes frágiles, de edad avanzada y con enfermedad agresiva o factores de riesgo como la enfermedad fistulizante o perianal.[130,131] Además, existe otra circunstancia que es de vital importancia que podría modificar el riesgo de estos fármacos: el periodo preoperatorio.[132] La cirugía sigue siendo una opción terapéutica muy

frecuente en enfermedad refractaria a fármacos anti-TNF, especialmente en las fechas en las que se publicaron estos artículos, entre los que se incluye la persistencia de enfermedad activa pese al tratamiento con vedolizumab o ustekinumab.

4.2.2 Estudio POSTSURG

La evaluación de la seguridad de vedolizumab y ustekinumab durante el periodo preoperatorio y su implicación en el desarrollo posterior de complicaciones postoperatorias se evaluó en el estudio POSTSURG. En este caso, se evaluaron también de forma paralela el riesgo de complicaciones postoperatorias en pacientes tratados con fármacos anti-TNF durante el periodo preoperatorio y se comparó con una cohorte sin tratamiento biológico durante este periodo debido a resultados contradictorios en los distintos estudios publicados hasta esa fecha.[133]

Como resultado principal, nuestro estudio demuestra que la administración preoperatoria de fármacos biológicos no se asocia con complicaciones postoperatorias generales en pacientes con enfermedad inflamatoria intestinal, debido a que se observaron incidencias similares de complicaciones durante el periodo postoperatorio. Respecto a los fármacos anti-TNF, los resultados de metaanálisis iniciales sugirieron mayor riesgo de complicaciones en pacientes tratados con anti-TNF, especialmente en pacientes con enfermedad de Crohn. Sin embargo, publicaciones posteriores no objetivaron asociación entre la administración preoperatoria de anti-TNF con la aparición de complicaciones postoperatorias en estos pacientes. Los únicos dos estudios que evaluaron prospectivamente este efecto no demostraron que ninguno de los anti-TNF administración de fármacos anti-TNF durante el período preoperatorio se asocie con complicaciones postoperatorias en la enfermedad

inflamatoria intestinal. Por lo tanto, la retirada de estos fármacos previo a una intervención quirúrgica no disminuye la frecuencia o gravedad de las complicaciones postoperatorias.

Nuestro estudio es el primero en el que se analizan anti-TNF, vedolizumab y ustekinumab, utilizando como control una cohorte de pacientes con enfermedad inflamatoria intestinal sin tratamiento biológico preoperatorio. Nuestros resultados confirman que estos fármacos, independientemente del fármaco analizado, no se asocian con un mayor riesgo de complicaciones postoperatorias en el análisis multivariado. Sólo un estudio en pacientes con enfermedad de Crohn analiza los diferentes fármacos y su riesgo con resultados similares a los nuestros.[134]

Respecto a los resultados de estudios publicados sobre vedolizumab, no se identificó que este fármaco fuese un factor de riesgo independiente para el desarrollo de complicaciones postoperatorias.[116] Sin embargo, existe un único estudio donde se observa un aumento de incidencia de íleo postoperatorio en pacientes que recibieron vedolizumab durante el período preoperatorio cuando se compara con anti-TNF y pacientes no expuestos a tratamiento biológico.[117]

En nuestro estudio, se presenta la serie más amplia de pacientes tratados con ustekinumab en el periodo preoperatorio hasta la fecha de su publicación y su impacto en el periodo postoperatorio en enfermedad de Crohn. Solo dos estudios evaluaron la asociación entre la administración previa de ustekinumab y las complicaciones en la EC sin encontrar relación.[135,136] Respecto a los datos de colitis ulcerosa, sólo tres pacientes con este tratamiento estaban incluidos en nuestro estudio debido a su reciente aprobación para colitis ulcerosa. Por

tanto, pese a que no existen otras publicaciones en esta enfermedad, no se pudieron establecer conclusiones respecto a la asociación en esta enfermedad.

