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XIII CURSO GETECCU-SEGHNP
sobre EII Pediátrica

Terapia dual avanzada en EII pediátrica

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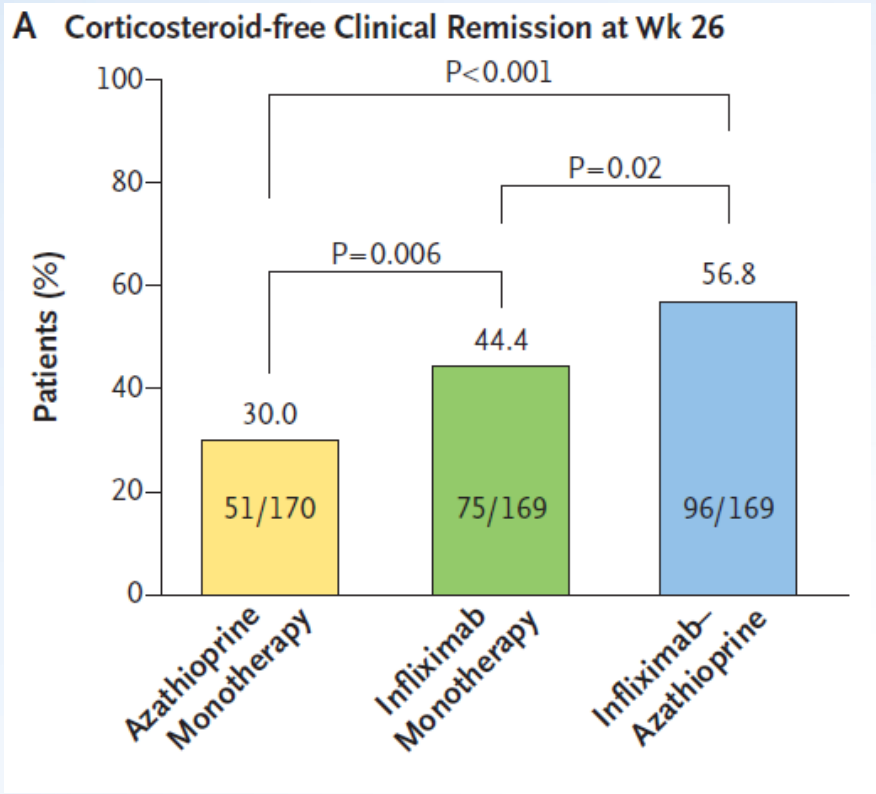
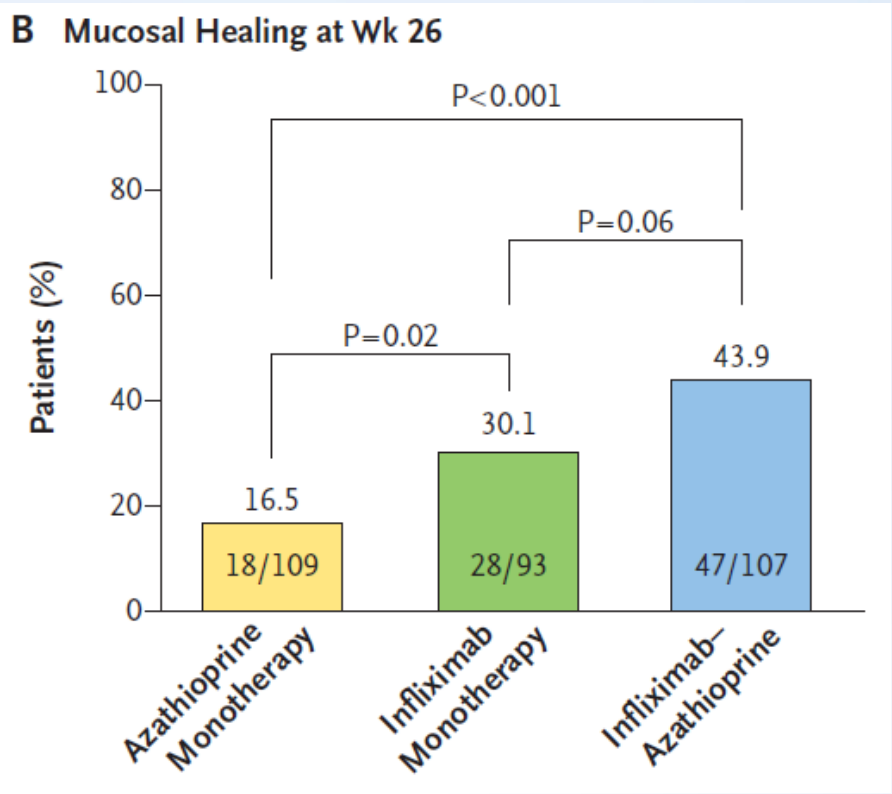
Conflictos de interés

- En los últimos 3 años he recibido remuneración por labor de consultoría, becas de investigación, u honorarios por actividades científicas de las siguientes empresas: Abbott, Abbvie, Adacyte, Celgene, Celltrion, Dr. Falk, FAES, Ferring, Janssen, Kern Pharma, Lactalis, Mead&Johnson, Nestlé Health Science, Nutricia, Recordati, Ordesa, Zambón

Combo-lovers…

Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease

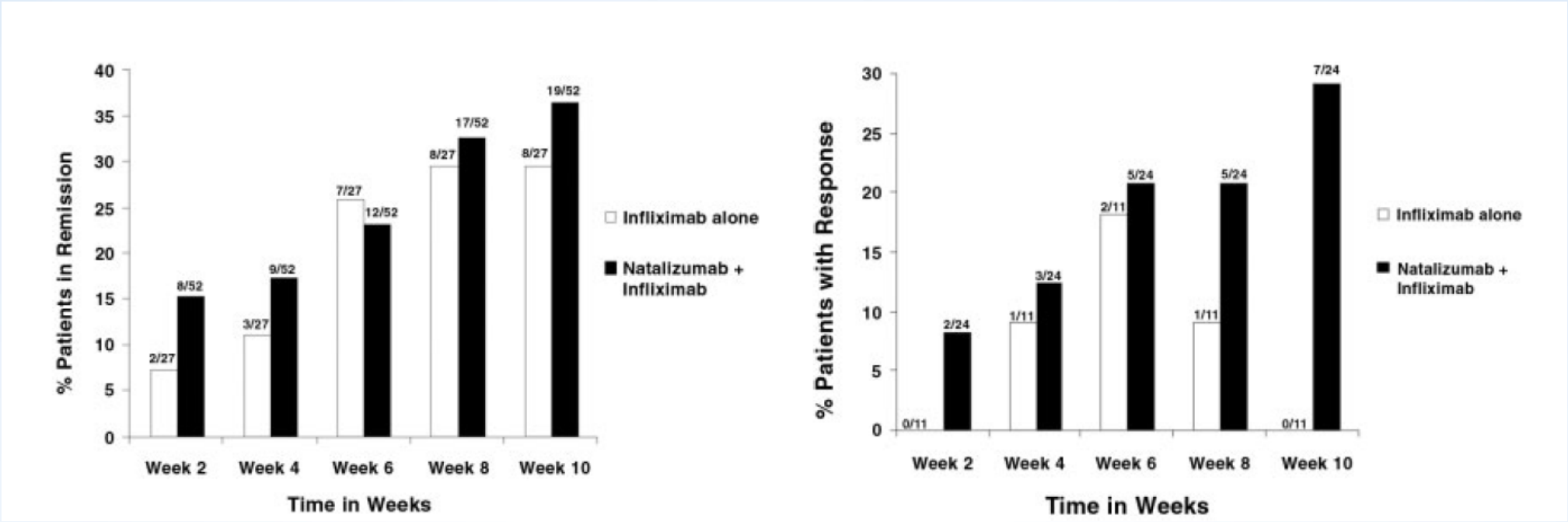




Colombel JF, et al. *N Engl J Med* 2010;362:1383-95

De la terapia *combo* a la *terapia avanzada dual*

Safety and Tolerability of Concurrent Natalizumab Treatment for Patients with Crohn's Disease Not in Remission While Receiving Infliximab

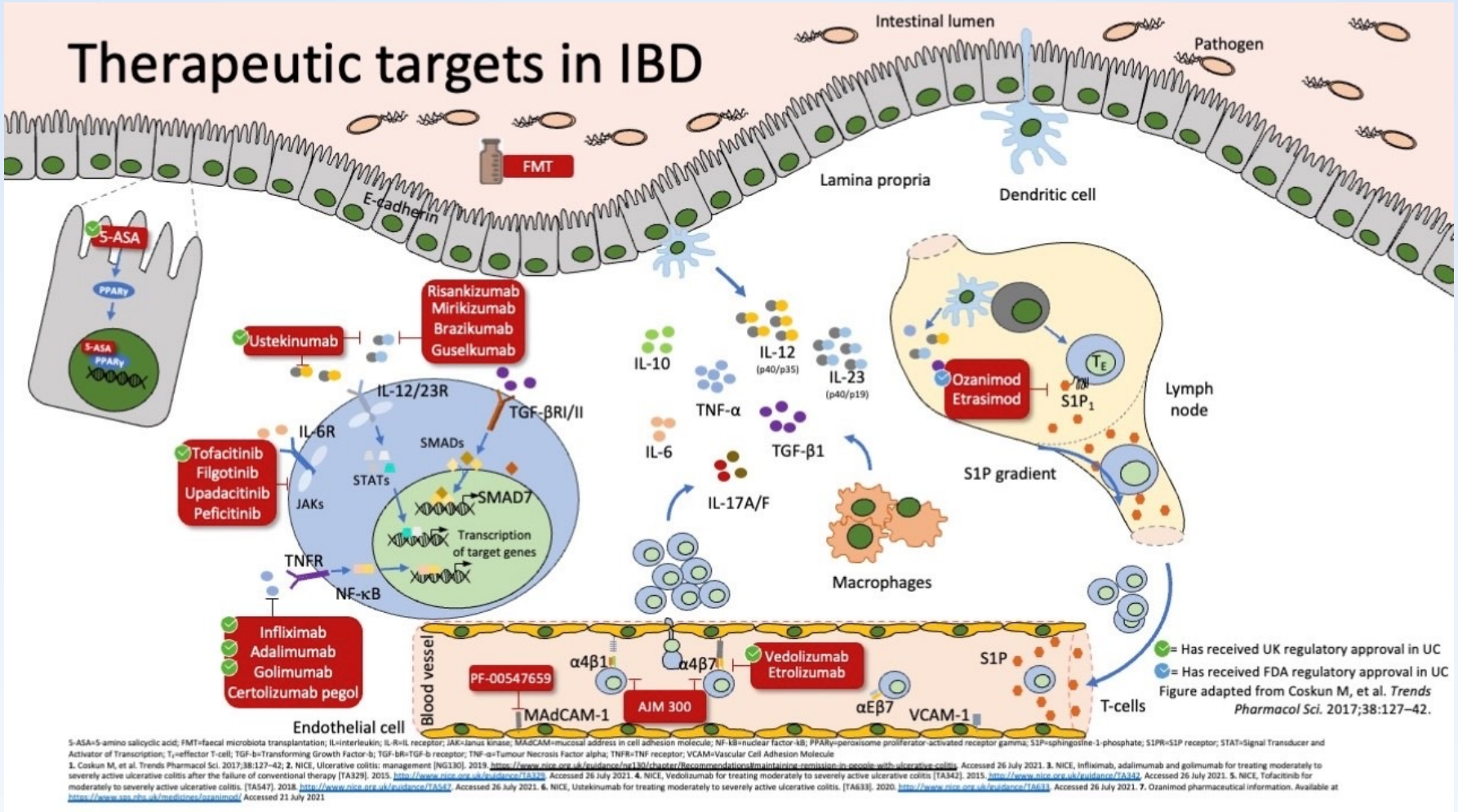


Sands BE, *et al. Inflamm Bowel Dis 2007;13:2–11*

El racional

- Diferentes vías inflamatorias implicadas en la EII
- Fallo de respuesta primaria y pérdida secundaria de respuesta a lo largo del tiempo
- Tasa de remisión *subóptima* con los tratamientos actuales
- Menor eficacia de los nuevos tratamientos en pacientes con fracaso previo al tratamiento anti-TNFα
- Retraso en la respuesta a diferentes tratamientos
- Coexistencia de otras enfermedades inmuno-mediadas o MEI que precisan la asociación de tratamientos

