Píldoras IMID:
Vida Real
en
Enfermedad de Crohn

25 de Noviembre de 2022

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Conflictos de intereses

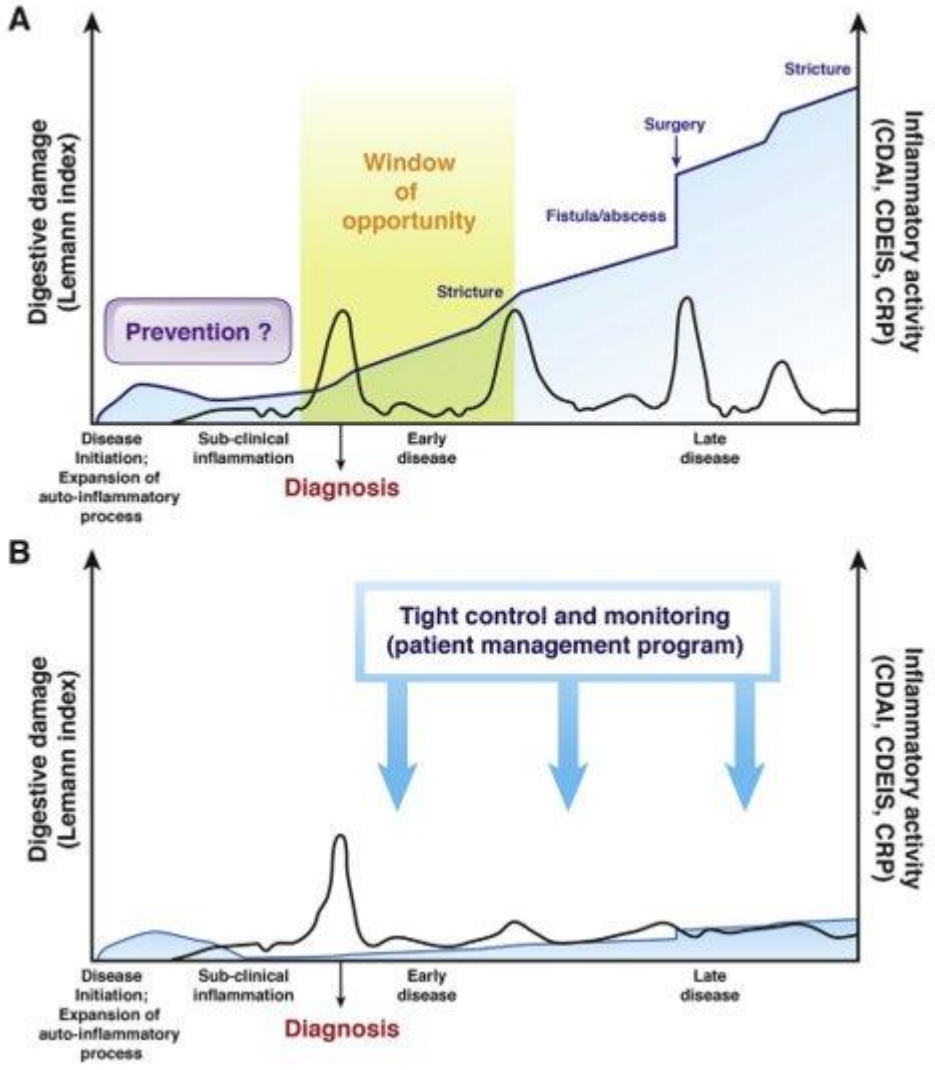
Vicente Merino: He recibido honorarios como consultor y ponente para Janssen, Abbvie, Astrazeneca, GSK y Pfizer. No poseo acciones de ninguna compañía farmacéutica.

Impacto de la Enfermedad de Crohn (EC)

La enfermedad de Crohn es una enfermedad inflamatoria, crónica y progresiva con un impacto sustancial en los pacientes y en el Sistema de salud:

- Mayor riesgo de cáncer[1]
- Altas tasas de cirugía[2]
- Calidad de vida reducida[3]
- Impacto económico[3,4]

La inflamación asociada a la EC resulta en daño intestinal progresivo[5]



CD, Crohn's disease; IBD, inflammatory bowel disease; QoL, quality of life; UC, ulcerative colitis.

1. Axelrad J, et al. *World J Gastroenterol* 2016;22:4794–4801; 2. Khoudari G, et al. *Clin Gastroenterol Hepatol* 2022;20:974–983; 3. Mehta F. *Am J Manag Care* 2016;22:51–60; 4. Zhao M, et al. *J Crohns Colitis* 2021;15:1573–1587;5. Burisch J, et al. *J Crohns Colitis* 2017;11:1200–1204;

Impacto de la Enfermedad de Crohn (EC)

Despite treatment, many patients still suffer **debilitating symptoms**, including **chronic diarrhoea**, **abdominal pain**, **rectal bleeding** and **fatigue**

Patients with active, moderate-to-severe CD exhibit poor health-related QoL compared with the general population[1–6]

Symptom burden in CD*

66.9%
Painful stomach cramps[7]

87%
Persistent diarrhoea[7]

70.5%
Weight loss[7]

64–78.1%
Symptoms affecting leisure activities[7,9]

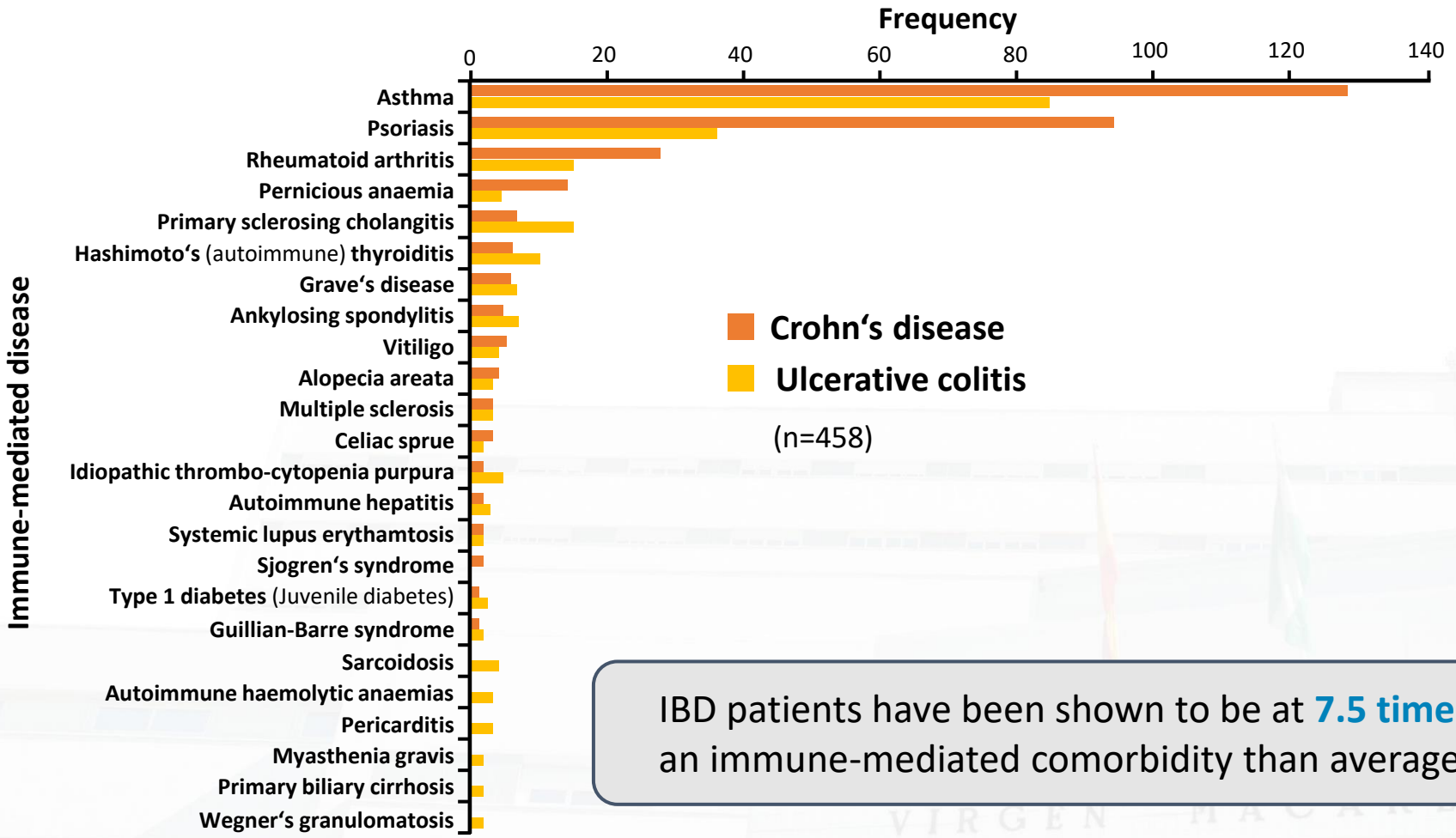
48–78.1%
Fatigue[7,8]

42.8%
Rectal bleeding[7]

*Not an exhaustive list of reported symptoms.
CD, Crohn's disease; IBD, inflammatory bowel disease; QoL, quality of life; UC, ulcerative colitis.
1. Lönnfors S, et al. *J Crohns Colitis* 2014;8:1281–1286; 2. Calvet X, et al. *Patient Prefer Adherence* 2018;12:1815–1823; 3. Park KT, et al. *Inflamm Bowel Dis* 2020;26:1–10; 4. Lie Hoivik M, et al. *J Crohns Colitis* 2012;6:441–453;
5. Bernklev T, et al. *Inflamm Bowel Dis* 2005;11:909–918; 6. Nordin K, et al. *Scand J Gastroenterol* 2002;37:450–457; 7. Ghosh S, et al. *J Crohns Colitis* 2007;1:10–20; 8. Grimstad T, et al. *J Crohns Colitis* 2015;9:725–730;
9. Becker HM, et al. *Can J Gastroenterol Hepatol* 2015;29:77–84

IBD burden frequently goes beyond the gut as extraintestinal manifestations

- Prevalence of various immune-mediated diseases in patients with IBD



IBD patients have been shown to be at **7.5 times** higher risk of developing an immune-mediated comorbidity than average those without IBD[2]

1. Conway G, et al. *Aliment Pharmacol Ther* 2017;45:814–23; 2. Panaccione R, et al. *J Crohns Colitis* 2017;11(Suppl 1):S437–S438.

¿Medimos la actividad de la enfermedad desde la perspectiva del paciente?