Aunque la exposición durante el periodo preoperatorio de los fármacos biológicos no se asoció en nuestro estudio a mayor riesgo de complicaciones postoperatorias, se detectaron otros factores de riesgo que sí se asociaron a complicaciones. Entre ellos, la realización de las cirugías de forma urgente o mediante laparotomía aumentó la tasa de complicaciones respecto a aquellos pacientes que se sometieron cirugías electivas o al abordaje laparoscópico. Estos factores ya han sido descritos en publicaciones previas.[137,138]. Dependiendo de la necesidad y estado del paciente en ese momento, hay factores que no se pueden modificar y mejorar desde el punto de vista preoperatorio como el tipo de abordaje quirúrgico o la realización urgente o electiva. Sin embargo, hay otros factores que podemos modificar más fácilmente, entre ellos, la anemia. La anemia severa es el factor que se asoció a complicaciones postoperatorias en nuestro estudio. En enfermedad inflamatoria intestinal, sólo existe un estudio publicado donde se observa una asociación entre la gravedad de ésta y el riesgo de complicaciones. [139] Sin embargo, es bien conocida su influencia durante el periodo preoperatorio de otras enfermedades recomendándose su optimización antes del tratamiento quirúrgico.[140,141] Uno de los factores relacionados con las complicaciones postoperatorios fue el nivel hospitalario del centro donde se realizaba la cirugía. Por ello, es recomendable la derivación de pacientes a centros con experiencia en el manejo de estos pacientes si la situación clínica lo permite.

Las infecciones en el periodo postoperatorio son las complicaciones más frecuentes en todos los artículos publicados por lo que tienen especial interés. En nuestra cohorte de pacientes, la exposición en periodo preoperatorio a fármacos biológicos se asoció con un mayor

riesgo de infecciones postoperatorias, aunque la significación estadística estuvo en el límite. Publicaciones de metaanálisis revelaron una incidencia ligeramente mayor de infecciones en pacientes en tratamiento con anti-TNF, pero este efecto no se observó con vedolizumab.[142] Sin embargo, sólo se ha observado un estudio que relacione la administración preoperatoria de anti-integrinas con una mayor proporción de infecciones superficiales de la herida, mientras que en otros no se ha observado ningún tipo de asociación [114,118]. Del mismo modo, la administración de ustekinumab no es un factor de riesgo para infecciones postoperatorias, a pesar de que su uso se asoció con sepsis intraabdominal después de la cirugía en un estudio de un único centro.[121,143] La hipoalbuminemia y los niveles elevados de proteína C reactiva, como reflejo de actividad inflamatoria, fueron factores determinantes para tener un mayor riesgo de infecciones en nuestro estudio.[144] Por este motivo, es imprescindible valorar los riesgos y beneficios, tratando de optimizar el estado preoperatorio del paciente por parte de un equipo multidisciplinar, evitar retrasos en el procedimiento quirúrgico, monitorizar el estado clínico y realizar la cirugía en centros de referencia cuando sea posible para evitar complicaciones.[145]

4.3 Limitaciones y fortalezas

4.3.1 Estudio VERSUS

Nuestro estudio tiene algunas limitaciones. Cabe destacar que, aunque ENEIDA es una base de datos mantenida prospectivamente, pero algunos parámetros como la proteína C reactiva, la hemoglobina, la calprotectina fecal o el índice de Harvey-Bradshaw no se incluyen en el registro. Al no utilizarse un protocolo predefinido para el manejo de los pacientes, las pruebas de laboratorio no se realizaron de forma rutinaria. En consecuencia, estos parámetros analíticos no estaban disponibles en todos los pacientes lo que puede dificultar su interpretación. Otra de las limitaciones es la falta monitorización en la cicatrización de la mucosa, sólo disponible en algunos pacientes. Esta actitud refleja la práctica clínica, donde solo los pacientes con una respuesta subóptima, con ausencia o pérdida de respuesta suelen ser evaluados para determinar la persistencia de la inflamación de la mucosa. Hay que tener en cuenta que el grupo que recibió vedolizumab presentaba algunos datos de mayor gravedad como la existencia de cirugía previa por enfermedad inflamatoria intestinal, un número mayor de fármacos anti-TNF previo, mayor tasa de corticoides al inicio del estudio, niveles más altos de proteína C reactiva y niveles más bajos de hemoglobina. Además, al ser un estudio de práctica clínica, la dosis extra de vedolizumab no se administró a todos los pacientes de forma sistemática. EL carácter retrospectivo limita la obtención de medidas de resultados informados por el paciente o “patient-reported outcome measures, PROMS”. Un aspecto interesante a valorar es el análisis de coste-efectividad de ambas estrategias que, debido a las limitaciones del sistema nacional de salud con diferentes costes según los hospitales y áreas de salud es difícil de estandarizar, lo que podría afectar a la generalización de los resultados y la toma de decisiones. Sin embargo y a pesar de estas limitaciones, los resultados obtenidos tras la realización de la ponderación

de la inversa de la probabilidad del tratamiento confirmaron que la durabilidad del ustekinumab fue mayor que la del vedolizumab.