Vías inflamatorias en la EII



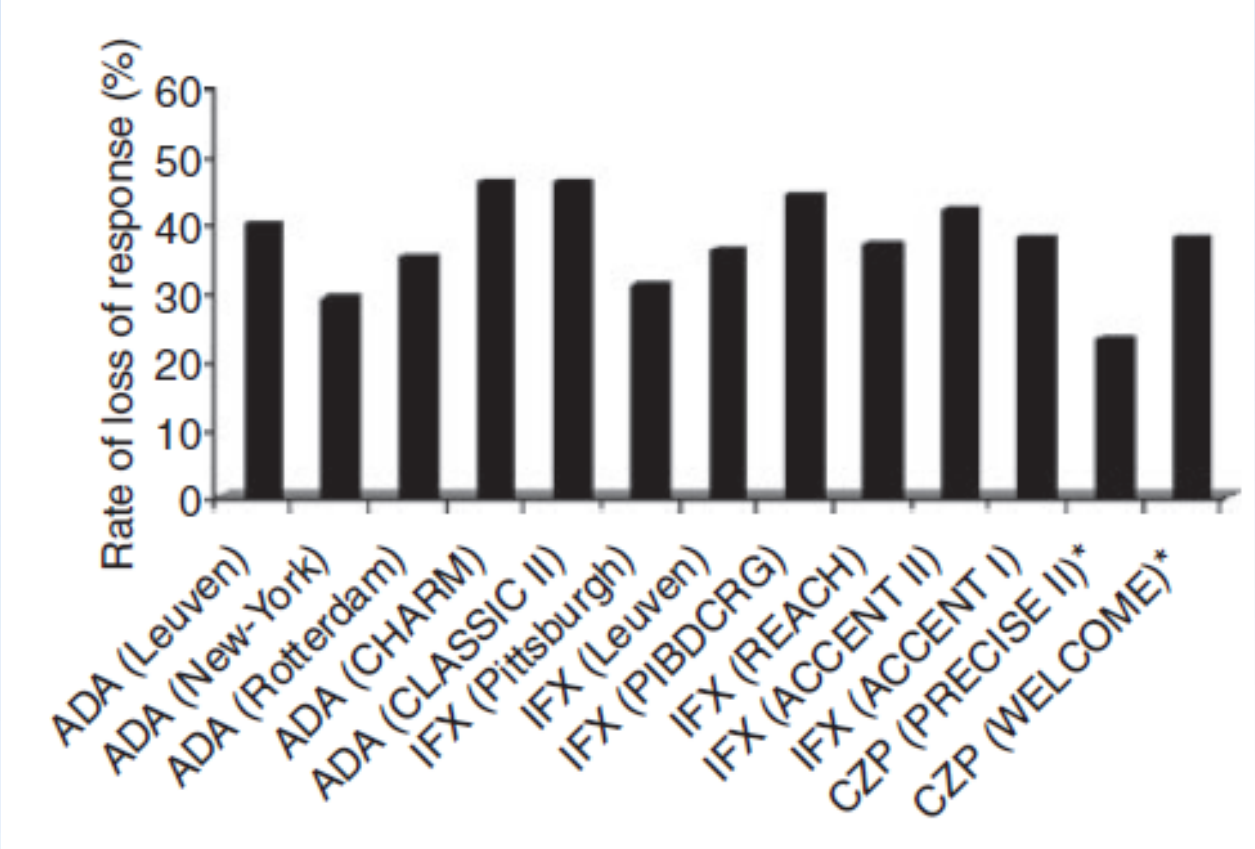
5-ASA=5-amino salicylic acid; FMT=faecal microbiota transplantation; IL=interleukin; IL-R=IL receptor; JAK=Janus kinase; MAdCAM=mucosal address in cell adhesion molecule; NF-kB=nuclear factor-kB; PPARγ=peroxisome proliferator-activated receptor gamma; S1P=sphingosine-1-phosphate; S1PR=S1P receptor; STAT=Signal Transducer and Activator of Transcription; T_E=effector T-cell; TGF-b=Transforming Growth Factor-b; TGF-bR=TGF-b receptor; TNF-α=Tumour Necrosis Factor alpha; TNFR=TNF receptor; VCAM=Vascular Cell Adhesion Molecule

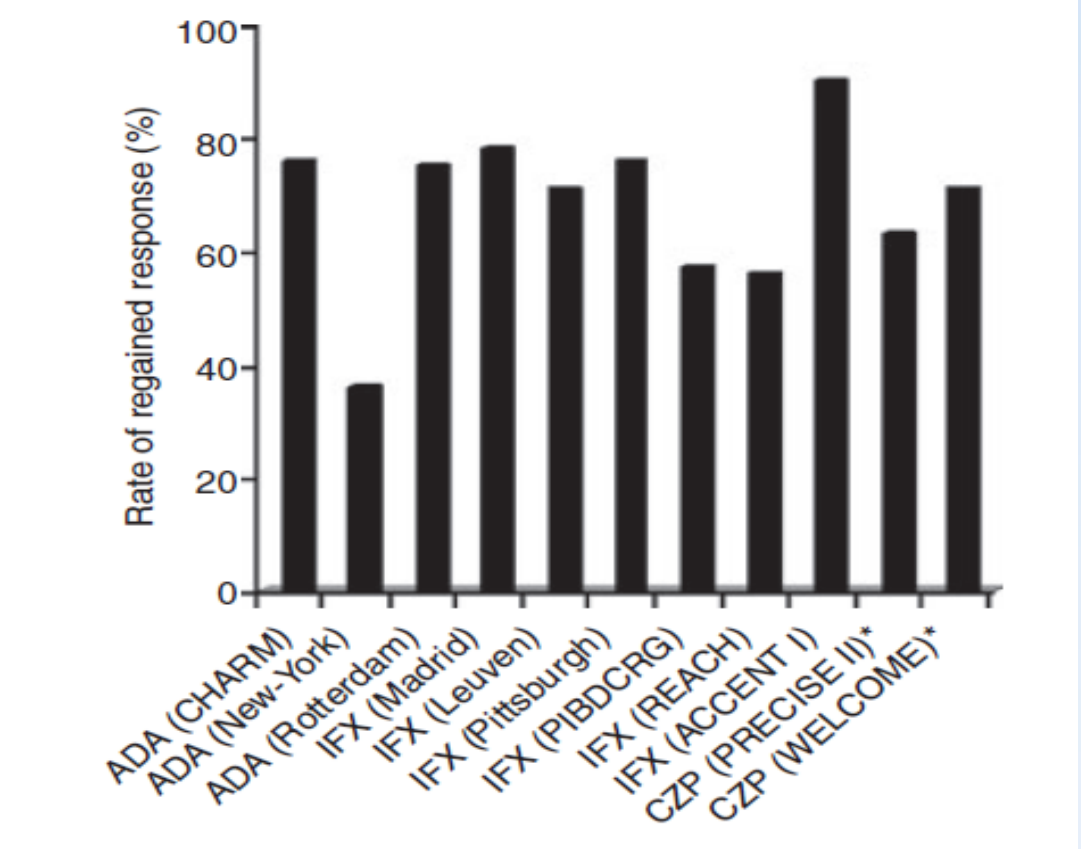
1. Coskun M, et al. Trends Pharmacol Sci. 2017;38:127–42; 2. NICE, Ulcerative colitis: management [NG130]. 2019. https://www.nice.org.uk/guidance/ng130/chapter/Recommendations#maintaining-remission-in-people-with-ulcerative-colitis. Accessed 26 July 2021. 3. NICE, Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [TA329]. 2015. http://www.nice.org.uk/guidance/TA329. Accessed 26 July 2021. 4. NICE, Vedolizumab for treating moderately to severely active ulcerative colitis [TA342]. 2015. http://www.nice.org.uk/guidance/TA342. Accessed 26 July 2021. 5. NICE, Tofacitinib for moderately to severely active ulcerative colitis. [TA547]. 2018. http://www.nice.org.uk/guidance/TA547. Accessed 26 July 2021. 6. NICE, Ustekinumab for treating moderately to severely active ulcerative colitis. [TA633]. 2020. http://www.nice.org.uk/guidance/TA633. Accessed 26 July 2021. 7. Ozanimod pharmaceutical information. Available at https://www.sps.nhs.uk/medicines/ozanimod/ Accessed 21 July 2021

La terapia avanzada en la EII-P sigue pasando siempre por el anti-TNFα

- Infliximab y Adalimumab como únicos biológicos aprobados para su uso en Pediatría
- Según criterios fármaco-económicos, el primer biológico en adultos sigue siendo el anti-TNFα (biosimilares en el mercado)
- A día de hoy, no hay posibilidad de establecer diferentes estrategias terapéuticas avanzadas en base a criterios específicos del paciente

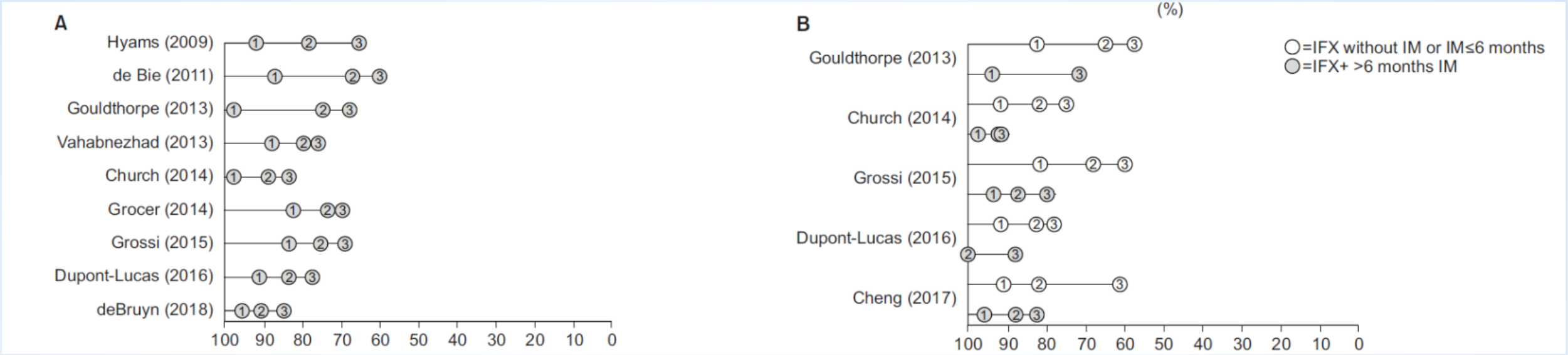
Pérdida secundaria de respuesta al anti-TNFα