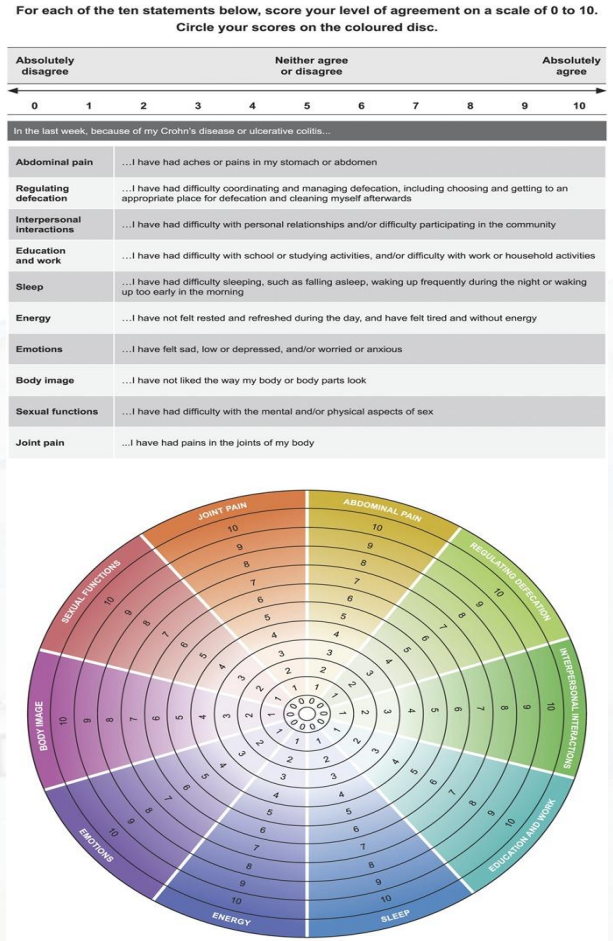
- IBDQ[1]
- IBD-C[2]
- SIBDQ[3]
- IBDDI[4]
- IBD-Disk[5]
- Y más[6]..

Índice de discapacidad de la enfermedad inflamatoria intestinal (EII)

Evaluación inicial
- **Alta puntuación**
- **Alta discapacidad**

1. Dolor abdominal
2. Regulación de defecación
3. Relaciones Interpersonales
4. Educación y trabajo
5. Sueño
6. Vitalidad
7. Emociones
8. Imagen del cuerpo
9. Función sexual
10. Dolor articular

Objetivo terapéutico
- **Baja puntuación**
- **Baja discapacidad**



For each of the ten statements below, score your level of agreement on a scale of 0 to 10. Circle your scores on the coloured disc.

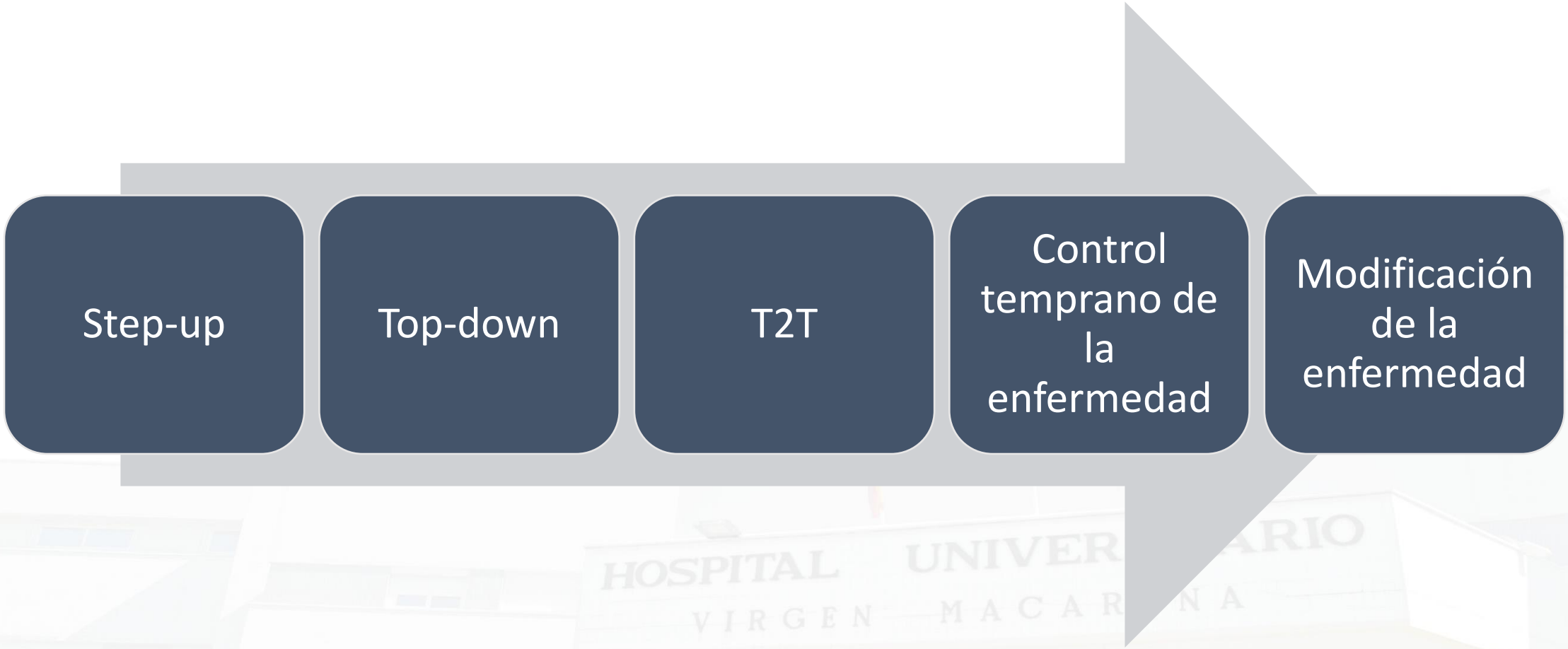
Absolutely disagree					Neither agree or disagree					Absolutely agree
0	1	2	3	4	5	6	7	8	9	10

In the last week, because of my Crohn's disease or ulcerative colitis...

Abdominal pain	...I have had aches or pains in my stomach or abdomen
Regulating defecation	...I have had difficulty coordinating and managing defecation, including choosing and getting to an appropriate place for defecation and cleaning myself afterwards
Interpersonal interactions	...I have had difficulty with personal relationships and/or difficulty participating in the community
Education and work	...I have had difficulty with school or studying activities, and/or difficulty with work or household activities
Sleep	...I have had difficulty sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning
Energy	...I have not felt rested and refreshed during the day, and have felt tired and without energy
Emotions	...I have felt sad, low or depressed, and/or worried or anxious
Body image	...I have not liked the way my body or body parts look
Sexual functions	...I have had difficulty with the mental and/or physical aspects of sex
Joint pain	...I have had pains in the joints of my body

1. Pallis AG, et al. Inflamm Bowel Dis 2004; 2. Bodger K, et al. Gut 2014; 3. Alcala MJ, et al. Inflamm Bowel Dis 2004; 4. Lo B, et al. Eur JG&H 2018; 5. Ghosh S, et al. Inflamm Bowel Dis. 2017; 6. Andel, et al. JCC 2020

Evolución de los objetivos terapéuticos en EII



Objetivos establecidos en los consensos

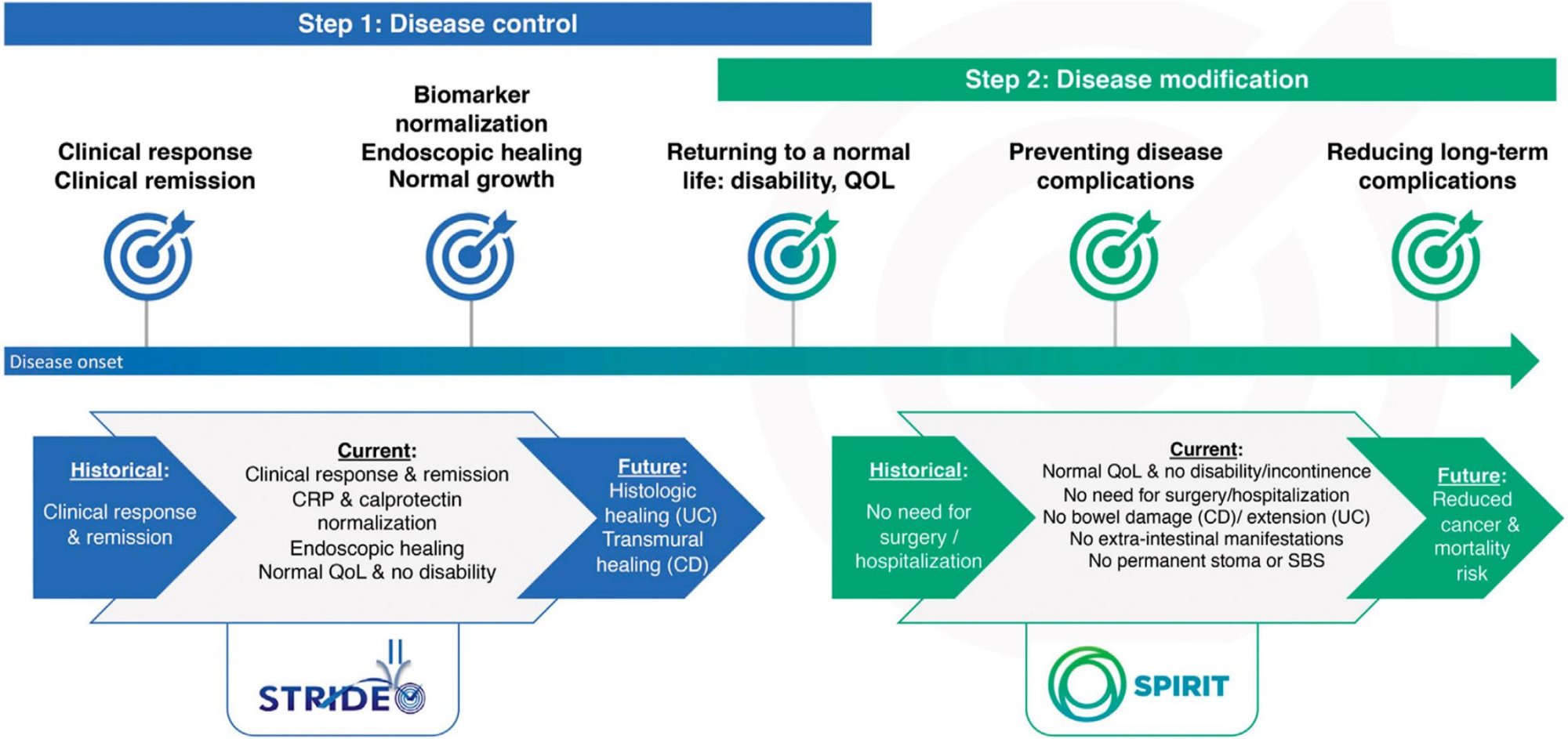


Figure 1. Summary of evolving short-term and long-term goals in inflammatory bowel diseases. CD, Crohn's disease; CRP, C-reactive protein; QoL, quality of life; SBS, short bowel syndrome; UC, ulcerative colitis.