Por otra parte, nuestro estudio tiene fortalezas importantes. En primer lugar, este estudio es la cohorte más grande publicada hasta la fecha de la publicación que compara la durabilidad de vedolizumab y ustekinumab en la vida real. En segundo lugar, incluye el mayor tiempo de seguimiento evaluado, con una mediana de 4,7 años para vedolizumab y de 2,8 años para ustekinumab. Además, las diferencias en las características basales entre los dos grupos se equilibraron mediante la ponderación de la inversa de la probabilidad evitando su influencia en los resultados. Otra fortaleza es la inclusión de pacientes que requirieron dosis intensificadas durante el seguimiento. La intensificación es una estrategia común en el manejo de estos pacientes ante una pérdida de respuesta, por lo que nuestro estudio refleja de forma fehaciente la durabilidad de ambos tratamientos en la práctica clínica real. Por último, se trata de un estudio multicéntrico que incluye datos de 30 centros nacionales, lo que permite una muestra más diversa y representativa, mejora la generalización de los resultados y proporciona resultados más aplicables a la práctica clínica habitual.

El estudio VERSUS aporta información relevante sobre la durabilidad de vedolizumab y ustekinumab, con un diseño sólido y representativo de la práctica clínica real. Su amplia cohorte, el ajuste estadístico de diferencias basales y la inclusión de estrategias de intensificación refuerzan la aplicabilidad de los hallazgos en la toma de decisiones clínicas.

4.3.2. Estudio POSTSURG

Una de las limitaciones de nuestro estudio es la recogida retrospectiva de datos. Además, la incidencia de los eventos considerados complicaciones postoperatorias podrían diferir entre los distintos estudios, ya que dependen de la definición realizada en cada estudio, pudiendo influir en los resultados. Sin embargo, en nuestro estudio se utilizó la clasificación Clavien-Dindo, que evalúa las complicaciones en este ámbito, se utilizó para evitar esta limitación permitiendo estandarizar y comparar nuestros datos con otros estudios. Otra de las limitaciones es la ausencia de otros parámetros que pudieran influir en las complicaciones como la comorbilidad del paciente o el riesgo asociado al procedimiento anestésico. La reciente aprobación de vedolizumab o ustekinumab provoca que el número de pacientes tratados con estos fármacos sea menor cuando se comparan con los tratamientos anti-TNF, un hecho que podría reducir la capacidad de detectar diferencias significativas entre grupos a largo plazo.

Como fortalezas de este estudio debemos destacar que presentamos la cohorte más grande hasta la fecha de publicación que compara los pacientes tratados con anti-TNF, vedolizumab y ustekinumab. Por otro lado, uno de los puntos fuertes de nuestro estudio es la utilización del apareamiento por índices de propensión. Este método nos permitió comparar cohortes equilibrando características que no habían sido igualadas en estudios previos debido a la no utilización de esta técnica. Además, nuestro estudio es una de las cohortes más grandes de pacientes con enfermedad inflamatoria intestinal que abarca hospitales de diferentes niveles, así como varios tipos de tratamientos biológicos. Esto permite que nuestros resultados representen las complicaciones postoperatorias de la práctica clínica habitual y no solo las de los centros de referencia.