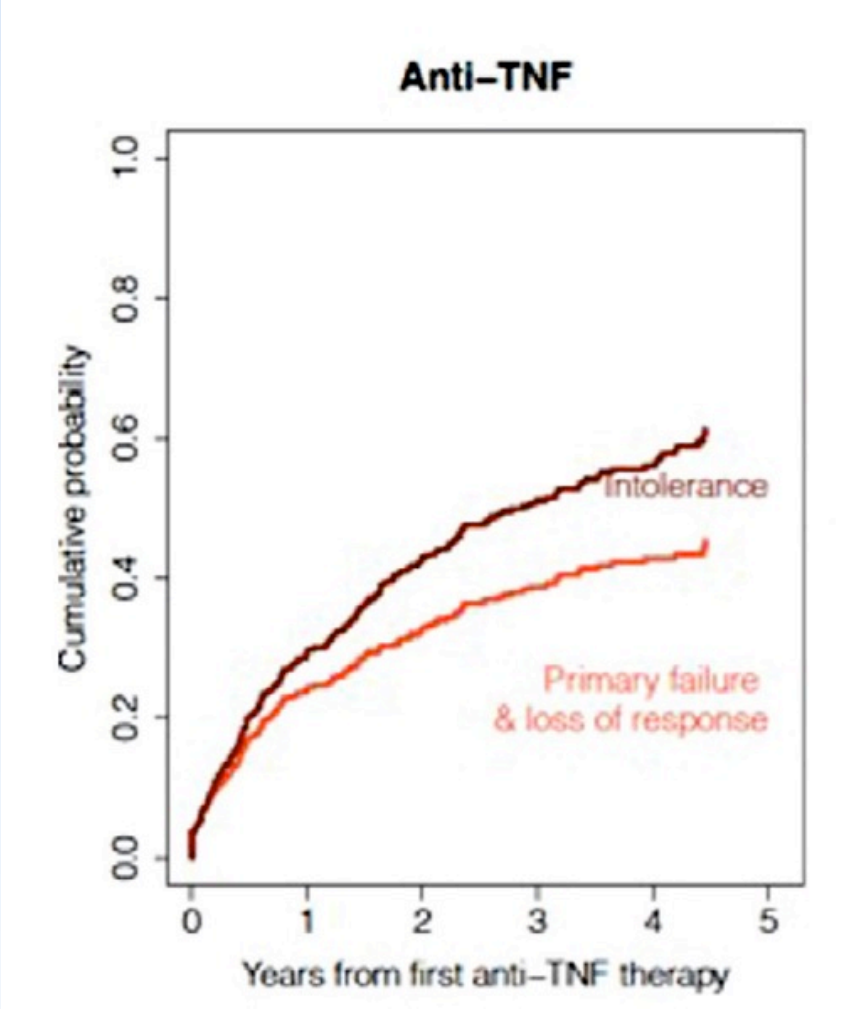
Ben-Horin S, *et al*. *Aliment Pharmacol Ther* 2011;33:987-95

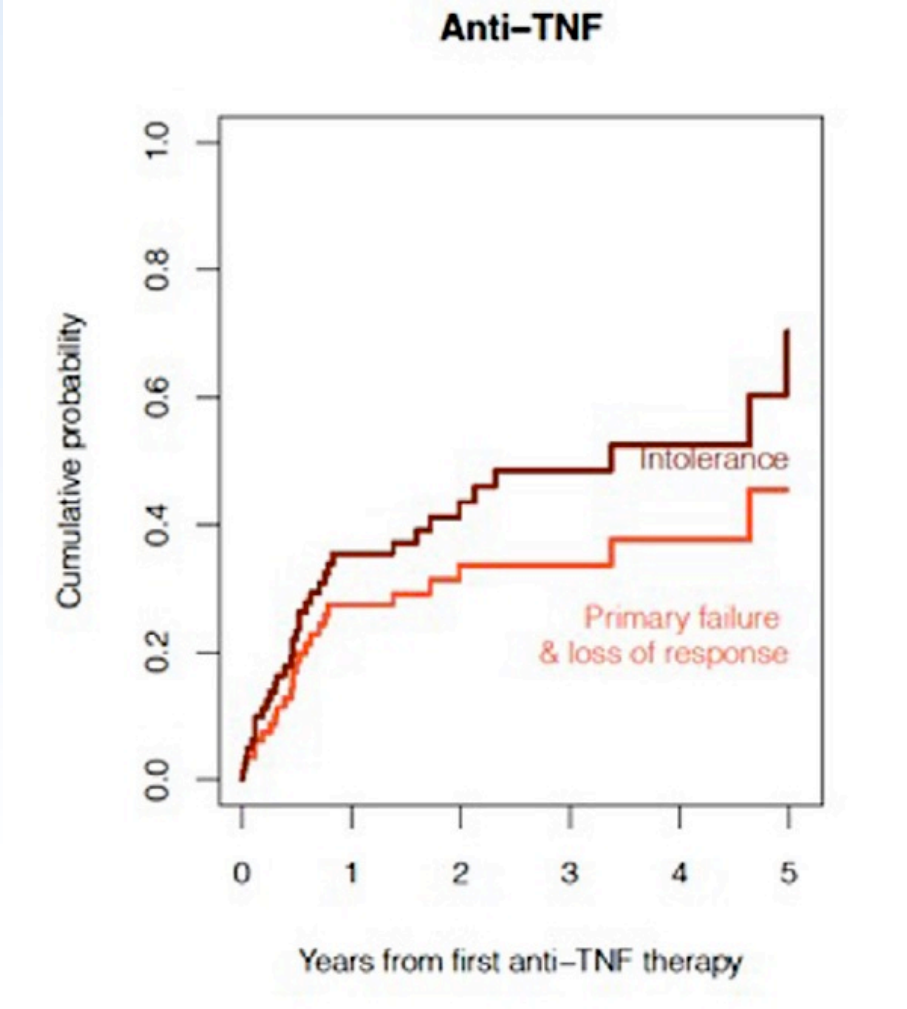
Long-Term Efficacy of Anti-Tumor Necrosis Factor Agents in Pediatric Luminal Crohn's Disease: A Systematic Review of Real-World Evidence Studies



Van Rheenen H, *et al*. *Pediatr Gastroenterol Hepatol Nutr* 2020;23:121-31

Long-term effectiveness and safety of anti-TNF in pediatric-onset inflammatory bowel diseases: A population-based study

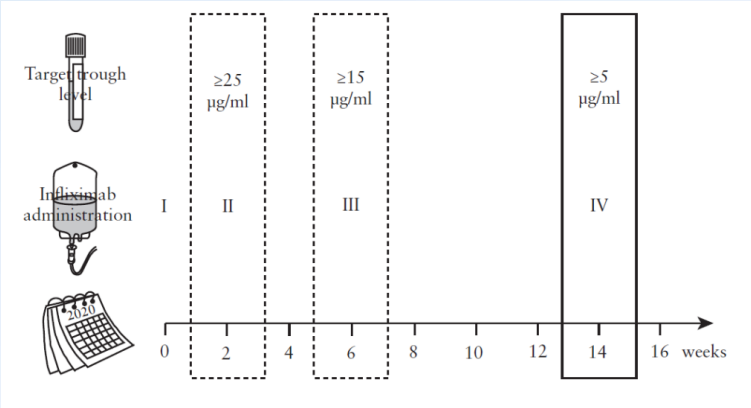


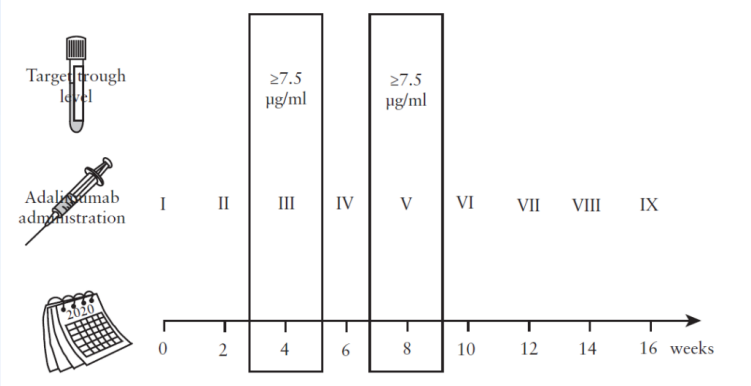


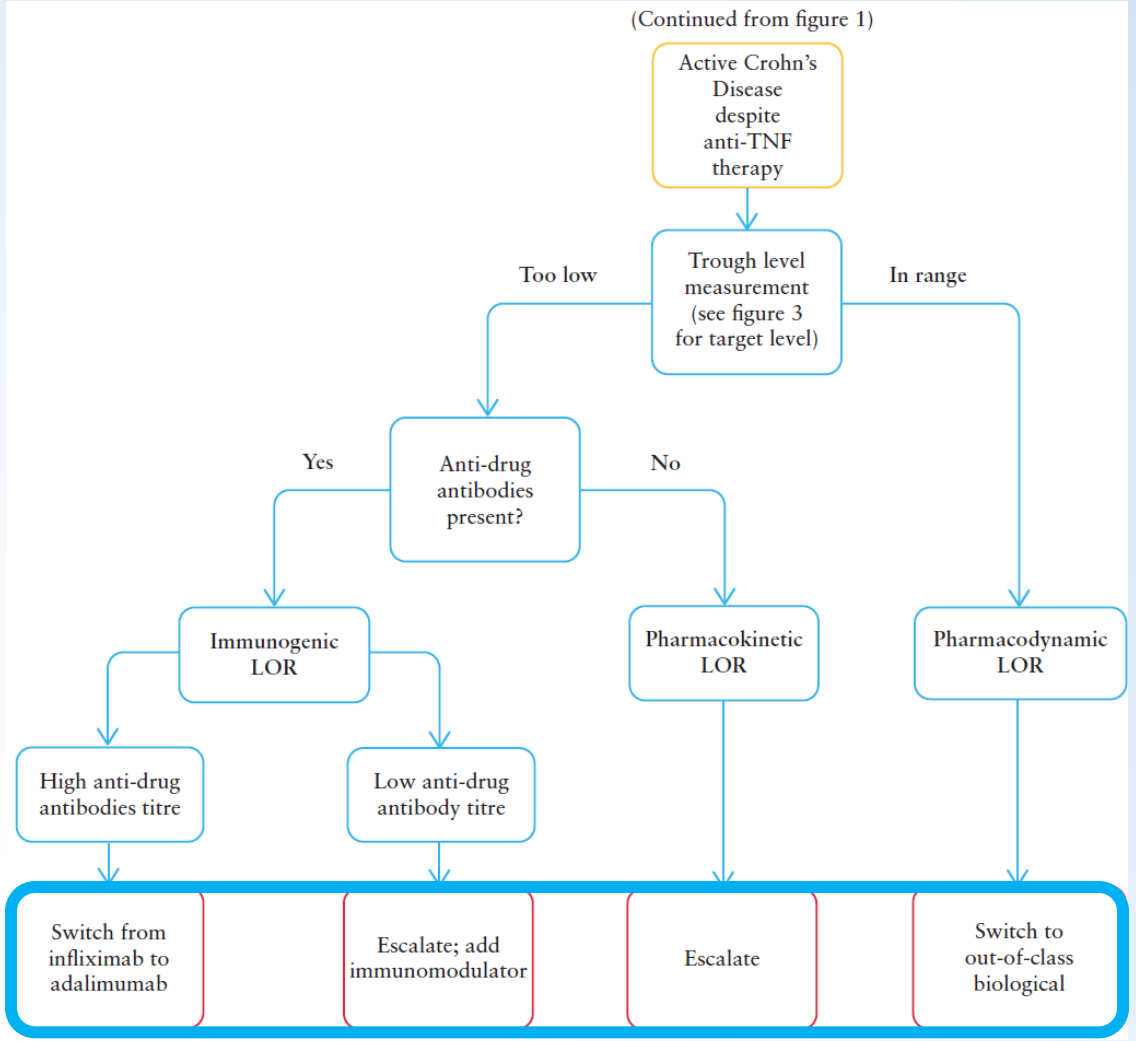
Fumery M, *et al*. *Dig Liver Dis* 2023 (Epub ahead of print)

Alternativas tras pérdida de respuesta al anti-TNFα

- ¿Cambio a otro anti-TNFα? (switch)
- ¿Cambio de diana terapéutica? (swap?)