Le Berre C et al, *Gastroenterol*, 2022

Herramientas: Biomarcadores para monitorización estrecha

- Endoscopia y resonancia magnética son costosas, y llevan tiempo
- Un buen marcador surrogado de actividad endoscópica reduciría el número de endoscopias
  - Papel de FeCal (y PCR)

PCR

- Correlaciona modestamente con actividad endoscópica
- Se asocia con respuesta terapéutica
- Predice recaidas

FeCal

- Puede ayudar a predecir respuesta terapéutica
- Puede predecir recaidas
- Correlaciona con curación mucosa

1. Peyrin-Biroulet L, et al. Am J Gastroenterol 2015;110:1324-38.
2. Maaser C, et al. J Crohns Colitis. 2019;13:144-64.

Herramientas: Therapeutic Drug Monitoring

Fármaco Biológico	Etapa del tratamiento	Puntos de corte sugeridos de las concetraciones séricas del fármaco para alcanzar la respuesta o remisión (µg/mL)	Puntos de corte sugeridos de las concetraciones séricas del fármaco para la curación de la mucosa (µg/mL)
Infliximab	Inducción (semana 2)	≥20	≥25
	Inducción (semana 6)	≥16-18	*
	Fin de inducción (semana 14)	≥5	≥7
	Mantenimiento	≥3	≥7
Adalimumab	Inducción (semana 4)	≥7	≥12
	Mantenimiento	≥5	≥8
Golimumab	Fin de inducción (semana 14)	≥2,5	*
	Mantenimiento	≥1	*
Vedolizumab	Inducción (semana 2)	≥28	*
	Inducción (semana 6)	≥20	*
	Fin de inducción (semana 14)	≥15	≥17
	Mantenimiento	≥12	≥14
Ustekinumab	Fin de inducción (semana 8)	≥3,5	≥7,0
	Mantenimiento	≥1	≥4,5

https://www.sefh.es/bibliotecavirtual/Guia_EII/guiaEII_.pdf?ts=20220127131022

RWE: demuestran la efectividad del tratamiento en la vida real

Ensayos Clínicos Aleatorizados (ECA)

Adherencia al tratamiento

Discontinuación del tratamiento

Cambios de tratamientos

Escalada y desecalada de dosis

Todos estos factores pueden ser usados como indicadores de efectividad y seguridad en vida real: enfermedad de Crohn y colitis ulcerosa

Globe animation adapted from: File:Rotating globe.gif - Wikimedia Commons.

Khan S, et al. J Clin Pharm Ther.2019;44:495-507.

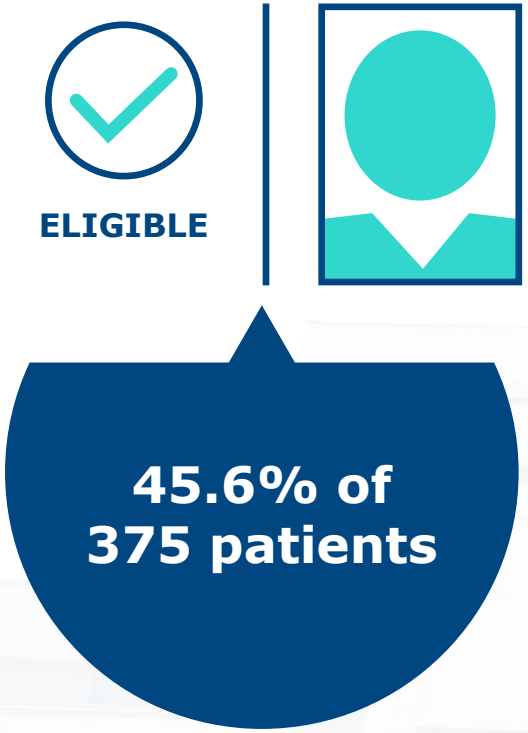
Ventajas y limitaciones de RWE vs ECA

VENTAJAS	LIMITACIONES
Reducción del consumo de tiempo y costes en comparación con los ECA	Para un análisis correcto, se debe recopilar una gran cantidad de datos
Se pueden detectar eventos adversos raros en RWE	Los datos suelen ser desordenados e incompletos
Tamaño de muestra más grande	La fuente de financiación puede sesgar los resultados del ensayo
Los criterios mínimos de exclusión permiten la generalización	Son necesarios sofisticados métodos estadísticos para obtener información y expertos que lo manejen e interpeten
Obtención de información en pacientes complejos con múltiples comorbilidades	Es necesario establecer un protocolo de investigación estandarizado antes de la investigación (alta probabilidad de sesgos)
Los registros se pueden utilizar para identificar rápidamente eventos inesperados y garantizar la seguridad del paciente	

Signal A, et al. Clin Transl Gastroenterol. 2014 Jan;5:e45.
de Lusignan S, et al. J Innov Health Inform. 2015;22:368-73.
Macaluso FS et al. Ther Adv Gastroenterol. 2021;14:1-11.
Kim HS et al. J Korean Med Sci. 2018;33(34):e213..

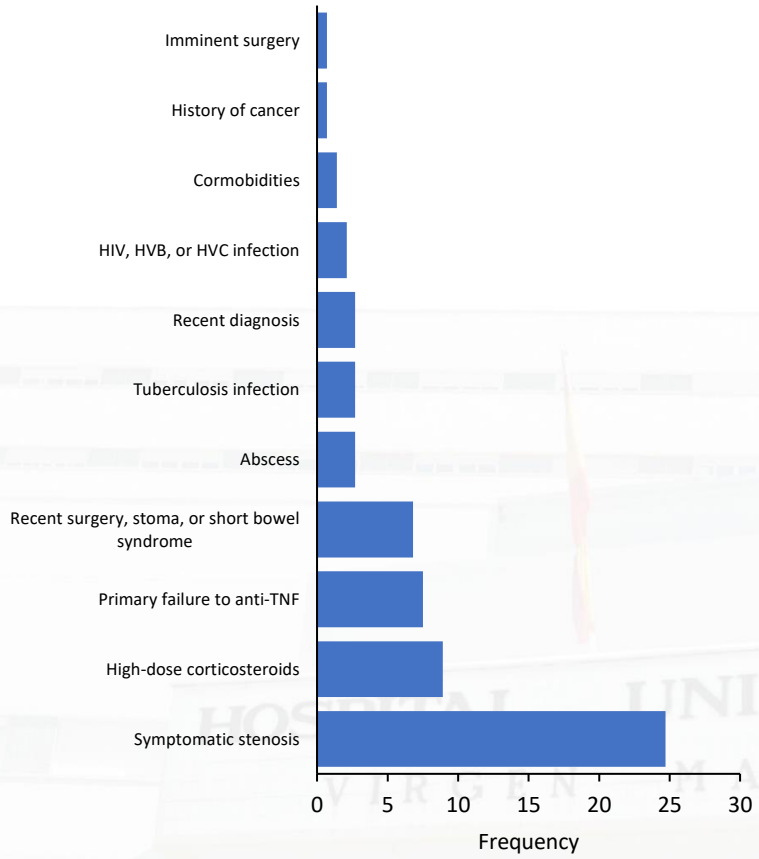
RWE: patients are not the same as patients in clinical trials

RWE patients are not the same as those participating in clinical trials

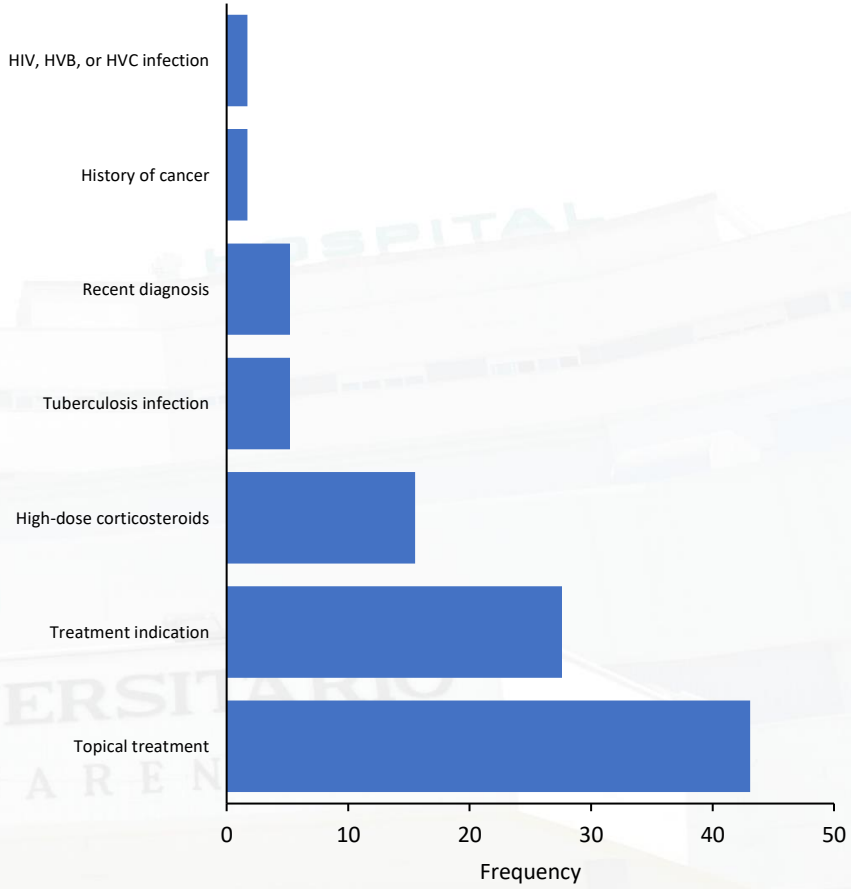


In the Spanish RWE study **EFIFECT**, only 45.6% of the 375 included patients would have been eligible for clinical trials

Causes of ineligibility for a randomized clinical trial in Crohn's disease



Causes of ineligibility for a randomized clinical trial in ulcerative colitis



HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TNF, tumour necrosis factor.

Ginard D, et al. Gastroenterol Hepatol. 2016;39:369-76.