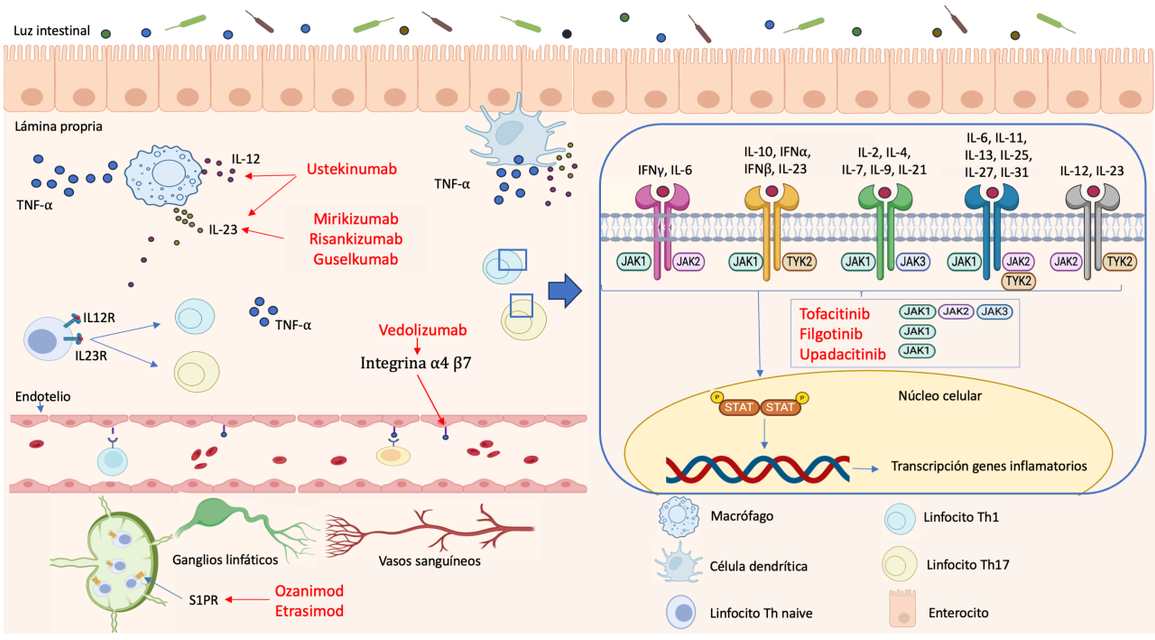
4.4 Otras líneas de investigación realizadas sobre fármacos en enfermedad inflamatoria intestinal

4.4.1 Contexto actual

Desde el 2014, momento en el que se aprobó vedolizumab para la colitis ulcerosa, y en un periodo de 10 años se han aprobado numerosos fármacos en la enfermedad inflamatoria intestinal, entre los que se encuentran fármacos con diferentes mecanismos de acción y dianas terapéuticas entre los que se incluyen los inhibidores de janus quinasas (JAK), IL-23, los moduladores de los receptores de esfingosina-1-fosfato (S1P) y los anticuerpos contra la citoquina 1A similar al TNF.[146] Además, están en desarrollo en estadios preclínicos otras moléculas terapias celulares como las CAR-T y tratamientos células T reguladoras.[148] En la figura 4 se describen los mecanismos inhibitorios de los nuevos fármacos aprobados en enfermedad inflamatoria intestinal. Los ensayos clínicos que han facilitado su aprobación se describen en la tabla 9.

Estamos viviendo una época de gran cambio en el manejo terapéutico de esta enfermedad, con grandes cambios en el algoritmo terapéutico, lo que hace especialmente interesante su estudio. A esto hay que añadir la aparición de otras formas de tratamiento como el tratamiento secuencial o el tratamiento combinado entre fármacos avanzados.[149] La combinación de tratamientos es una práctica habitual en la enfermedad inflamatoria intestinal entre corticoides, inmunomoduladores y un fármaco biológico. Sin embargo, en los próximos años probablemente se conocerán más datos sobre la combinación de más de un fármaco biológico y/o otras moléculas pequeñas.

Figura 4. Vías inmunológicas y dianas terapéuticas de los fármacos biológicos aprobados desde 2014 como tratamiento de la enfermedad inflamatoria intestinal.



Fuente: elaboración de la autora. Realizado en Biorender.com

Abreviaturas: TNF: factor de necrosis tumoral, IL: interleucina, IFN: interferón, JAK: janus quinasa, TYK: tirosina quinasa, S1PR: receptor de esfingosina 1 fosfato

Tabla 9. Resultados de los ensayos clínicos de fase 3 de las nuevas moléculas aprobadas para el tratamiento de la enfermedad inflamatoria intestinal