Van Rheenen PF, *et al*. *J Crohns Colitis* 2021;15:171-94

STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

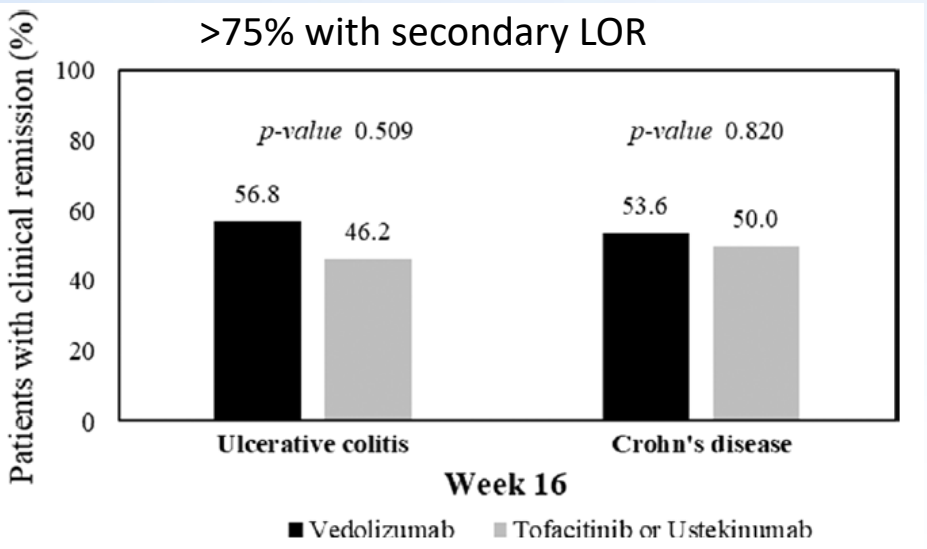
	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of FC[a]	EH
Crohn's disease					
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative colitis					
Oral 5-ASA	4	8	8	10	13
Oral Steroids	2	2	5	8	11
Locally active steroids[b]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

Turner D, *et al*. *Gastroenterology* 2021;160:1570-83

Eficacia de los nuevos biológicos tras fracaso de anti-TNFα

Comparative effectiveness of second-line biological therapies for ulcerative colitis and Crohn's disease in patients with prior failure of anti-tumour necrosis factor treatment

>75% with secondary LOR



Hyun HK, *et al.* BMC Gastroenterol 2022;22:143

Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment

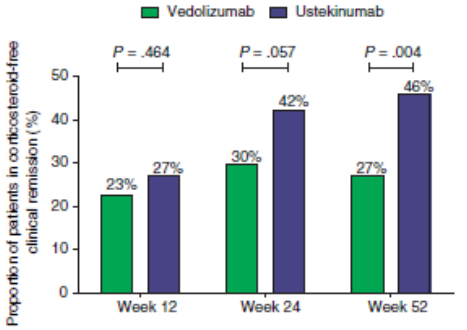


FIGURE 2 Unadjusted proportion of Crohn's disease patients achieving corticosteroid-free clinical remission (HBI ≤4). HBI, Harvey Bradshaw Index

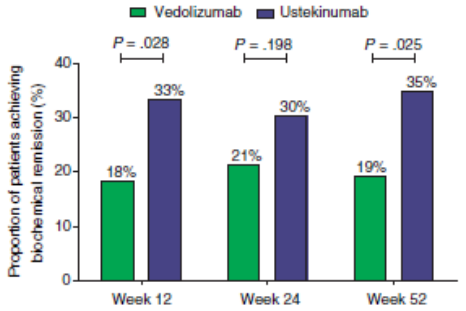


FIGURE 3 Unadjusted proportion of Crohn's disease patients achieving biochemical remission (CRP ≤5 mg/L and faecal calprotectin ≤250 µg/g). CRP, C-reactive protein

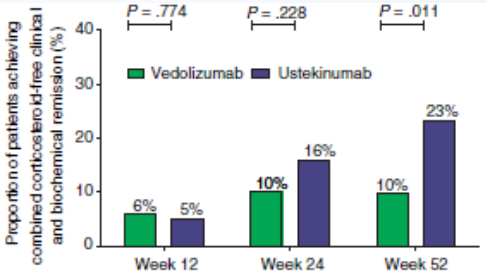
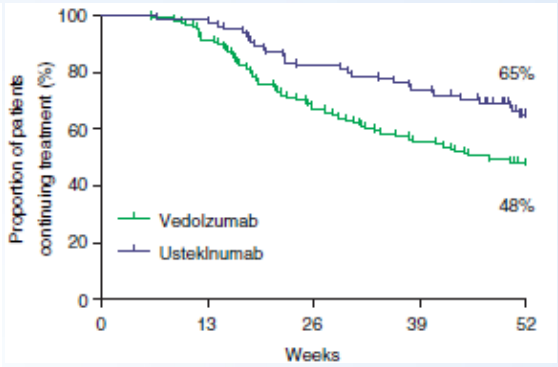


FIGURE 4 Unadjusted proportion of Crohn's disease patients achieving combined corticosteroid-free clinical and biochemical remission (HBI ≤4, CRP ≤5 mg/L and faecal calprotectin ≤250 µg/g). CRP, C-reactive protein; HBI, Harvey Bradshaw Index



Biemans VBC, *et al. Aliment Pharmacol* Ther 2020;52:123-34

¿Situación singular en el paciente pediátrico?

- En nuestra experiencia personal, pocos pacientes responden tras el cambio de biológico (según ficha técnica) tras pérdida secundaria de respuesta al anti-TNFα
- Necesidad de estrategias *maximizadas* de respuesta al biológico de segunda línea (mantenimiento con dosis ev de inducción, reinducción, intensificación…)
- ¿Factores implicados?
  - Bloqueo de la vía TNF de larga duración
  - Tratamientos intensificados
  - Inflamación activa mantenida y perpetuada por otras vías
  - ¿Efecto rebote al suspender el tratamiento anti-TNFα?

Alternativas tras la pérdida de respuesta al antiTNF

- ¿Cambio a otro anti-TNF? (switch)
- ¿Cambio de diana terapéutica? (swap?
- ¿Combinar terapias avanzadas?

Biológicos

- Acs anti-integrina (Vedolizumab, Etrolizumab)
- Acs anti IL12-23 (Ustekinumab)
- Acs anti IL23 (Risankizumab, Guselkumab, Mirikizumab)

Moléculas pequeñas

- Inhibidores JAK (Tofacitinib, Filgotinib, Upadacitinib)
- Moduladores del receptor S1-P (Ozanimod, Etrasimod)

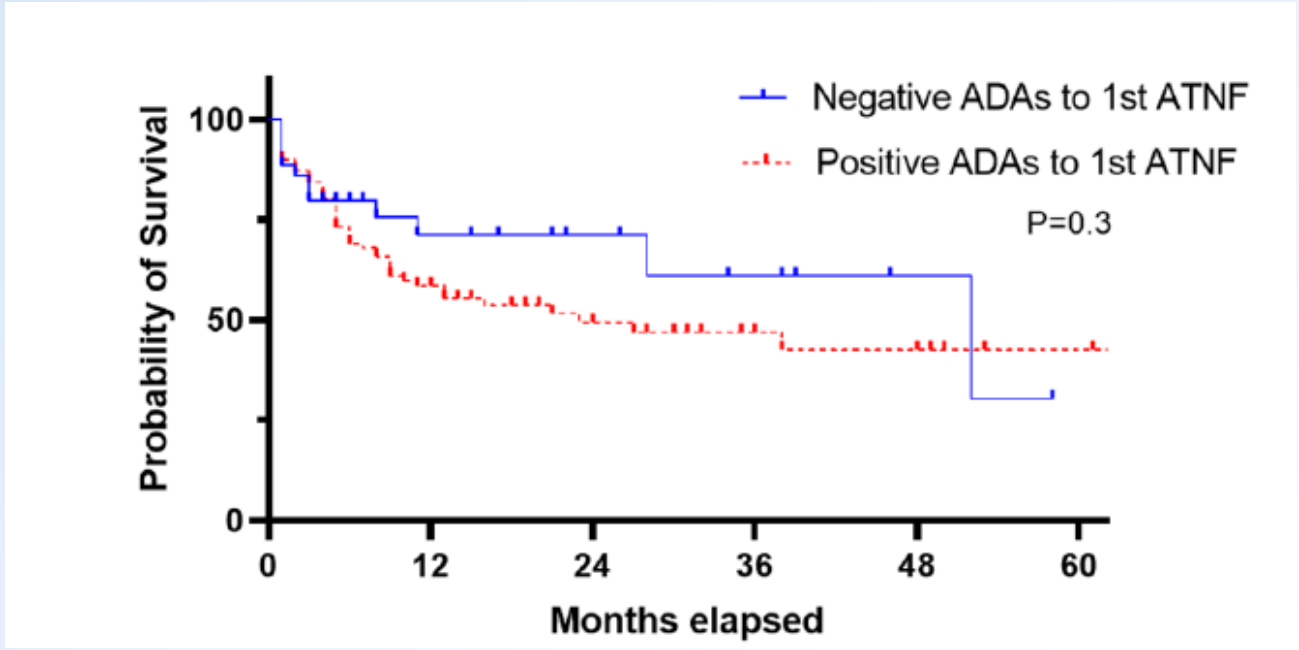
Posibles escenarios clínicos para la terapia dual avanzada

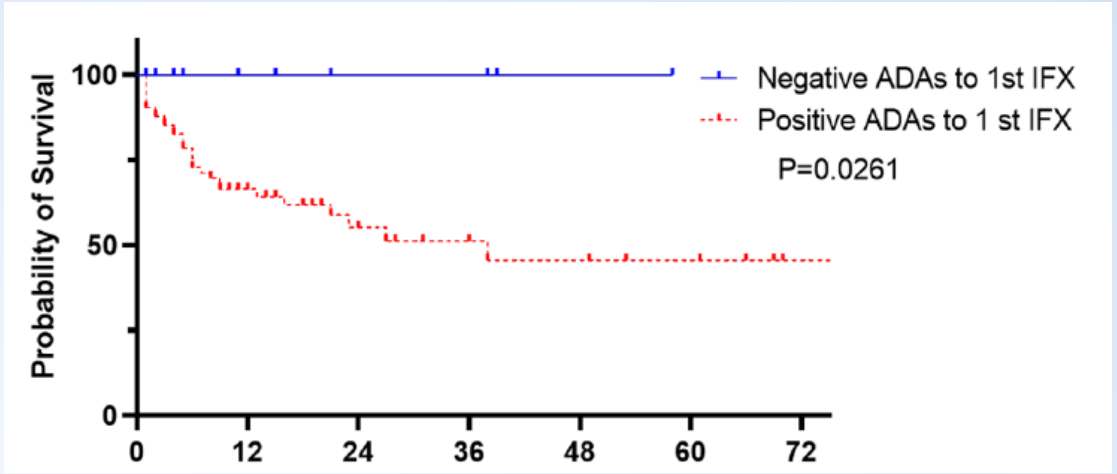
- ¿Respuesta parcial a anti-TNF?
- ¿Pérdida secundaria de respuesta a anti-TNF?
- Efectos adversos del anti-TNF respondedores a otro tratamiento avanzado (preservando el anti-TNFα)
- MEI asociadas
- Enfermedad inmuno-mediada asociada