Durable remission

Real-world data on the effectiveness of UST **align with clinical trial observations** (1 of 6)

Real-world data in patients with CD (1/4)

Publication	Study design	Patient demographic	Patients followed	Main findings

ENEIDA: Iborra M, et al. 2019[1]	• Multicentre study of patients with refractory CD from the ENEIDA registry starting UST; patients were followed up to assess the real-world, short-term effectiveness of UST in refractory CD	Patients with CD:
		• 64% ≥2 previous anti-TNFs, 32% 1 previous anti-TNF
		• 56% previous surgery
		• 36% on CSs
		• 11.7 years disease duration
			N=305	• At baseline, 217 patients had an HBI >4
				• Clinical remission was achieved in:
				  • 47% of patients at **Week 8**
				  • 58% of patients at **Week 14**
				• AEs were reported in 12% of patients

ENEIDA: Iborra M, et al. 2020[2]	• Multicentre study of patients with refractory CD from the ENEIDA registry starting UST; patients were followed up for 1 year to assess the real-world, long-term effectiveness of UST in refractory CD	Patients with CD:
		• 61% ≥2 previous anti-TNF, 35% 1 previous anti-TNF therapies
		• 55% previous surgery
		• 33% on CS
		• 11.06 years disease duration
			N=407	• At baseline, 295 patients had an HBI >4
				• Clinical remission was achieved in:
				  • 57% of patients at **Week 26**
				  • 64% of patients at **Week 52**
				• AEs were recorded in 14.7% of patients
				• These results were consistent with the previously published results from the ENEIDA registry of 305 patients with CD who were treated with UST[1]
				• **After 52 weeks**, treatment was discontinued in 27.5% of patients

AE, adverse event; CD, Crohn's disease; CS, corticosteroid; HBI, Harvey–Bradshaw Index; TNF, tumour necrosis factor; UST, ustekinumab.

1. Iborra M, et al. *Aliment Pharmacol Ther* 2019;50:278–288; 2. Iborra M, et al. *Aliment Pharmacol Ther* 2020;52:1017–1030.

Durable remission

Real-world data on the effectiveness of UST **align with clinical trial observations** (2 of 6)

Real-world data in patients with CD (2/4)

Publication	Study design	Patient demographic	Patients followed	Main findings
SUSTAIN: Chaparro M, et al. 2022[1]	• Retrospective, multicentre study in patients with active, refractory CD • Primary outcome was UST retention rate	Active CD with ≥1 intravenous dose of UST for ≥6 months • 69.1% >2 previous biologics • 96.5% 1 previous anti-TNF • 60.7% previous surgery • 39.1% EIMs • 14.1 years disease duration	N=463	**At Week 16**: • 56% of patients were in remission • 70% of patients had a response • 26.1% of patients required dose escalation or intensification (of these, 24.8% did not subsequently reduce dose) After a median follow-up of **15 months**: • 77% of patients continued treatment • The incidence rate of UST discontinuation was 18% per patient-year of follow-up • 50 AEs were reported in 8.4% of patients; 4 of them were severe (2 infections, 1 malignancy and 1 fever)
Plevris N, et al. 2021[2]	• Retrospective study of patients with CD who received UST across eight Scottish National Health Service health boards	Diagnosis of active CD • 75% >2 previous biologics • 98.6% 1 previous anti-TNF • 55.1% previous surgery • 29.6% EIMs • 9.9 years disease duration	N=216	**At 12 months**, the cumulative rates were: • 32.0% of patients were in clinical remission • 32.7% of patients had mucosal healing • 19.3% of patients were in deep remission (clinical remission plus mucosal healing) The rate of SAEs was 13.6 per 100 patient-years of follow-up

AE, adverse event; CD, Crohn's disease; EIM, extraintestinal manifestation; SAE, serious adverse event; TNF, tumour necrosis factor; UST, ustekinumab.

1. Chaparro M, et al. *Inflamm Bowel Dis* 2022; doi:10.1093/ibd/izab357 [Epub ahead of print]; 2. Plevris N, et al. *J Gastroenterol Hepatol* 2021;36:2067–2075.

Durable remission

Real-world data on the effectiveness of UST **align with clinical trial observations** (3 of 6)

Real-world data in patients with CD (3/4)

Publication	Study design	Patient demographic	Patients followed	Main findings
PROSE: Forss A, et al. 2021[1]	• Swedish Inflammatory Bowel Disease Registry: Prospective multicentre study of adult patients with CD who initiated UST according to recommended doses at 20 hospitals • Primary outcomes were clinical response and remission at Week 16	Confirmed ICD diagnosis of CD with active disease • 72% previous biologics, 94% >1 previous biologic • 32% previous surgery • 44% stricturing disease	N=114	94% had failed ≥1 and 51% ≥2 biologic agents (anti-TNF agents or vedolizumab) **At Week 16**: • 92% of patients continued with UST • 40% of patients achieved a response or remission • 26% of patients achieved clinical remission • 24% of patients showed a clinical response • Median CRP concentration (n=65) decreased from 6 mg/l to 4 mg/l (p=0.006) No incident malignancies or infections requiring antibiotic treatment were reported
ICC: Straatmijer T, et al. 2021[2] Biemans V, et al. 2020[3]	• Initiative on Crohn's and Colitis registry (Netherlands): Prospective, nationwide multicentre study of patients with CD who initiated UST • The primary outcome was CS-free clinical remission at Week 104	Established CD diagnosis starting UST in regular care • 99.2% failed >1 previous biologic, 42.9% failed vedolizumab	N=252	**After 24 weeks**: • 35.7% of patients with active perianal fistula showed complete clinical resolution[2] **At Week 104**: • 34.0% of all patients with at least 2 years of follow-up had CS-free clinical remission • 32.8% of patients with combined clinical and biochemical disease activity at baseline had CS-free clinical remission **After 104 weeks**: • Patients had a 54.8% probability of remaining on UST The main reason for treatment discontinuation **after 52 weeks** was loss of response (66.7%). No new safety issues were observed

CD, Crohn's disease; CRP, C-reactive protein; CS, corticosteroid; ICC, Initiative on Crohn's and Colitis; ICD, International Classification of Diseases; TNF, tumour necrosis factor; UST, ustekinumab.

1. Forss A, et al. *Scand J Gastroenterol* 2021;56:680–686; 2. Straatmijer T, et al. *J Crohns Colitis* 2021;15:1920–1930; 3. Biemans V, et al. *J Crohns Colitis* 2020;14:33–45.

Durable remission

Real-world data on the effectiveness of UST **align with clinical trial observations** (4 of 6)

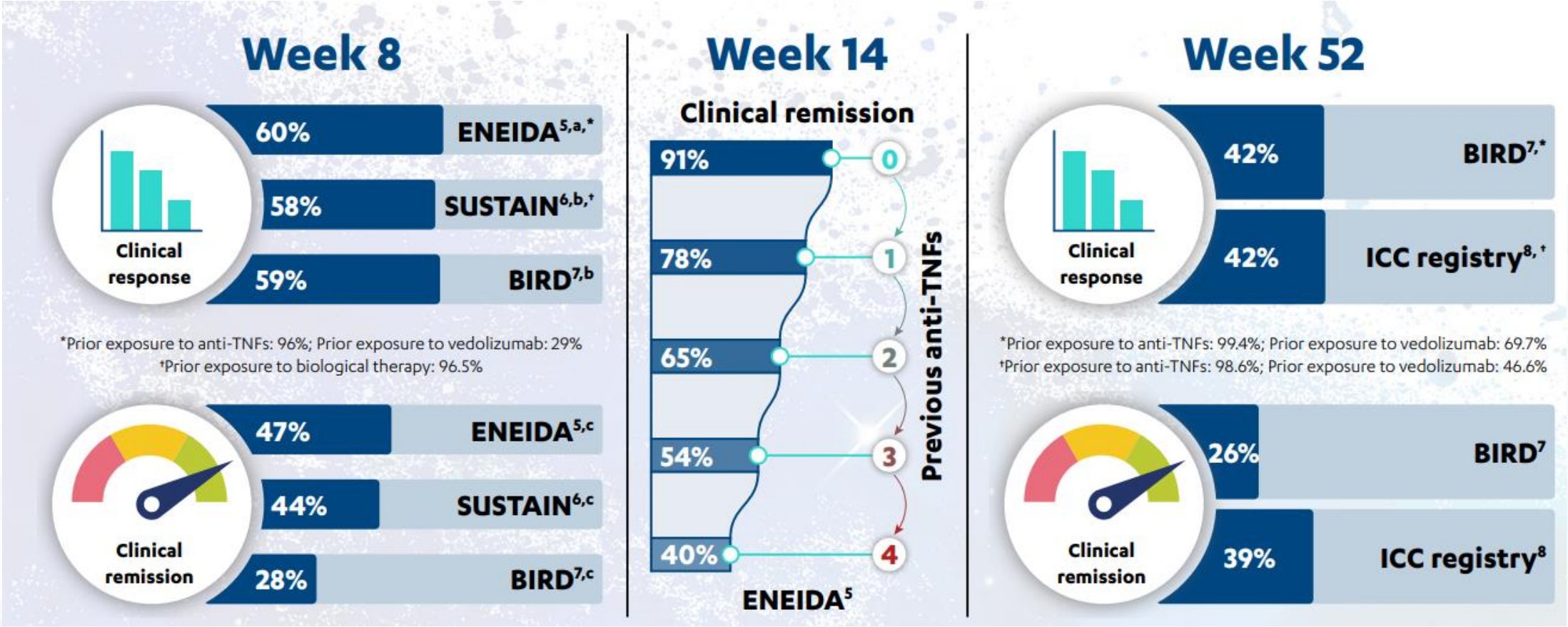
Real-world data in patients with CD (4/4)

Publication	Study design	Patient demographic	Patients followed	Main findings
Liefferinckx C, et al. 2019[1]	• Observational, national, retrospective multicentre, cohort study in patients with CD in Belgium • Outcomes investigated included response and remission rates at Week 8, 16 and 52	All had previous exposure to ≥1 anti-TNF • 69.7% >2 previous biologics, 94.4% >1 prior biologic • 59.2% previous surgery • 23.1% EIMs • 40.8% perianal disease	N=152	**After 1 year**: • 42.1% of patients had clinical response • 25.7% of patients had clinical remission • 38.8% of patients achieved CS-free clinical response • 24.3% of patients achieved CS-free remission • 38.8% of patients discontinued therapy during the 12 months of follow-up
Bar-Gil Shitrit A, et al. 2020[2]	• Prospective, multicentre, Israeli study in patients with active CD treated with UST for 24 weeks	Patients with active CD: All had previous exposure to ≥1 biologic • 80.5% >2 previous biologics, 19.4% 1 previous biologic • 51.3% previous surgery • 62.5% stricturing and penetrating disease	N=106	**At Week 24**: • 52% of these patients had a clinical response, with mean HBI reduction from 8.34±3.8 to 6.8±4.4 (p=0.001) • 31.1% of patients achieved clinical remission • 90.5% of patients continued treatment • 15 patients reported minor AEs; 10.4% discontinued treatment

AE, adverse event; CD, Crohn's disease; CS, corticosteroid; EIM, extraintestinal manifestation; HBI, Harvey–Bradshaw Index; TNF, tumour necrosis factor; UST, ustekinumab.