	Tipo de ensayo clínico	Ramas de tratamiento	Eficacia	Seguridad
IL-23: mirikizumab[150]	Doble ciego, aleatorizado Fase 3. CU	Inducción: - 300 mg ev semana 0, 4 y 8 - Placebo Mantenimiento: - 200 mg sc cada 2 semanas	- Remisión clínica semana 12 vs. placebo: 24% vs. 13% (p<0,001) - Remisión clínica semana 52 vs. placebo: 50% vs. 25% (p<0,001)	No diferencias entre los grupos
IL-23: risankizumab[151]	Doble ciego, aleatorizado Fase 3. EC	- 600 mg ev dosis única - 1200 mg ev dosis única - Placebo	Remisión clínica semana 12 (p<0,001) - 600 mg: 45% - 1200 mg: 42% - Placebo: 25%	No diferencias entre grupos
Inhibidores JAK: tofacitinib[152]	Doble ciego, aleatorizado Fase 3. CU	- 10 mg vo cada 12 horas - 5 mg vo cada 12 horas - Placebo	Remisión semana 8, vs. placebo - 19% vs. 8%, p<0,007 - 17% vs. 4%, p<0,001	No diferencias entre grupos

Inhibidores JAK: filgotinib[153]	Doble ciego, aleatorizado Fase 2. EC	- 200 mg vo cada 24 horas - Placebo	Remisión clínica semana 10: - 47% vs. 23% (p<0,005)	No diferencias entre grupos
Inhibidores JAK: filgotinib[154]	Doble ciego, aleatorizado Fase 3. CU	- 200 mg vo cada 24 horas - 100 mg vo cada 24 horas - Placebo	Remisión clínica adaptada semana 10 (clínica más endoscópica) vs. placebo <u>No expuestos a biológicos:</u> - 200 mg: 26% vs. 15% (p= 0,02) - 100 mg: 19% vs. 15% (p=0,3) <u>Expuestos a biológicos:</u> - 200 mg: 12% vs. 4% (p=0,01) - 100 mg: 10% vs. 4% (p=0,06)	No diferencias entre las distintas ramas
Inhibidores de JAK: upadacitinib[155]	Doble ciego, aleatorizado Fase 3, EC	Inducción: - 45 mg vo cada 24 horas - Placebo Mantenimiento: - 30 mg vo cada 24 horas	Remisión clínica adaptada semana 12 (clínica y endoscópica): - 50% vs. 29% (p=0,0001) Remisión clínica semana 52 (vs. placebo):	No diferencias entre grupos

		- 15 mg vo cada 24 horas - Placebo	- 48% vs. 4% (p<0,001) - 37% vs. 4% (p<0,001)	
Inhibidores JAK: upadacitinib[156]	Doble ciego, aleatorizado Fase 3, CU	Inducción - 45 mg vo cada 24 horas - Placebo Mantenimiento: - 30 mg cada 24 horas - 15 mg cada 24 horas - Placebo	Remisión clínica adaptada semana 8 (clínica y endoscópica): - 33% vs. 4% (p=0,0001) Remisión clínica semana 52 (vs. placebo): - 52% vs. 12% (p=0,0001) - 42% vs.15% (p=0,0001)	No diferencias entre grupos
Moduladores de S1PR: etrasimod[157]	Doble ciego, aleatorizado Fase 3, CU	- 2 mg vo cada 24 horas - Placebo	Remisión clínica adaptada semana 12 (clínica y endoscópica): - 25% vs. 15% (0=0,03) Remisión clínica adaptada semana 52 (clínica y endoscópica): - 32% vs. 7% (p<0,0001)	No diferencias entre grupos

Moduladores de S1PR: ozanimod[158]	Observador ciego, un solo grupo Fase 2, EC	- 0,25 mg vo cada 24 horas 4 días-> 0,5 mg vo cada 24 horas 3 días -> 1 mg vo cada 24 horas posteriormente	Reducción SES-CD media -2,2 (DE 6)	Buen perfil de seguridad
Moduladores de S1PR: ozanimod[159]	Doble ciego, aleatorizado Fase 3, CU	- 1 mg vo cada 24 horas - Placebo	Remisión clínica adaptada (clínica y endoscópica) semana 10: - 18% vs. 6% (p<0,001) Remisión clínica adaptada (clínica y endoscópica) semana 52: - 37% vs. 19% (p<0,001)	Más EA en la rama de tratamiento durante la fase de mantenimiento (49% vs. 37%). No diferencias en EA graves.