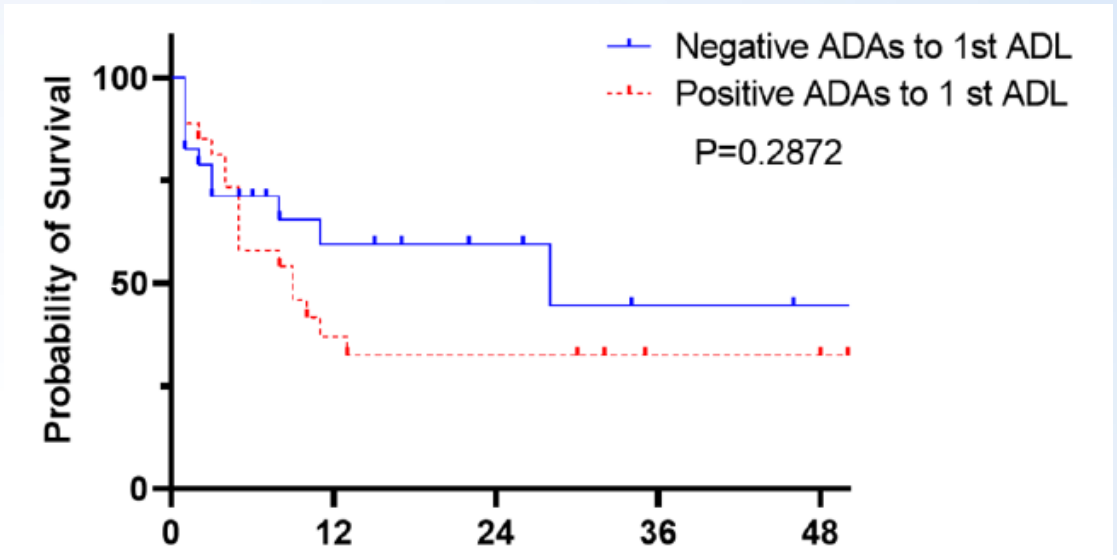
Fallo a anti-TNFα y mantenimiento del tratamiento; diferentes escenarios

- Fallo primario de respuesta ✖
- Pérdida de respuesta inmunogénica con anticuerpos anti-droga presentes !!
- Reactivación de la enfermedad con niveles de fármaco adecuados
- Respuesta *disociada al* anti-TNF (luminal, perianal, transmural; persistente, recidivante, *de novo*)

Risk of consecutive immunogenic failure in switchers of anti-tumor necrosis factor alpha among patients with inflammatory bowel diseases







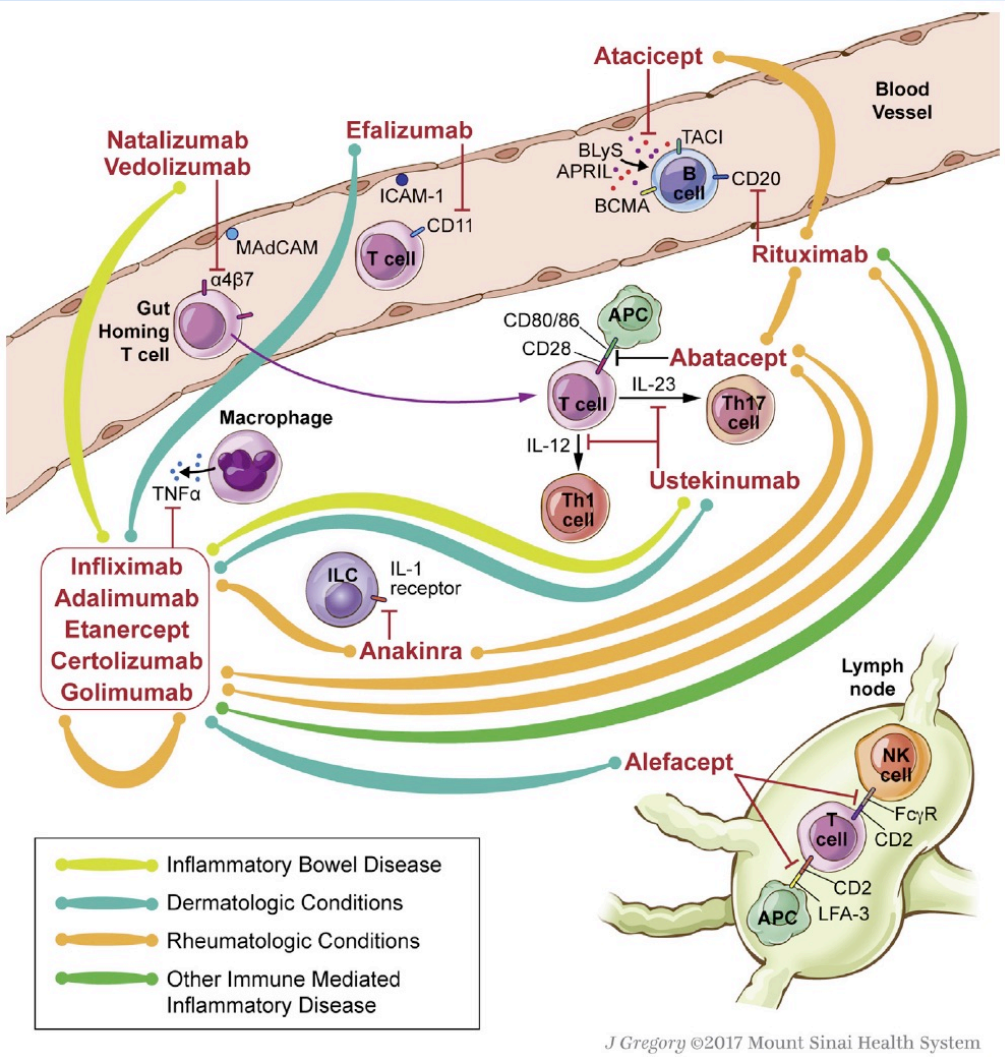
Yanai H, *et al*. *Ther Adv Gastroenterol* 2022;15:1-12

Fallo a anti-TNF; diferentes escenarios

- Fallo primario de respuesta 
- Pérdida de respuesta inmunogénica con anticuepros anti-droga presentes !!
- Reactivación de la enfermedad con niveles de fármaco adecuados 
- Respuesta *disociada al* anti-TNF (luminal, perianal, transmural; persistente, recidivante, *de novo*) 

El nuevo *trending topic…*

Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders



J Gregory ©2017 Mount Sinai Health System

Table 2. Publications on the Use of Combined Biologic Agents in the Treatment of Dermatologic Conditions

Reference	Year	Study type	Disease	Number of subjects	Medications (n)	Efficacy	Adverse events	Follow-up period
Cuchacovich et al[10]	2012	Case report	Psoriasis + PSA	1	Etanercept + UST	Composite psoriatic disease activity index, significant improvement	None	11 mo
Babalola et al[11]	2015	Case report	Psoriasis + PSA	1	Etanercept + UST	Resolved joint and skin manifestations	Unstable angina/cardiac stent	6 mo
Heinecke et al[12]	2013	Case report	Psoriasis + PSA	1	UST + etanercept → adalimumab	Skin improved but joint symptoms continued	Furuncles + autoimmune hemolytic anemia	—
Gniadecki et al[13]	2016	Case series	Psoriasis + PSA	4	UST + etanercept (2) or adalimumab → golimumab (1) or adalimumab → certolizumab (1)	Improved skin and joint symptoms	Herpes zoster, retrotonsillar abscess, erysipelas, bacterial pneumonia, cellulitis	7–62 mo 16.2 patient-years of exposure
Adisen et al[15]	2008	Case report	Psoriasis + PSA	1	Efalizumab + etanercept	Improved skin and joint symptoms	None	1.5 mo
Kitamura et al[16]	2009	Case report	Psoriasis + PSA	1	Efalizumab + etanercept	Improved skin and joint symptoms	Pulmonary tuberculosis	~18 mo
Hamilton[17]	2008	Case series	Psoriasis + PSA	20	Efalizumab + etanercept or etanercept → infliximab	Improved skin and joint symptoms	URI, LRI, SCC, BCC, dysplastic nevus, actinic keratoses	16 mo (range, 8–46 mo)
Krell[19]	2006	Case series	Psoriasis + PSA	3	Alefacept + etanercept	Improved skin and joint symptoms	None	—

Table 3. Publications on the Use of Combined Biologic Agents in the Treatment of Rheumatologic Conditions

Reference	Year	Study type	Disease	Number of subjects	Medications (n)	Efficacy	Adverse events (n)	Follow-up
Sheehy et al[21]	2006	Case report	HLA-B27-associated arthropathy	1	IFX + etanercept	Improved joint inflammation and pain	None	>6 mo
Weinblatt et al[24]	2007	RCT + LTE	RA	121	Etanercept + abacacept or placebo	No differences at 6 and 12 mo	Combination: higher AEs, SAEs, related SAEs, discontinuation because of AEs at 1 year; trend continued in LTE	RCT- 12 mo LTE- 24 mo
Genovese et al[26]	2004	RCT	RA	242	Anakinra + etanercept vs etanercept	No difference	Combination: higher SAEs (14.8% vs 2.5%), discontinuation because of AEs (7.4% vs 0%), injection reactions (70.4% vs 40%), 1 death	24 wk
Morgan et al[28]	2008	Observational study	RA	8	CD4 monoclonal antibody + bivalent TNF antagonist	Improved joint swelling and pain	Maculopapular rash (5), infusion reactions	17–49 mo
Koumakis et al[32]	2009	Case series	RA	2	RTX + etanercept	Resulted in remission	None	4 y; 18 mo
Feuchtenberger et al[33]	2009	Case series	RA	2	RTX + etanercept	Significantly improved disease activity	Pneumonia, acute bronchitis in 1 patient	6 y
Blank et al[34]	2009	Retrospective cohort	RA	6	RTX → etanercept + RTX if no response	Significant improvement with combination	Oral herpes simplex	18.5 mo of mean exposure
Rigby et al[36]	2013	Open label study	RA	176	RTX + background biologic	Physical function improved at 24 and 48 wk	24.3 SAEs/100 patient-years, cellulitis, pneumonia, bronchitis, septic shock, 3 deaths	48 wk
Greenwald et al[37]	2011	RCT	RA	51	RTX or placebo + adalimumab or etanercept	——	Placebo vs rituximab: AEs (83% vs 94%), SAEs (0% vs 6%); similar infectious rates	24 wk
Van Vollenhoven et al[38]	2015	RCT	RA	27	RTX + placebo or atacicept	No difference in clinical response	Combination vs placebo, treatment period: AEs (94.4% vs 100%), discontinuation because of AEs (22.2% vs 11.1%), infections (44.4% vs 66.7%) Follow-up: 12 SAEs	25-wk treatment period 32-wk follow-up
Weinblatt et al[39]	2006	RCT	RA	169	Abatacept or placebo + background biologic	Lack of clinical benefit with combination	Combination vs placebo: AEs (95.1% vs 89.1%), discontinuation because of AEs (8.7% vs 3.1%), infection (5.8% vs 1.6%); malignancy (7% vs 2%)	1 y
Record et al[40]	2011	Case series	Juvenile idiopathic arthritis	4	Abatacept + anakinra	Improved disease control in all subjects	None	8–17 mo