1. Liefferinckx C, et al. *J Crohns Colitis* 2019;13:1401–1409; 2. Bar-Gil Shitrit A, et al. *United European Gastroenterol J* 2020;8:418–424.

Ustekinumab en práctica clínica real



TRATAMIENTO TEMPRANO EN ENF.DE CROHN

La importancia de un comienzo temprano

La definición de París de EC "temprana" para estudios clínicos:[1]
- Duración de la enfermedad ≤18 meses
- Sin fármacos modificadores de la enfermedad previos (inmunomoduladores, biológicos)

El tratamiento efectivo temprano **disminuye la actividad inflamatoria** (frente al tratamiento posterior/convencional)[2]

La intervención temprana en la EC podría **prevenir** el **daño intestinal**, la **discapacidad** y la necesidad de **resección intestinal**, y podría cambiar la historia natural de la enfermedad[3]

El tratamiento temprano puede **reducir** significativamente **el riesgo de complicaciones** y **aumentar el tiempo de remisión**[4]

La **intervención temprana** es un objetivo prometedor para los ensayos de **modificación de la enfermedad**[5]

1. Peyrin-Biroulet L, et al. Am J Gastroenterol 2012;107:1770–1776; 2. Colombel JF, et al. Gastroenterology 2017;152:351–361; 3. Zhu M, et al. BMC Gastroenterol 2020;20:241; 4. Danese S, et al. Gut 2017;66:2179–2187; 5. Rodríiguez-Lago I, et al. Ann of Gastroenterol 2020;33:443–452.

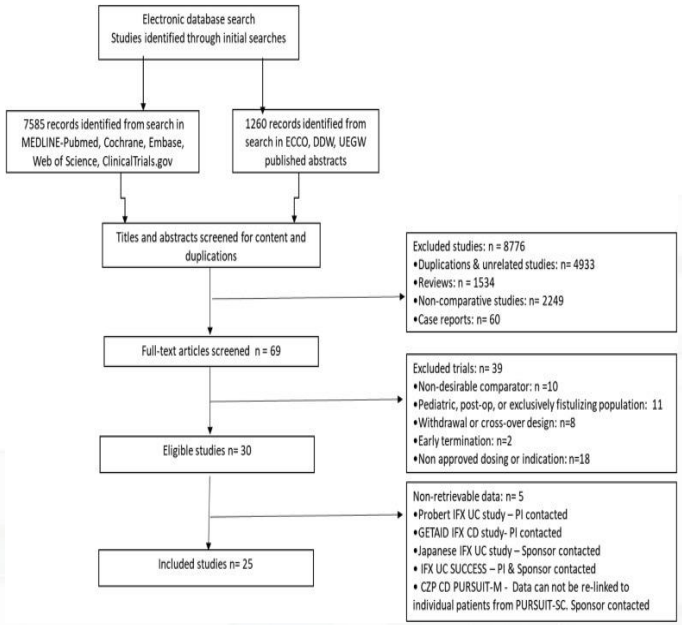
El uso temprano de biológicos se asocia con mejores resultados clínicos en comparación con el manejo tardío/convencional

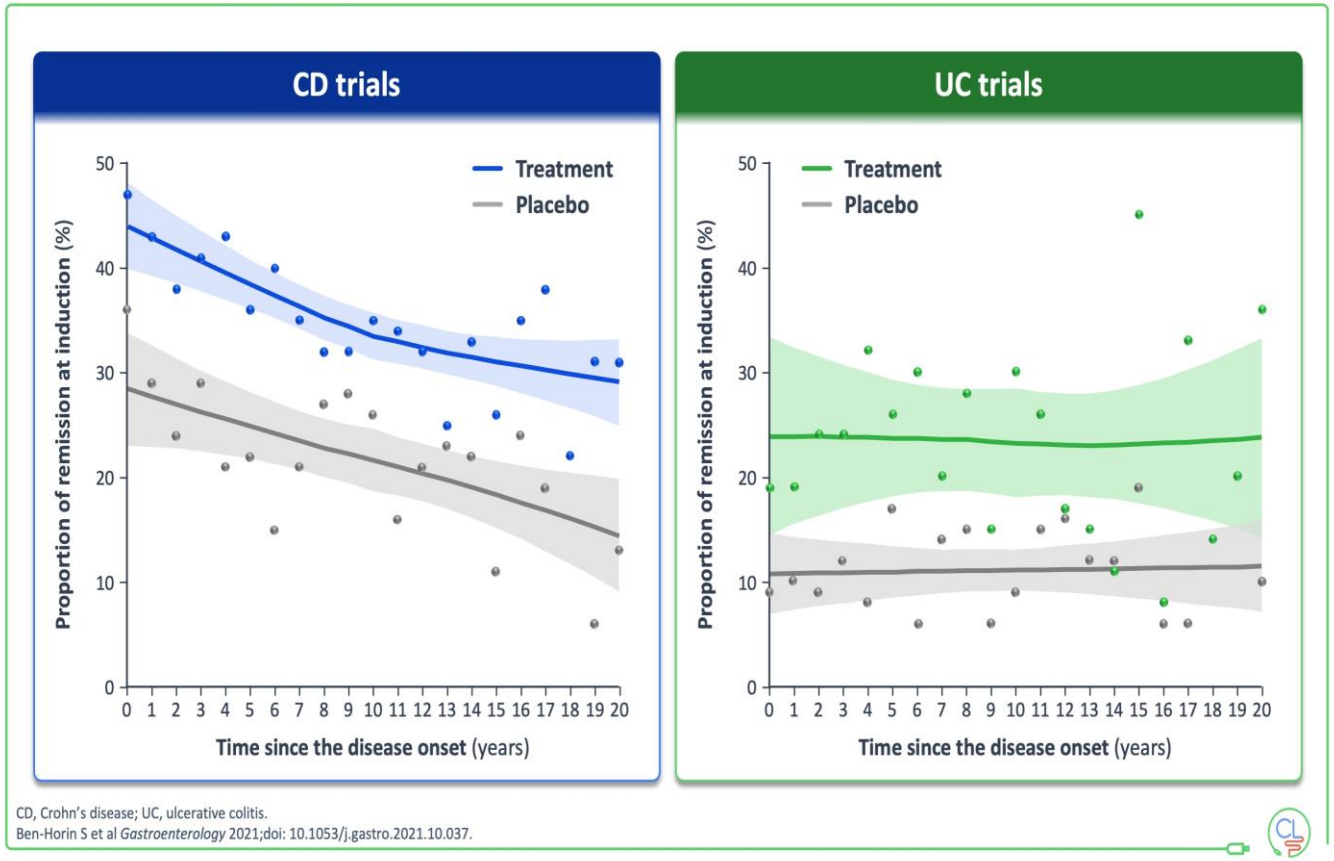
- Mejores resultados clínicos en pacientes adultos y pediátricos
- Tasas de recaída más bajas
- Mayores tasas de remisión clínica
- Mayores tasas de curación de mucosa
- No solo en ensayos clínicos prospectivos, sino también en entornos del mundo real

Ungaro RC, et al. *Aliment Pharmacol Ther* 2020;51:831–842.

Eficacia de los fármacos biológicos en la EII de corta duración frente a la de larga duración

- Revisión sistemática y metaanálisis
- 25 ECA (N=6168 EC y N=3227 CU)
- IFX, ADL, CER, GOL, NAT y VED





CD, Crohn's disease; UC, ulcerative colitis.
Ben-Horin S et al *Gastroenterology* 2021;doi: 10.1053/j.gastro.2021.10.037.

EC→Tasas de inducción a la remisión más altas en el grupo de placebo y pacientes en brazos activos con enfermedad de corta duración de **≤18 meses vs >18 meses (41,4% vs 29,8%)**

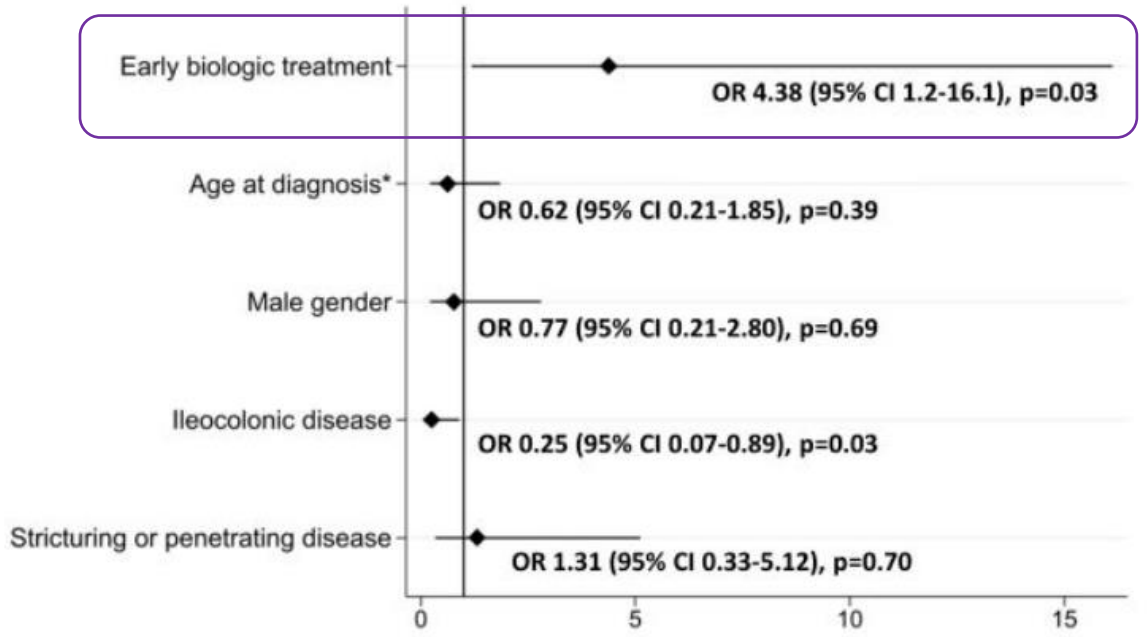
Ben-Horin S, et al. Gastroenterol 2022;162:482–494.