Abreviaturas: IL: interleucina, UC: colitis ulcerosa, ev: endovenoso, EC: enfermedad de Crohn, JAK: quinasa, S1PR: receptor de esfingosina 1 fosfato, mg: miligramos, vo: vía oral, SES-CD: índice endoscópico simple de actividad en enfermedad de Crohn, DE: desviación estándar, EA: efectos adversos

4.4.2 Estudio REASUC

La complejidad del tratamiento de la enfermedad inflamatoria intestinal no sólo radica en la elección del fármaco. Existen múltiples presentaciones de las enfermedades, pacientes con diferentes grados de inmunosupresión, otras comorbilidades que dificultan el manejo entre las que se pueden destacar la fragilidad y los procesos oncológicos y, la frecuente asociación de diferentes enfermedades inmunomediadas.[160] Esto ocasiona que la eficacia y seguridad de los tratamientos varíe en los distintos escenarios. Una de estas formas de presentación es el brote grave de colitis ulcerosa donde tras el fracaso de corticoides y una segunda línea terapéutica con infliximab o ciclosporina, la colectomía se posicionaba como la única opción viable hasta hace unos años. Sin embargo, la colectomía, especialmente cuando se realiza como un procedimiento de emergencia, se ha asociado a mayores tasas de complicaciones médicas y postoperatorias. Estas complicaciones incluyen disminución de la calidad de vida posterior, disminución de la fertilidad, morbilidad psicológica y otros problemas relacionados con la bolsa de colostomía.29–31 Por ello, los objetivos del tratamiento hospitalario de la colitis ulcerosa grave son evitar la colectomía y prevenir las complicaciones.

En pacientes que presentan un brote grave de colitis ulcerosa, refractario a corticoides y ante el fracaso de infliximab o ciclosporina, se podría valorar de forma individualizada, considerando el estado del paciente y la experiencia del centro, la administración de un tratamiento de rescate secuencial. Sin embargo, esta estrategia se asocia con una morbimortalidad no despreciable y deberían valorarse los riesgos y beneficios en un equipo multidisciplinar y con el propio paciente 6,7. Sólo se han publicado series de casos clínicos que evalúen la eficacia de vedolizumab, ustekinumab e inhibidores de JAK como tratamiento del brote grave de colitis ulcerosa. Por ello, en el siguiente estudio se valoró la tasa libre de colectomía y la seguridad de una tercera línea de tratamiento en enfermedad refractaria a corticoides y con fracaso a infliximab o ciclosporina.

Detalles de la publicación

- **Título:** Effectiveness and safety of a third-line rescue treatment for acute severe ulcerative colitis refractory to infliximab or ciclosporin (REASUC study)

- **Autores:** María José García, Sabino Riestra, Aurelien Amiot, Mette Julsgaard, Irene García de la Filia, Margalida Calafat, Mariam Aguas, Luisa de la Peña, Cristina Roig, Berta Caballol, María José Casanova, Klaudia Farkas, Trine Boysen, Luis Bujanda, Camila Cuarán, Daniela Dobru, Fotios Fousekis, Carla Jerusalén Gargallo-Puyuelo, Edoardo Savarino, Xavier Calvet, José María Huguet, Limas Kupcinskas, Julia López-Cardona, Tim Raine, Joep van Oostrom, Javier P. Gisbert, María Chaparro.

- **Revista**: Aliment Pharmacol Ther. 2024 May;59(10):1248-1259. DOI: 10.1111/apt.17938. PMID: 38445785

- **Factor de impacto en 2024:** 6,6
  - Cuartil en Farmacia y Farmacología: D1, posición 21/354, percentil 94,2%
  - Cuartil en Aparato Digestivo: Q1, posición 18 /143, percentil 87,8%

- **Abstract:**
  - Background: The advent of new therapeutic agents and the improvement of supporting care might change the management of acute severe ulcerative colitis (ASUC) and avoid colectomy.
  - Aims: To evaluate the colectomy-free survival and safety of a third-line treatment in patients with ASUC refractory to intravenous steroids and who failed either infliximab or ciclosporin.

- Methods: Multicentre retrospective cohort study of patients with ASUC refractory to intravenous steroids who had failed infliximab or ciclosporin and received a third-line treatment during the same hospitalization. Patients who stopped second-line treatment due to disease activity or adverse events (AEs) were eligible. We assessed short-term colectomy-free survival by logistic regression analysis. Kaplan-Meier curves and Cox regression models were used for long-term assessment.