Table 4. Publications on the Use of Combined Biologic Agents in the Treatment of Other Immune-Mediated Inflammatory Disorders

Reference	Year	Study type	Disease	Number of subjects	Medications	Efficacy	Adverse events	Follow-up
Morarji et al[41]	2012	Case report	Necrotising scleritis	1	IFX + RTX	Resolution of scleritis	None	12 mo

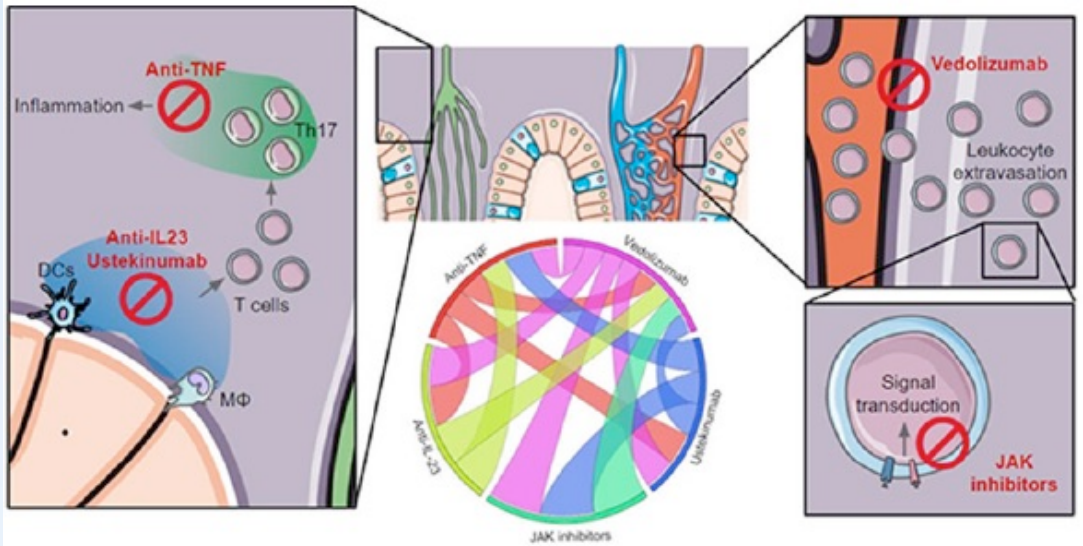
Hirten RP, *et al*. Clin Gastroenterol Hepatol 2018;16:1374-84

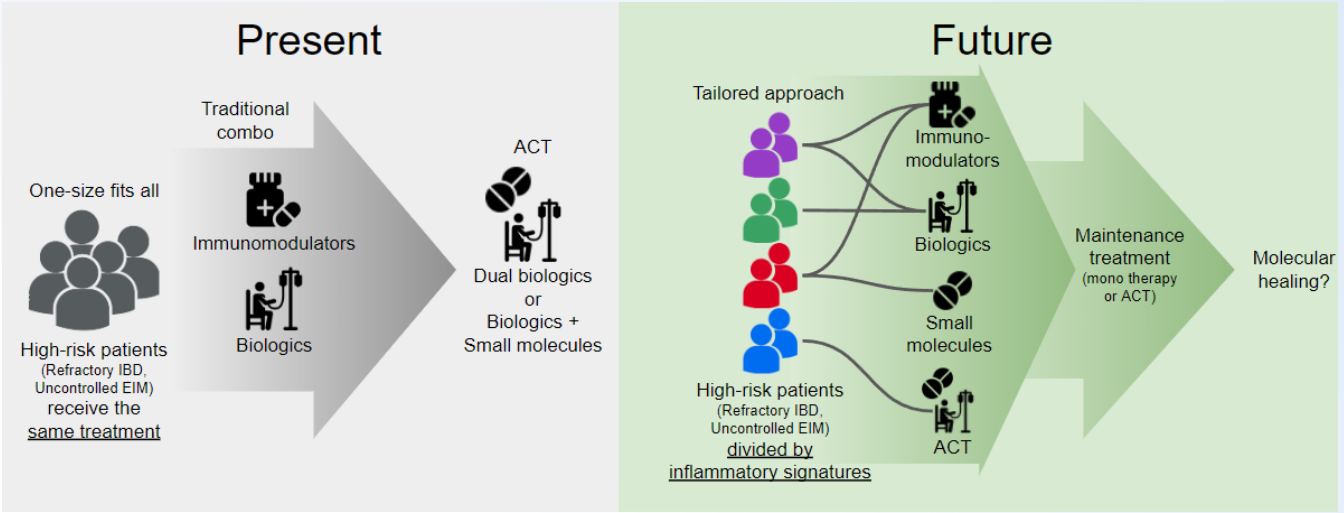
The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment)

Table 3 Possible ACT combinations in IBD

	Anti-TNF	Vedolizumab	Ustekinumab	Anti IL-23 (eg, guselkumab)	JAK inhibitors (eg, tofacitinib)
Anti-TNF	---	Yes	Yes	Yes	Too little evidence
Vedolizumab	Yes	---	Yes	Yes	Yes
Ustekinumab	Yes	Yes	---	Very similar MOA	Yes
Anti IL-23 (eg, guselkumab)	Yes	Yes	Very similar MOA	---	Too little evidence
JAK inhibitors (eg, tofacitinib)	Too little evidence	Yes	Too little evidence	Too little evidence	---

IBD, inflammatory bowel disease; JAK, Janus kinase; MOA, mechanism of action.





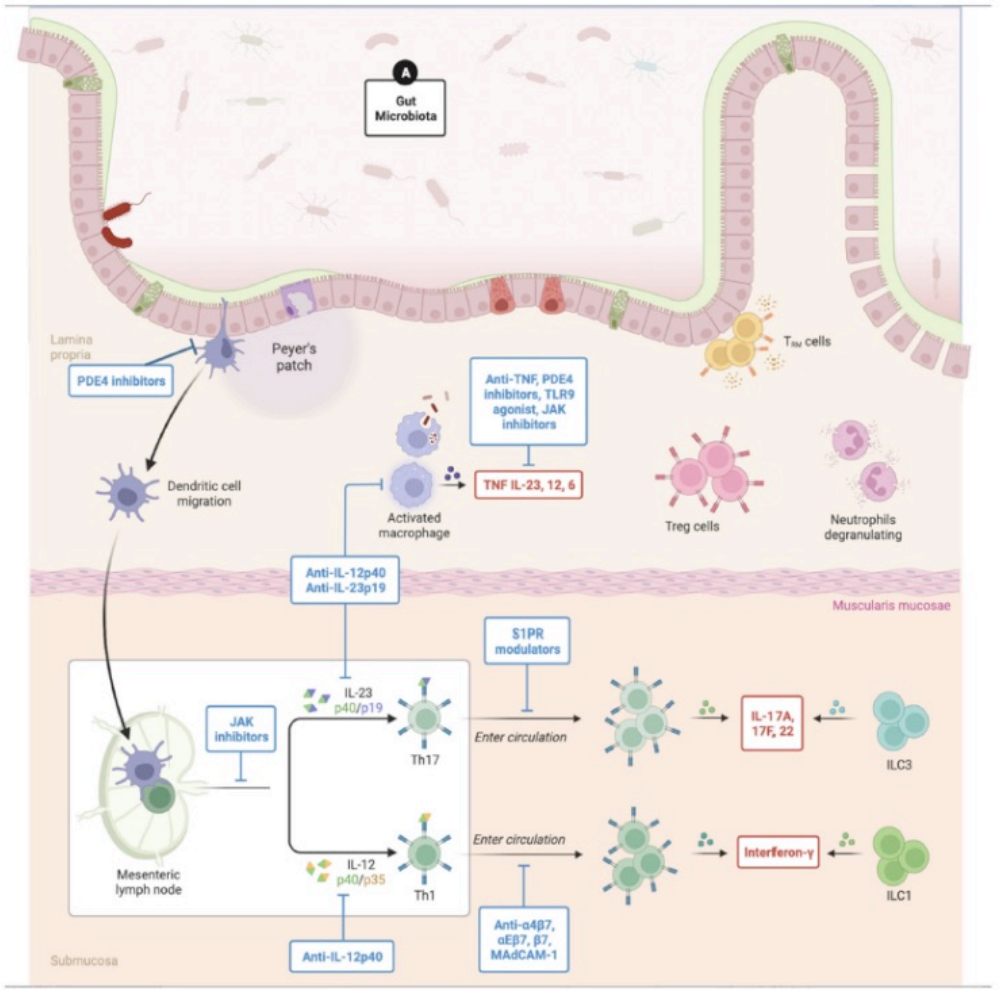
Danese S, *et al*. *Gut* 2022;71:2380-7

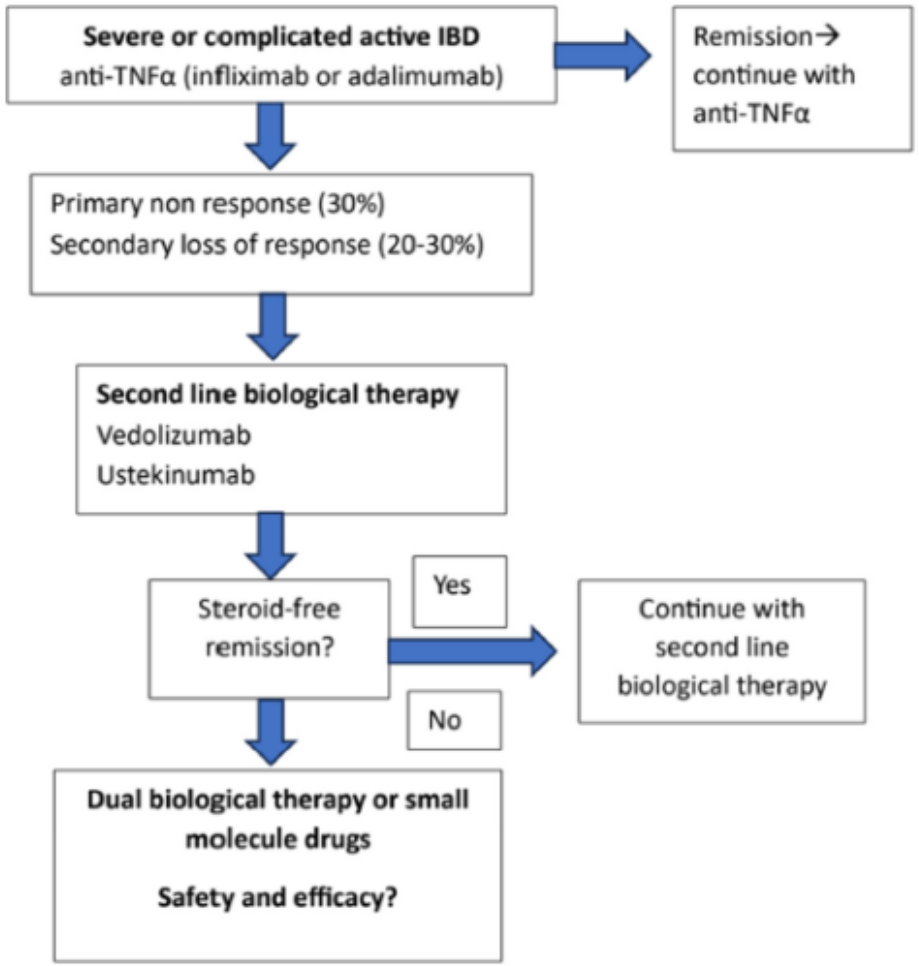
Una nueva etapa en el tratamiento de la EII…

- Hasta ahora la combinación de terapias se ha hecho bajo un punto de vista *oportunista,* basada más en la disponibilidad que en la hipótesis de un posible efecto aditivo o sinérgico
- Avanzamos hacia un nuevo escenario en el que la combinación de terapias se hará bajo las siguientes premisas:
  - Diferentes mecanismos de acción
  - Mínimo solapamiento
  - Efecto aditivo, supra-aditivo o sinérgico
  - Toxicidad infra-aditiva
  - Probablemente de manera precoz y de manera intensificada para obtener el mejor resultado

Stalgis C, *et al*. *Gastroenterology* 2021;161:394-9

Dual biological therapy and small molecules in pediatric inflammatory bowel disease





Penagini F, *et al*. *Pharmacol Res* 2023:196:106935.