Impacto clínico del abordaje temprano

- Estudio retrospectivo unicéntrico
- Objetivo: evaluar la eficacia del tto biológico temprano para conseguir **curación transmural**
- Temprano vs tardío (<12 ó >12 meses desde diagnóstico)

El tratamiento temprano con biológico asocia independientemente con mayores tasas de curación transmural

Figure 1: Multivariate logistic regression model for the prediction of the achievement of transmural healing



Estudios que actualmente exploran el abordaje temprano

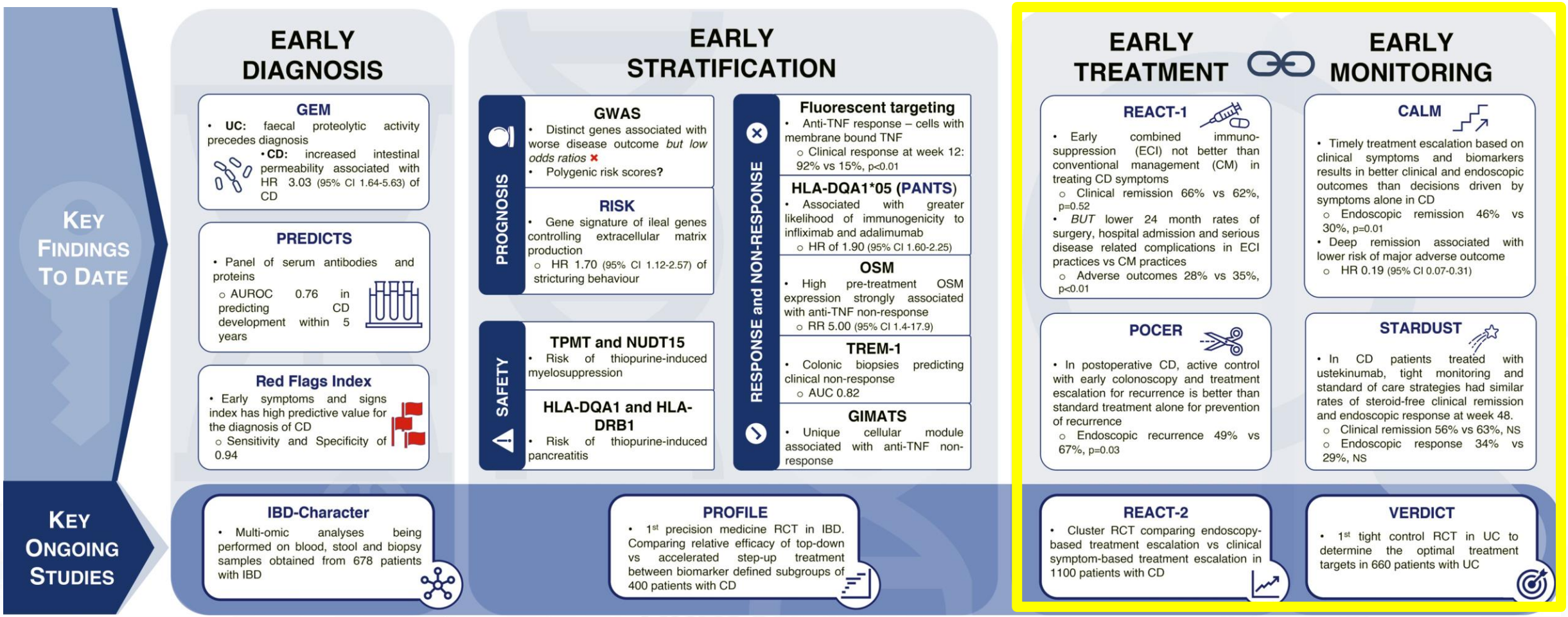


Figure 3. Diagram to summarize data from the most promising current and future studies exploring early diagnosis, early stratification, early treatment, and monitoring. Highlighting findings from the key studies to date on early diagnosis, stratification, treatment, and monitoring. Subsequently highlighting the most promising upcoming studies, which will provide key data to support further progress in these topics.

Noor NM, Sousa P, Paul S, Roblin X. Early Diagnosis, Early Stratification, and Early Intervention to Deliver Precision Medicine in IBD [published online ahead of print, 2021 Sep 4]. Inflamm Bowel Dis. 2021;izab228.

Table 3 List of relevant cohort studies on early intervention in CD

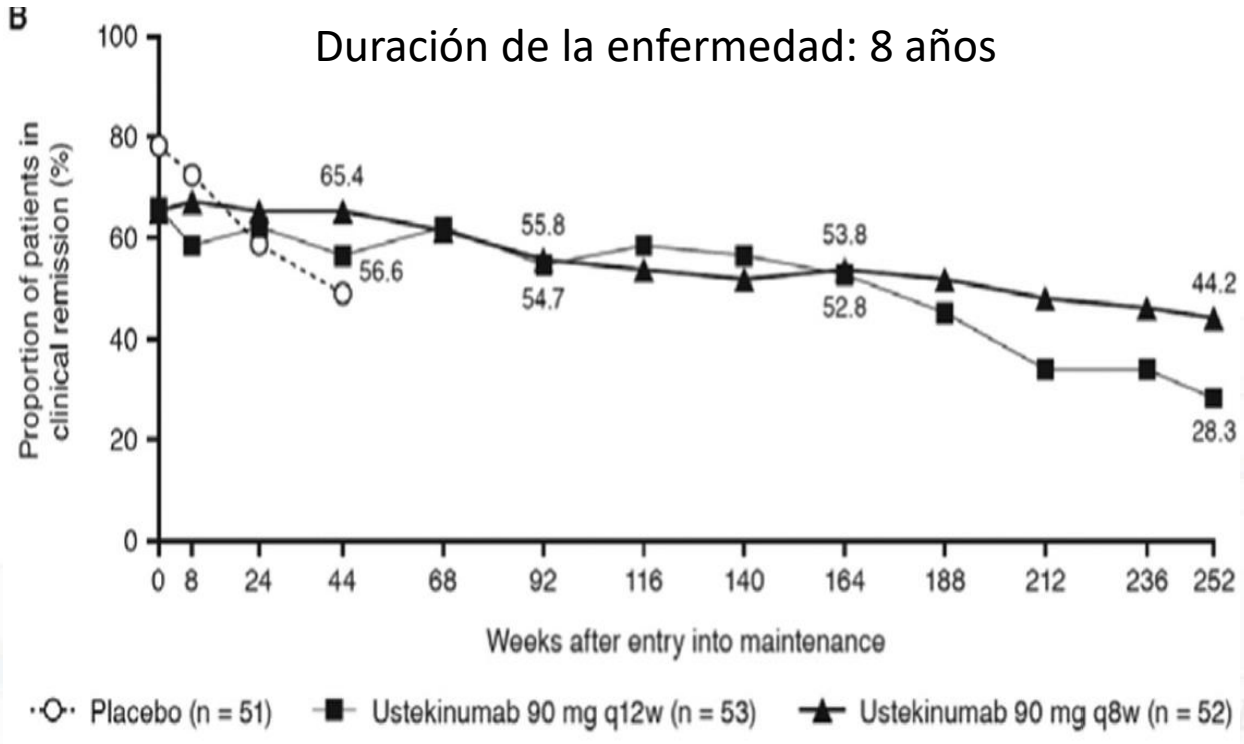
Author (Year)	Study design	Intervention/control	Early CD definition	Primary outcome	Significant results
Safroneeva *et al* (2015)[38]	Prospective observational cohort	Early use of anti-TNF and/or immunomodulators	24 months	Development of complications	Early treatment was associated with reduced risk of bowel strictures (HR 0.496, p=0.004 for IM; HR 0.276, p=0.018 for anti-TNF) Early immunosuppression was associated with reduced risk of intestinal surgery (HR 0.322, p=0.005), perianal surgery (HR 0.361, p=0.042) and any disease complication (HR 0.567, p=0.006)
Kwak *et al* (2014)[39]	Retrospective cohort	Early immunomodulator use versus conventional therapy	6 months in the ET group	Clinical remission	Clinical remission and corticosteroid-free remission rates higher in the ET group (p=0.043 and p=0.035). Adverse events also more frequent in the ET group (p=0.029)
Kim *et al* (2016)[41]	Retrospective study	Early immunomodulator use versus conventional therapy	6 months in the ET group	Need for surgery	ET was associated with lower risk of surgery (p=0.017) and delayed onset of complications (p=0.050)
Nuij *et al* (2015)[40]	Retrospective cohort	Early anti-TNF versus conventional step-up approach	≤16 months	IBD-related complications	No differences in terms of IBD-related complications and rates of mucosal healing between the two groups

anti-TNF, antitumour necrosis factor α; CD, Crohn's disease; ET, early treatment; IBD, inflammatory bowel disease; IM, immunomodulator.

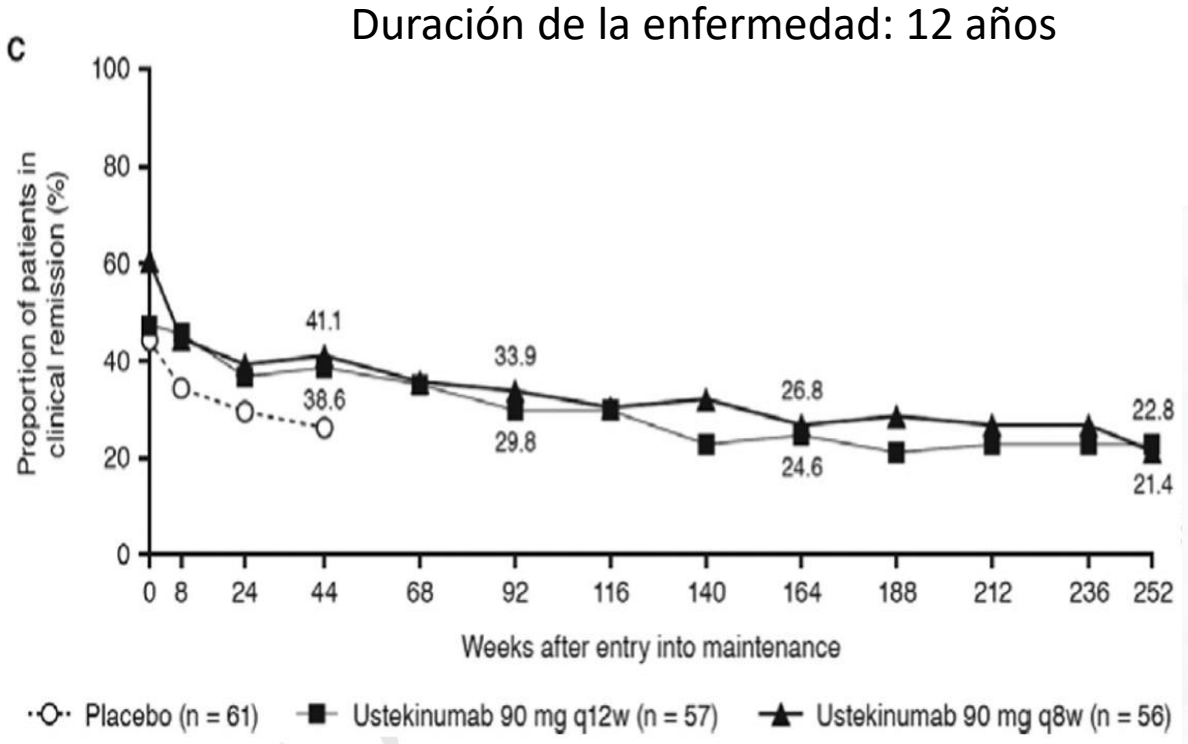
Early treatment UST: CD data

UNITI/IM-UNITI

Bionaive patients



TNF-failure patients



Sandborn et al. *Clin Gastroenterol Hepatol*. 2022 Mar;20(3):578-590.