- Results: Among 78 patients, 32 received infliximab and 46 ciclosporin as second-line rescue treatment. Third-line treatment was infliximab in 45 (58%), ciclosporin in 17 (22%), tofacitinib in 13 (17%) and ustekinumab in 3 (3.8%). Colectomy was performed in 29 patients (37%) during follow-up (median 21 weeks). Of the 78 patients, 32 and 18 were in clinical remission at, respectively, 12 and 52 weeks. At the last visit, 25 patients were still on third-line rescue treatment, while 12 had stopped it due to clinical remission. AEs were reported in 26 (33%) patients. Two patients died (2.6%), including one following colectomy.

- Conclusion: Third-line rescue treatment avoided colectomy in over half of the patients with ASUC and may be considered a therapeutic strategy.

4.4.3 Estudio UREAL

Como hemos visto, existen múltiples fármacos de reciente aprobación o que se aprobarán en los próximos años. Entre estos fármacos se encuentra upadacitinib, un anti-JAK selectivo con inhibición predominante de la proteína JAK 1.[161] En julio de 2022, la Agencia Europea del Medicamento aprobó este fármaco como tratamiento de la colitis ulcerosa y en abril 2023 como tratamiento de la enfermedad de Crohn.

Upadacitinib ha demostrado, en ensayos clínicos aleatorizados, su superioridad sobre placebo para inducir y mantener la remisión en pacientes con enfermedad de Crohn y colitis ulcerosa, tanto en pacientes naive como tras fracaso de a agentes biológicos previos.[156,162] Sin embargo, los resultados de los ensayos clínicos deben confirmarse en la práctica clínica. Como hemos comentado previamente, el uso de fármacos en los ensayos clínicos difiere al de práctica clínica habitual en varios aspectos, como las características de los pacientes, entre las que se incluyen la mayor refractariedad a los tratamientos previos y la comorbilidad, lo que limita la generalización de los resultados de los ensayos clínicos. En este sentido, los estudios de práctica habitual son cruciales para conocer el beneficio real de un determinado fármaco y proporcionar información complementaria a los ensayos clínicos sobre la eficacia y seguridad de los tratamientos en entornos reales.

Por ello, y ante la escasa evidencia científica actual, se realizó un estudio retrospectivo multicéntrico cuyo objetivo era evaluar la durabilidad, eficacia y seguridad de upadacitinib en pacientes con enfermedad de Crohn y colitis ulcerosa.

Detalles de la publicación

- **Título**: Persistence, effectiveness, and safety of upadacitinib in Crohn's disease and ulcerative colitis in real life: results from a Spanish nationwide study (UREAL study)

- **Autores**: María José García, Yanire Brenes, Miren Vicuña, Fernando Bermejo, Mónica Sierra-Ausín, Raquel Vicente, María Teresa Arroyo, Pilar Martínez Montiel, Albert Villoria, Juan Ángel Ferrer, Vicent Hernández, Alexis Piñero, Marta Carrillo-Palau, María Dolores Martín-Arranz, José Miranda-Bautista, Ramón Pajares, Laura Arranz Hernández, Ana Bejarano, Jordi Guardiola, Eduardo Iyo, Carmen Muñoz-Villafranca, Aurora Talavera, Horacio Alonso-Galán, Manuel Barreiro-de Acosta, Maia Bosca-Watts, Teresa Vázquez Rey, Ana Echarri, María del Carmen Rodríguez-Grau, Ana Gutiérrez, José María Huguet, M. Carmen López-Martín, Francisco Mesonero, Isabel Pérez-Martínez, Rocío Plaza., Patricia Ramírez de la Piscina, Javier P. Gisbert, María Chaparro.

- **Revista**: Am J Gastroenterol 2024, Am J Gastroenterol. 2024 Nov 26 doi: 10.14309/ajg.0000000000003243. Epub ahead of print. PMID: 39588977.

- **Factor de impacto en 2023:** 8,5
  - Cuartil en Aparato Digestivo: D1, posición 13 /143, percentil 91,3%

- **Abstract**:
  - Background: Real-world data on the effectiveness of upadacitinib for inflammatory bowel disease (IBD) are limited. Aims: To assess upadacitinib persistence, effectiveness, and safety in a real-world scenario.

- Methods: Retrospective multicentre study of IBD patients who received upadacitinib before 31st December 2022 and at least 12 weeks before the recruitment date. Clinical effectiveness was assessed based on partial Mayo score for ulcerative colitis (UC) and Harvey-Bradshaw index for Crohn's disease (CD).