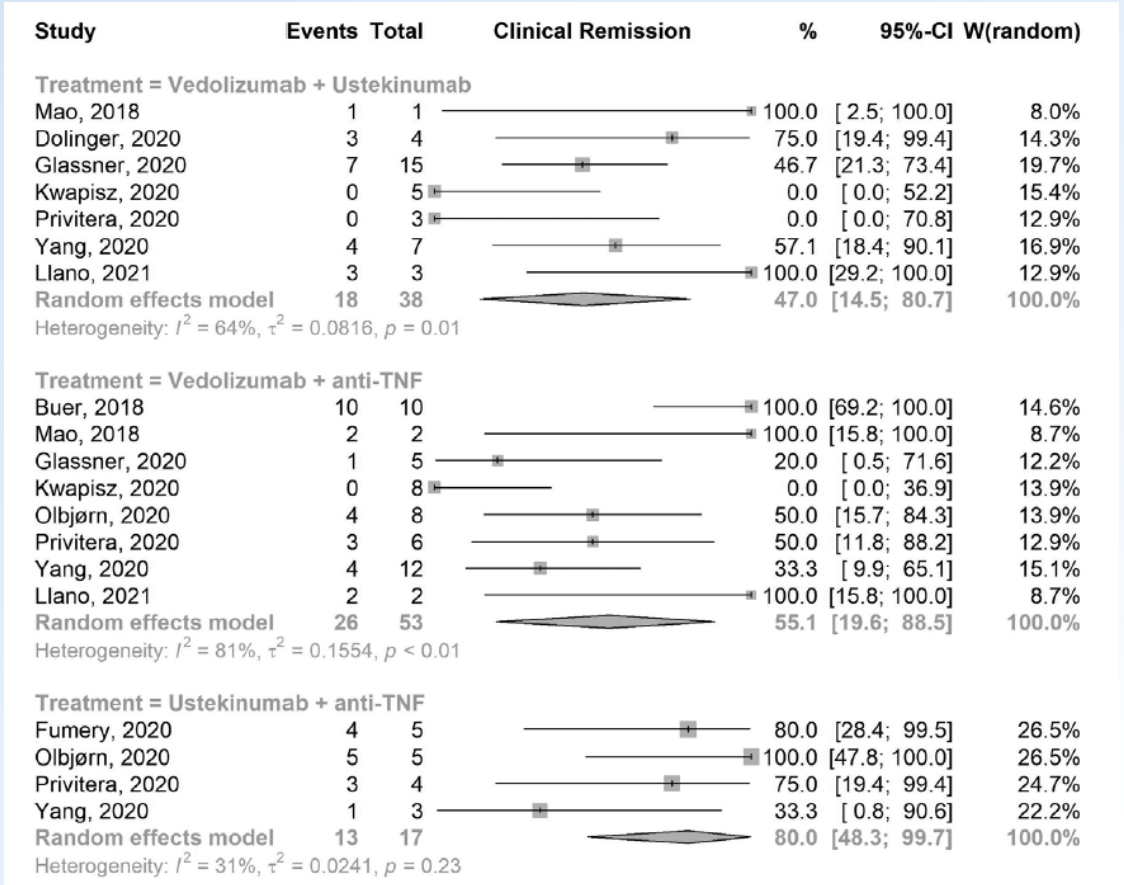
Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease

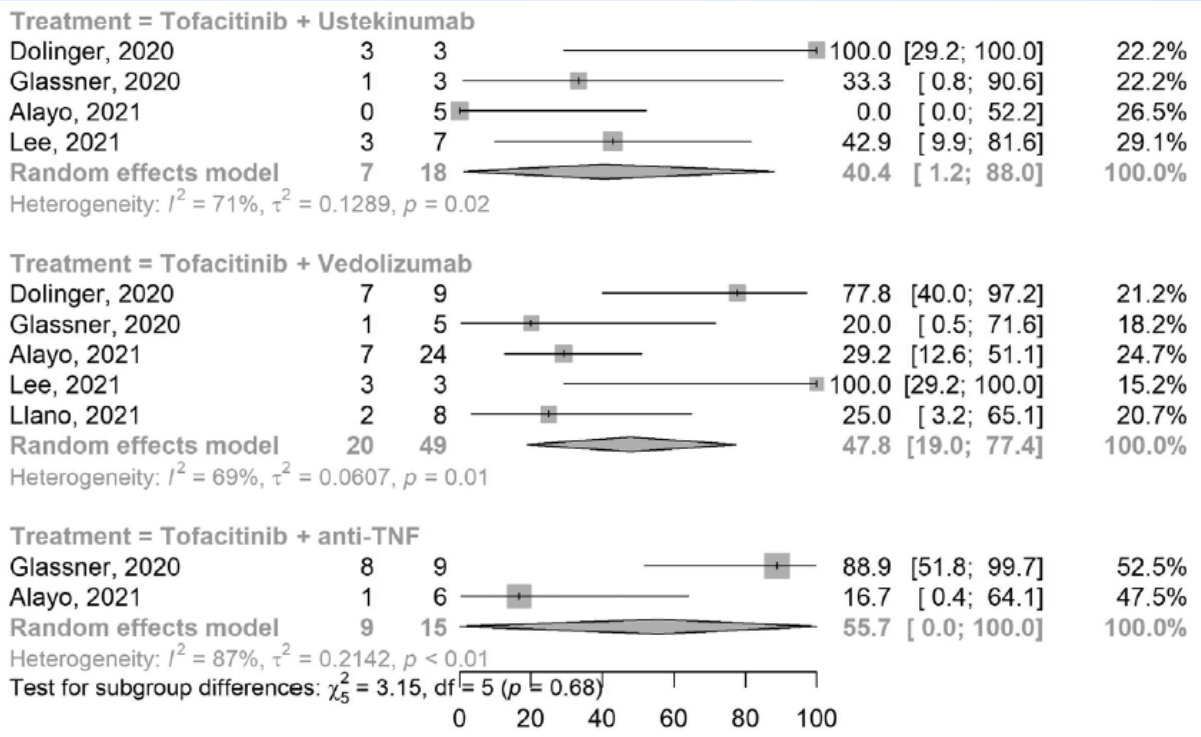
	Study type	Country (single/ multicenter)	IBD type, *n* (*N* = 266)[a]	No. of previous biologics, median (IQR/range)	No. of therapeutic trials, *n* (*N* = 271)[a]	Combinatorial treatments	Median duration of follow-up (weeks)	No. of therapeutic trials discontinued DT, *n*/*N* (%)
Sands et al[7]	Randomized controlled trial	United States (multicenter)	CD (52)	0	52	NAT + aTNF	m 32	5/52 (9.6%)
Buer et al[28]	Prospective cohort	Norway (multicenter)	CD (4) UC (6)	NA (R 1–3)	10	VDZ + aTNF	68	2/10 (20.0%)
Mao et al[29]	Case series	United States (single)	CD (3)	3 (IQR 2–5)	3	VDZ + aTNF VDZ + UST	NA	0/3 (0%)
Dolinger et al[32b]	Retrospective cohort	United States (single)	CD (7) UC (8) IBD-U (1)	3 (IQR 1–2.5)	16	VDZ + UST Tofa + UST Tofa + VDZ	26	3/16 (18.8%)
Fumery et al[33]	Case series	France (single)	CD (4) UC (1)	2 (IQR 0–4)	5	UST + aTNF VDZ + aTNF	24	NA
Glassner et al[10]	Retrospective cohort	United States (single)	CD (30) UC (18) IBD-U (1)	2 (IQR 1–2)	52	VDZ + aTNF VDZ + UST UST + aTNF Tofa + aTNF Tofa + VDZ	16	NA
Kwapisz et al[9]	Retrospective cohort	United States (single)	CD (14) UC (1)	4 (R 1–7)	15	VDZ + aTNF UST + aTNF VDZ + UST	24	1/15 (6.7%)
Olbjorn et al[34b]	Retrospective cohort	Norway (single)	CD (9) UC (4)	1 (R 1–2)	13	VDZ + aTNF UST + aTNF	NA	12/13 (92.3%)
Privitera et al[35]	Retrospective cohort	Italy (multicenter)	CD (10) UC (3)	2.5 (IQR 2–3)	13	VDZ + aTNF UST + aTNF VDZ + UST	28	4/13 (30.8%)
Yang et al[11]	Retrospective cohort	United States/Canada (multicenter)	CD (22)	4 (R 2–5)	24	VDZ + aTNF UST + aTNF VDZ + UST	39	15/24 (62.5%)
Alayo et al[30]	Retrospective cohort	United States (multicenter)	CD (10) UC (25)	2 (IQR 1–3)	35	Tofa + aTNF Tofa + UST Tofa + VDZ	16	20/35 (57.1%)
Lee et al[31]	Retrospective cohort	United States (single)	CD (19)	4 (IQR 3–4)	19	Tofa + aTNF Tofa + UST Tofa + VDZ	42.3	5/19 (26.3%)
Llano et al[36]	Retrospective cohort	United States (single)	CD (3) UC (10) IBD-U (1)	2 (R 1–4)	14	VDZ + aTNF VDZ + UST Tofa + VDZ	31	5/14 (35.7%)

- Trece estudios (12 observacionales, 1RCT)
- 266 pacientes (7 diferentes combinaciones)
- Biológicos previos: 0-4
- Seguimiento: 16-68s
- Combinación más frecuente: VDZ + aTNF (56) o tofa (57)
- VDZ + aTNF: 77% respuesta clínica, 55% remisión clínica, 38% respuesta endoscópica, 18% remisión endoscópica
- VDZ + tofa: 59% respuesta clínica, 47% remisión clínica, 46% respuesta endoscópica, 24% remisión endoscópica