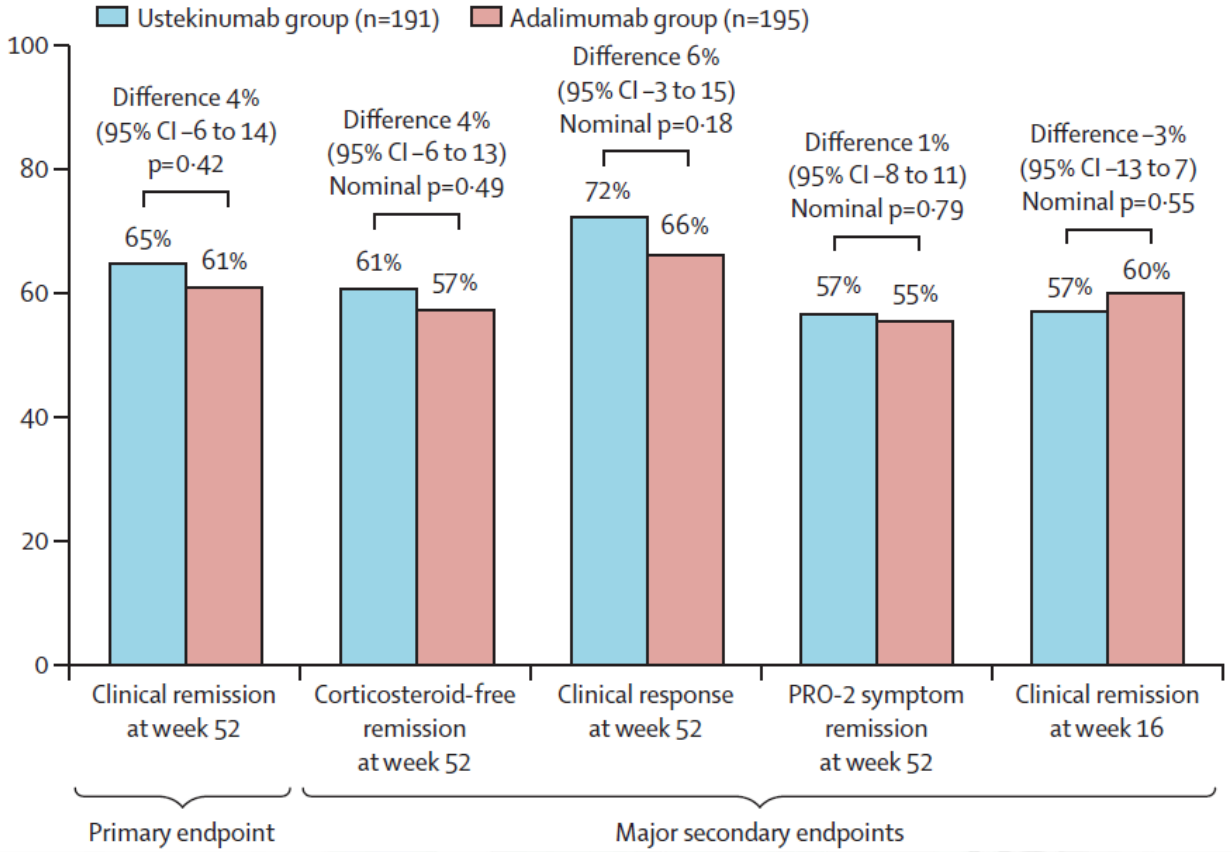
Early treatment UST: SEAVUE

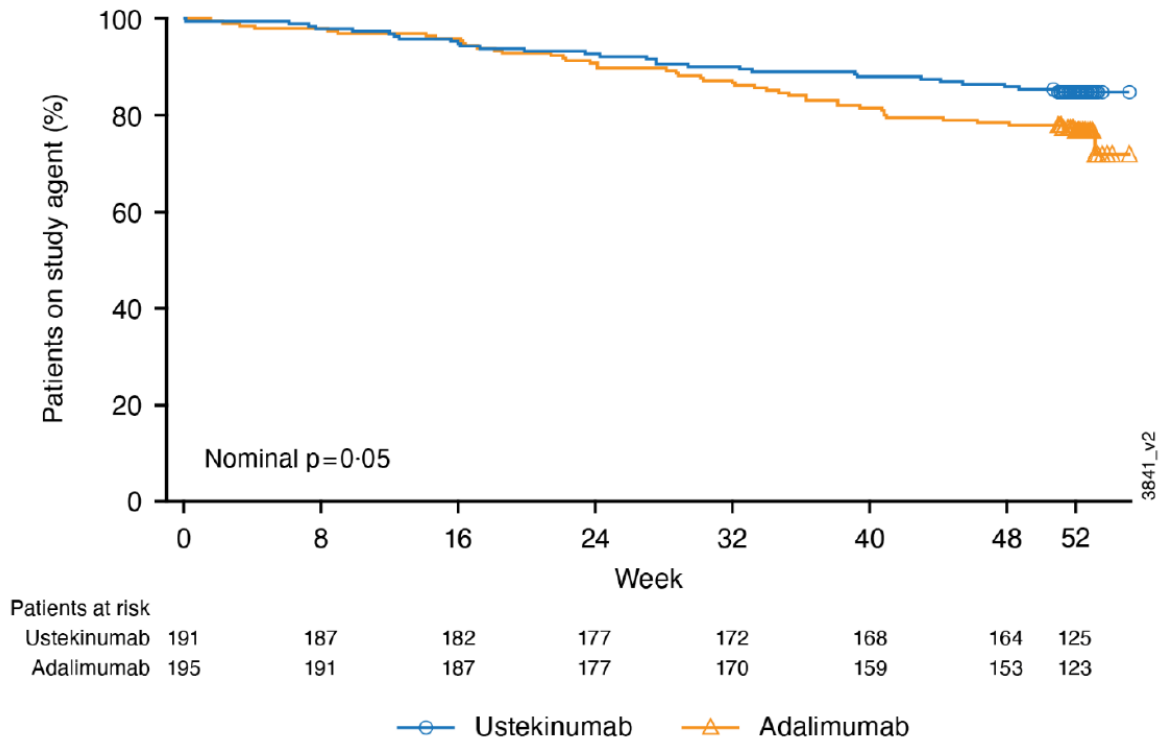
- ECA: UST vs ADA
- Pacientes con EC moderada grave
- Bio-navie (previamente no expuestos a biológicos)
- Fracaso o intolerancia a terapia convencional
- No se permitieron modificaciones de dosis

	Adalimumab	Ustekinumab	Total
Randomized patients	**195**	**191**	**386**
Age at diagnosis, median (years)	30.0	28.8	**29.6**
CD duration in years, median (mean)	2.62 (5.8)	2.57 (5.4)	**2.58 (5.6)**
CDAI score, median (mean)	291.0 (300)	287.0 (302)	**289.5 (301)**
SES-CD, median (mean)	8.0 (9.8)	7.0 (9.9)	**8.0 (9.9)**
IBDQ score (32-224), Median	121.0	115.0	**117.5**
Fecal calprotectin-mg/kg, median(mean)	545.5 (1272)	895.0 (1392)	**671.0 (1331)**
CRP (mg/L), median (mean)	5.51 (11.9)	6.21 (14.5)	**5.73 (13.2)**
On corticosteroids, including budesonide	75 (38.5%)	70 (36.6%)	**145 (37.6%)**
Pred-equiv. dose, median (n)	20mg (48)	20mg (43)	**20mg (91)**
≥1 prior intra-abdominal Crohn's-related surgeries	37 (19.0%)	29 (15.2%)	**66 (17.1%)**

Sands BE et al, Lancet 2022

Early treatment UST: SEAVUE





Treatment retention measured by time-to-treatment discontinuation through week 52 was analysed and compared using the Kaplan-Meier estimator and log-rank test in post hoc analysis.

- No hubo diferencias significativas de eficacia y seguridad en ambos grupos en semana 52
- Un 15% de los pacientes con UST y 24% con ADL abandonaron el estudio antes de la semana 52

Sands BE et al, Lancet 2022

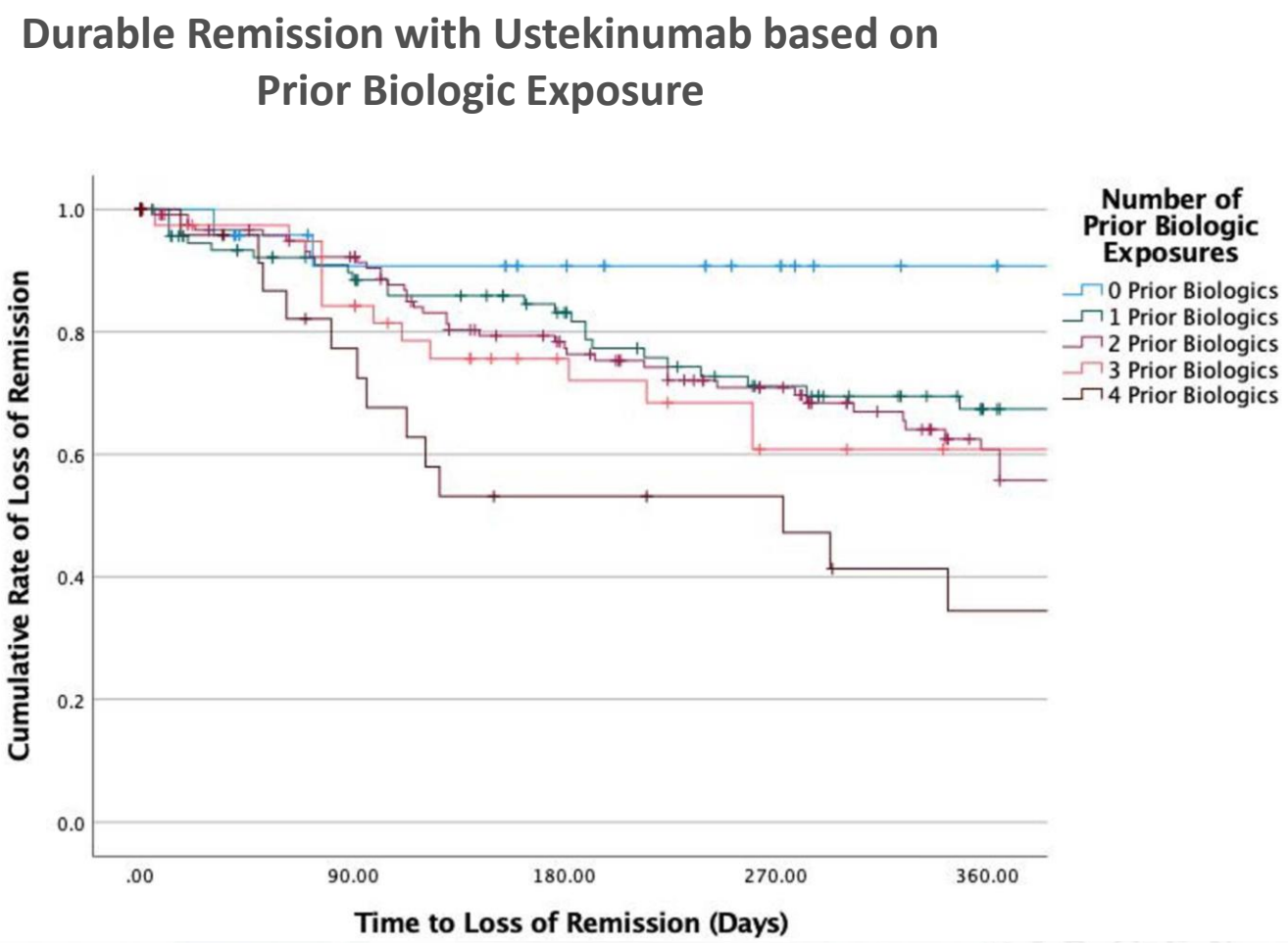
Patient Demographics based on Prior Biologic Exposure Status