- Results: We included 100 patients (68 with CD, and 32 with UC). Patients had previously received a median of four advanced therapies. Twenty-three discontinued the treatment (median follow-up 7.6 months). CD (vs. UC) (Hazard Ratio [HR] 3.7;95%Confidence Interval (CI):1.04-12.9), and age below 40 years at upadacitinib initiation (HR 2.4;95%CI:1.0-5.8) were associated with treatment discontinuation in multivariable analysis. Clinical remission for IBD was achieved in 59% of patients at week 8, 64% at week 12, and 42% at week 52. The proportion of patients with UC previously exposed to tofacitinib (n=25) who achieved clinical remission was 78% at week 12, and 50% at week 52. Factors associated with clinical remission at week 12 were UC diagnosis (Odds Ratio [OR] 4.6;95%CI:1.3-17), mild or moderate activity at baseline (OR 8;95%CI:1.1-56) and not smoking (OR 4.4;95%CI:1.5-13). Dose escalation recaptured remission in 60% of patients with relapse. Eighty percent of patients with active immune-mediated diseases or extraintestinal manifestations improved with upadacitinib. Forty-three patients reported adverse events, 11 of them serious.

- Conclusion: Upadacitinib is effective and safe for treating highly refractory IBD patients, even in previously treated with JAK inhibitors.

5. CONCLUSIONES

5. Conclusiones

Primera. La durabilidad de ustekinumab es mayor que la de vedolizumab en pacientes con enfermedad de Crohn tras fracaso o intolerancia a fármacos anti-TNF.

Segunda. Vedolizumab y ustekinumab son eficaces como tratamiento de la enfermedad de Crohn. Los pacientes tratados con ustekinumab consiguieron mayor remisión clínica durante los primeros 2 años después del inicio del tratamiento cuando en comparación con los pacientes tratados con vedolizumab.

Tercera. La intensificación del tratamiento demostró ser una estrategia capaz de aumentar la durabilidad del tratamiento tanto de vedolizumab como de ustekinumab.

Cuarto. Vedolizumab y ustekinumab demostraron un buen perfil de seguridad sin diferencias entre los dos tratamientos.

Quinto. La administración preoperatoria de tratamientos biológicos, en los que se incluyen los fármacos anti-TNF, vedolizumab y ustekinumab, no aumentan el riesgo de complicaciones postoperatorias generales en la enfermedad inflamatoria intestinal, aunque puede ser un factor de riesgo específico para las infecciones postoperatorias.

Sexto. La realización de cirugía urgente, el abordaje mediante laparotomía y la anemia grave deben considerarse como factores de riesgo para el desarrollo de complicaciones postoperatorias.

Séptimo. La presencia de hipoalbuminemia, el abordaje mediante laparotomía y unos niveles más altos de proteína C reactiva aumentan el riesgo de desarrollar infecciones postoperatorias.

Octavo. Se deben intentar optimizar el estado preoperatorio del paciente para evitar o prevenir en la medida de lo posible la presencia de complicaciones y/o infecciones durante el periodo postoperatorio.

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7. ANEXO I: PRODUCCIÓN CIENTÍFICA DE LA DOCTORANDA DURANTE LA ELABORACIÓN DE LA TESIS

7. Anexo I: producción científica de la doctoranda durante la elaboración de la tesis

Durante la elaboración de la tesis se han realizado otros estudios de investigación con una temática diferente al objetivo de esta tesis. Estos trabajos se han realizado en diferentes ámbitos, entre las que se incluyen publicaciones con primera autoría como otros de tipo colaborativo, unicéntricos y/o multicéntricos.

Hay que destacar que vivimos en una época en la que la colaboración es clave para poder realizar estudios de investigación representativos de la población a la que tratamos, que aporte conocimiento y modifique el futuro tratamiento de los pacientes para poder mejorar el pronóstico de la enfermedad y la calidad de vida de los pacientes. Todos estos estudios no podrían realizarse sin el altruismo y generosidad de todos los investigadores colaboradores y los pacientes con el objetivo de avanzar en el conocimiento de la enfermedad inflamatoria intestinal. Las publicaciones que se presentan a continuación surgen desde varios ámbitos: dentro del mismo servicio, dentro del propio centro, estudios colaborativos con GETECCU, otros estudios nacionales e incluso internacionales.

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