Demographics Based on Prior Biologic Exposure Status	All UST treated n=1113	Biologic naïve n=106	1 Biologic n=289	2 Biologics n=437	3 Biologics n=187	4 Biologics n=94
Median follow-up in days (IQR)	386d (204-562)	340d (200-545)	407d (205-549)	368d (194-546)	469d (235-706)	444d (223-603)
Age diagnosis, median years (IQR)	23 (16-33)	30 (22.8-44.3)	26 (19-40)	21 (15-31)	20 (14-30)	18.5 (13-27.3)
Age at UST initiation, median years (IQR)	38 (28-52)	48 (32-52)	40 (28-55)	37 (26-49)	38 (28-51)	34 (26-45.3)
Disease duration, median years (IQR)	11 (5-20)	5 (1-26)	9 (4-18)	12 (6-19)	15 (8-22)	13 (9-20)
BMI (kg/m^2), median (IQR)	24.4 (21.3-28.3)	26 (21.2-28.1)	24.9 (21.8-30)	23.3 (21-28.2)	23.5 (21.1-30)	24.9 (21.7-28)
C-reactive protein, median (IQR)	1.7 (0.5-6.7)	1.1 (0.1-3.7)	1.2 (0.4-5.1)	2.0 (0.5-8.6)	2.6 (0.7-6.2)	1.9 (0.5-8.9)
Albumin, median (IQR)	4.0 (3.5-4.3)	4.1 (3.5-4.3)	4.2 (3.7-4.3)	4.0 (3.5-4.3)	3.8 (3.4-4.2)	3.9 (3.5-4.1)
Female gender, n (%)	576 (51.8)	36 (34)	154 (53.3)	217 (49.7)	122 (65.2)	47 (50.0)
Never smoker, n (%)	835 (75)	80 (75.5)	222 (76.8)	314 (71.9)	140 (74.9)	79 (84.0)
Prior CD-related hospitalization, n (%)	805 (72)	52 (49.1)	180 (62.3)	339 (77.6)	153 (81.8)	81 (86.2)
Disease extent*						
L1, n (%)	217 (19.5)	32 (30.2)	73 (25.3)	74 (16.9)	23 (12.3)	15 (16.0)
L2, n (%)	173 (15.5)	12 (11.3)	57 (19.7)	72 (16.5)	21 (11.2)	11 (11.7)
L3, n (%)	723 (65.0)	62 (58.5)	159 (55.0)	291 (66.6)	143(76.5)	68 (72.3)
Stricturing/penetrating disease history, n (%)	678 (60.9)	48 (45.3)	163 (56.4)	272 (62.2)	134 (71.7)	61 (64.9)
Perianal disease, n (%)	413 (37.1)	22 (20.8)	74 (25.6)	200 (45.8)	70 (37.4)	47 (50.0)
Baseline ulceration, n (%)	915 (82.2)	92 (86.8)	238 (82.4)	353 (80.8)	154 (82.4)	78 (83.0)
Prior surgery, n (%)	658 (59.1)	34 (32.1)	135 (46.7)	284 (65.0)	133 (71.1)	72 (76.6)
Prior *C. diff*, n (%)	181 (16.3)	8 (7.5)	30 (10.4)	82 (18.8)	42 (22.5)	19 (20.2)
Prior malignancy, n (%)	94 (8.4)	16 (15.1)	33 (11.4)	25 (5.7)	14 (7.5)	6 (6.4)

BMI: body mass index; C. diff: Clostridioides difficile; CD: Crohn's disease; IQR: interquartile range; UST: ustekinumab;
*Based on Montreal classification: L1=ileal; L2=colonic; L3=ileocolonic

Johnson et al. Am J Gastroenterol. 2022; Epub 30SEP. doi: 10.14309/ajg.0000000000002047.

Durable Remission with Ustekinumab based on Prior Biologic Exposure

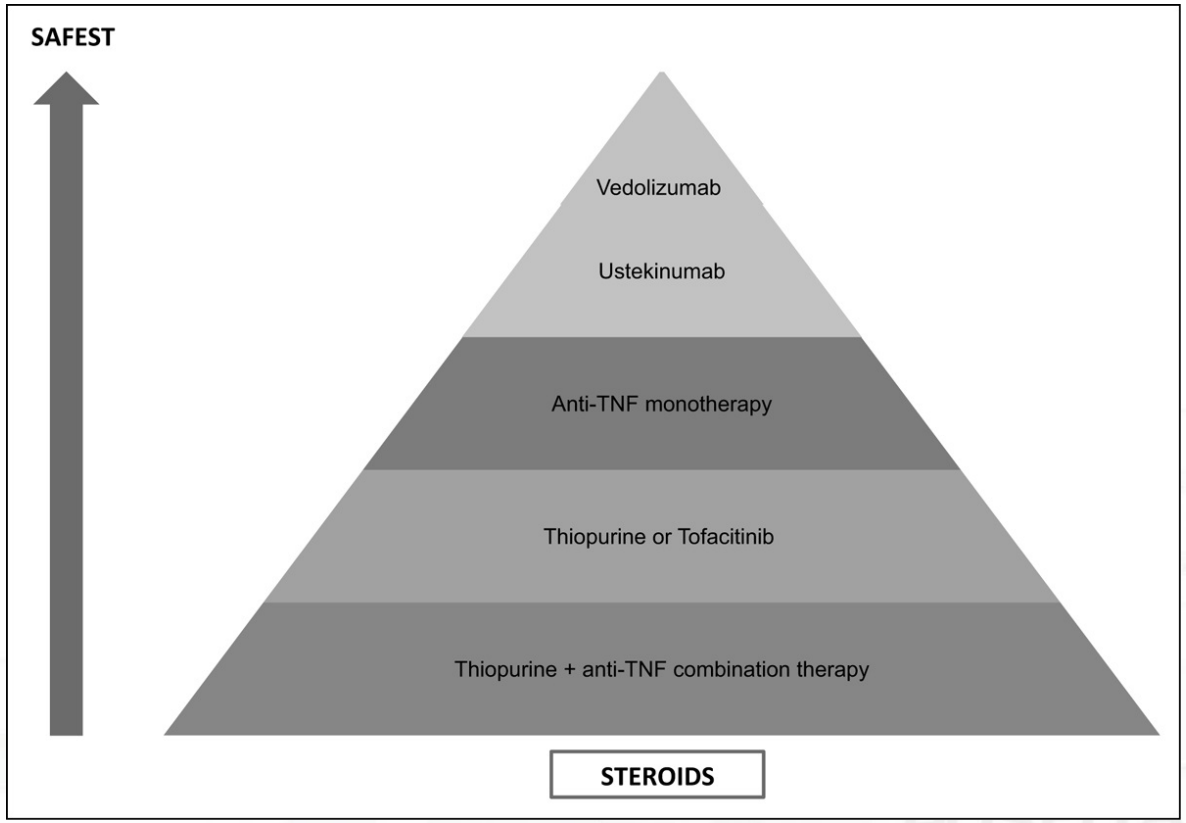


Rates of durable remission* were significantly reduced based on the number of prior biologic exposures, (aHR per biologic exposure, 0.829; 95% CI, 0.74-0.94)†

*Durable remission defined as achieving and maintaining clinical remission without loss of remission throughout duration of follow-up
†after adjusting for disease duration, albumin, history of stricturing or penetrating disease, prior perianal disease, and history of bowel surgery

Johnson et al. Am J Gastroenterol. 2022; Epub 30SEP. doi: 10.14309/ajg.0000000000002047.

Seguridad de los tratamientos para la Enfermedad Inflamatoria Intestinal

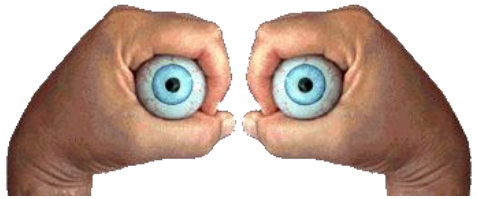


	Infections	Opportunistic infections	Malignancies	Immunologic issues	Thrombosis	Metabolic disorders
Thiopurine/Anti-TNF combo	++	++	+	+	–	+
Tofacitinib	+	+	N/A	–	+	+
Anti-TNF monotherapy	+	++	+	++	–	+
Vedolizumab	+/–	–	N/A	+	–	+/–
Ustekinumab	+/–	–	N/A	+	–	–

++: Strong association; +: association; +/–: possible association → adverse events reported in clinical trials, although incidence rates are comparable with placebo; –: no association; N/A: data not available. TNF, tumor necrosis factor; Include combo, combination therapy.

Queiroz NSF, Regueiro M. Curr Opin Gastroenterol. 2020 Jul;36(4):257-264.

Conclusiones



- La enfermedad de Crohn tiene un alto impacto en la calidad de vida de lo pacientes y en el sistema

- La utilización de PROMs podrían ayudar al control de la enfermedad

- Los estudios RWE generan evidencia que puede ayudar a la optimización del tratamiento (efectividad y seguridad a largo plazo)

- El tratamiento temprano→ beneficio claro→ definir perfil de pacientes

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MUCHAS GRACIAS POR SU ATENCIÓN

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