Alayo QA, *et al*. *Crohns Colitis* 360 2022;4:doi: 10.1093/crocol/otac002

Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease



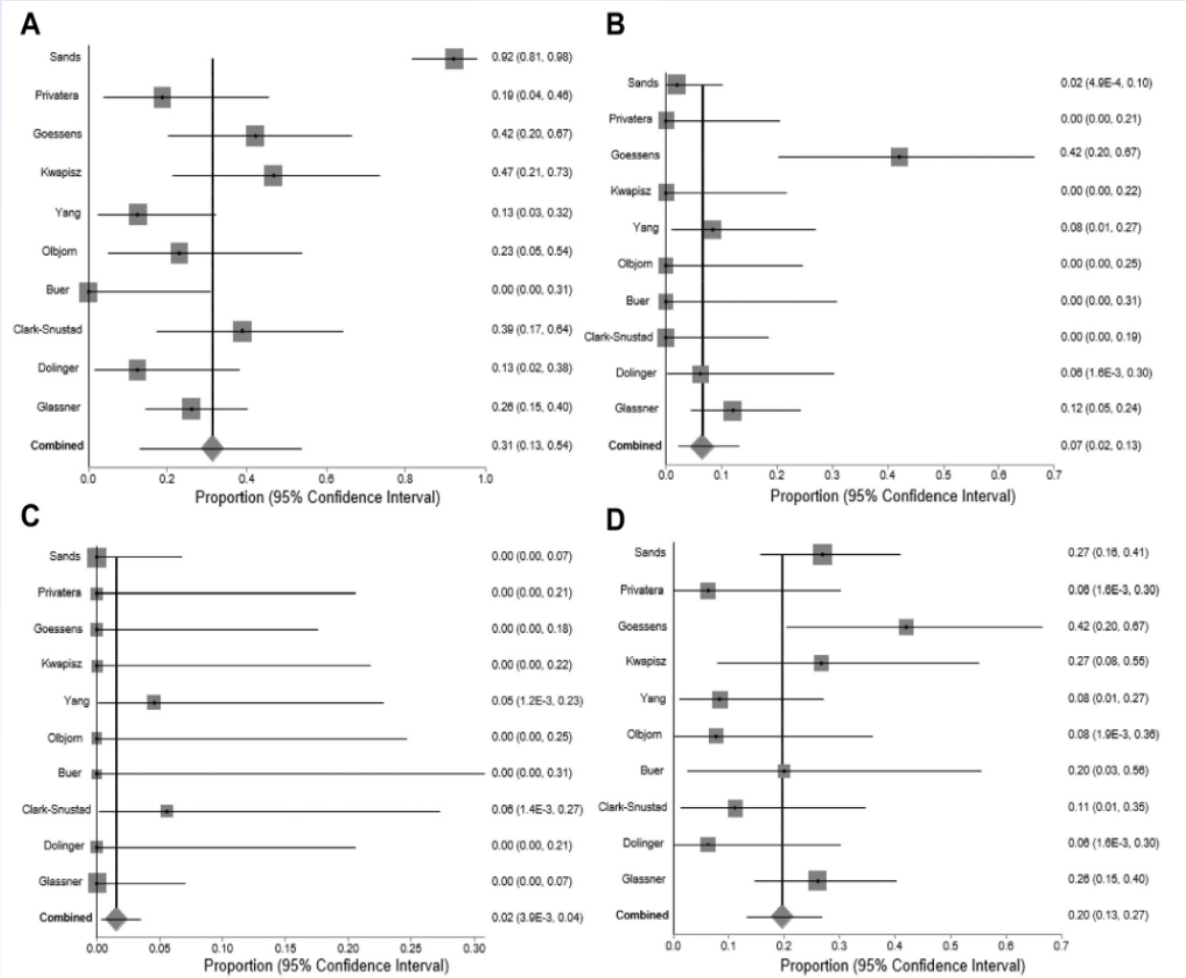


Conclusions: DBT or SBT appears to be generally safe and may be effective in IBD patients, but the evidence is very uncertain.

Alayo QA, *et al*. *Crohns Colitis* 360 2022;4:doi: 10.1093/crocol/otac002

Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Characteristic	Data	Reported patients or combinations
Duration of treatment, wk	24 (13–32)	231
Previous biologics, wk	2 (2–4)	160
Corticosteroids at baseline	43%	88/204
Immunomodulator at baseline	44%	75/172
Previous exposure to therapy	61%	62/101
Indication for therapy		
Medically refractory intestinal disease	81%	225/279
EIM	12%	34/279
Both	5%	14/279
Other	2%	6/279
Dual therapy		
Anti-TNF and anti-integrin	48%	138/288
Anti-TNF and ustekinumab	7%	20/288
Anti-TNF and tofacitinib	3%	10/288
Vedolizumab and ustekinumab	19%	54/288
Vedolizumab and tofacitinib	11%	32/288
Ustekinumab and tofacitinib	6%	16/288
Anti-TNF and other	3%	8/288
Vedolizumab and other	3%	8/288
Ustekinumab and other	1%	2/288



- 30 estudios
- 279 pacientes (9 tipos combinaciones)
- Sgto medio 32s
- 81% EII refractaria , 12% MEI, 5% ambas, 2% otros
- Remisión clínica y endoscópica 52% (DB); 32% (BMP)
- Respuesta clínica y endoscópica 72% (DB), 58% (BPM)
- Remisión libre esteroides 48%
- 10% precisaron cirugía

Ahmed W, *et al*. *Clin Gastroenterol Hepatol* 2022;20:e361-e379

Dual Biologic Therapy for the Treatment of Pediatric Inflammatory Bowel Disease: A Review of the Literature

Study	Year	Study Types	Therapy	Number of Patients	Duration of Combination Therapy (Average)	Efficacy	Adverse Events
Bass et al.	2019	CR	VDZ + ADA	1	9 mth	Clinical response with a significant reduction in inflamatory markers.	None.
Olbjořrn et al.	2020	CS	IFX + UST IFX + VDZ	5 8	36 mth 10 mth	Clinical remission in 9 of the 13 patients.	5 patients had severe paradoxical psoriasis on maintenance therapy with IFX.
Howard et al.	2021	CS	VDZ + UST	3	7 mth	Clinical remision; no endoscopic remission was observed.	None.
Goyal et al.	2020	RS	Anty-TNF + VDZ VDZ + UST IFX + anakinra	6 2 1	11 mth	4 (44%) patients achieved clinical remission;	One patient had a staphylococcal skin infection.
Dolinger et al.	2021	RS	VDZ + tofacitnib VDZ + UST UST+ tofacitinb	9 4 3	6 mth	12 (75%) patients achieved steroid-free clinical remission at 6 months; One of them required surgery, the other 2 patients needed to switch to therapy.	One serious adverse event of septic arthritis occurred after 2 months of treatment with vedolizumab and tofacitinib.

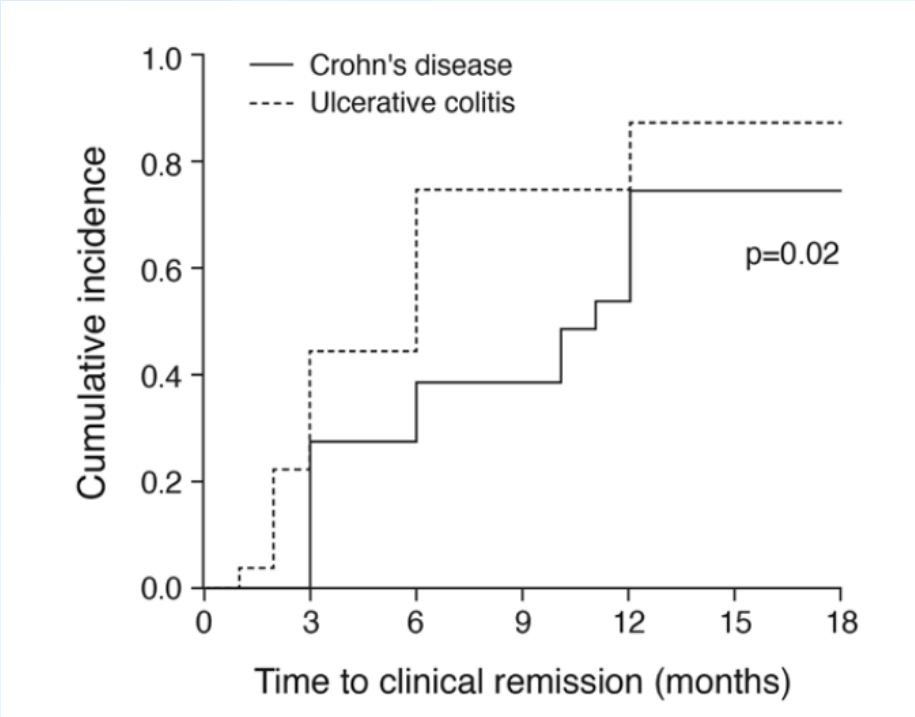
ADA, adalimumab; CR, case report; CS, case series; IFX, infliximab; mth, month; TNF, tumor necrosis factor; UST, ustekinumab; and VDZ, vedolizumab.

- 5 estudios
- 42 pacientes
- 7 combinaciones
- Respuesta 74% EC; 77% CU

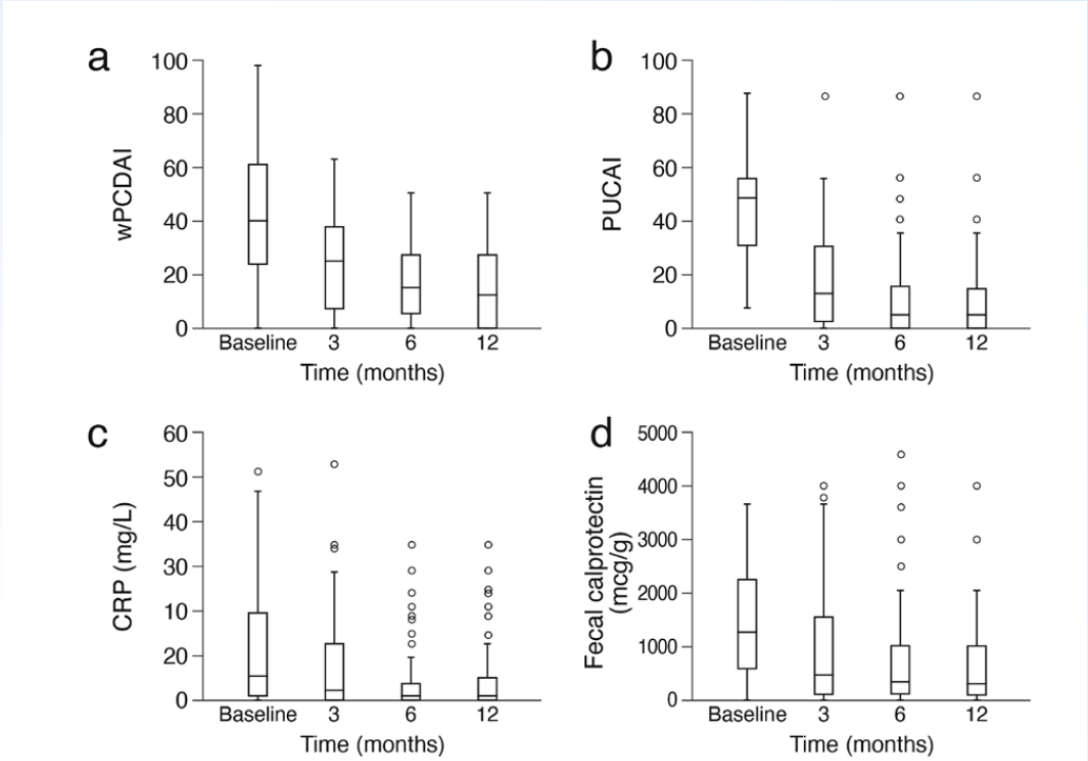
Wlazlo M, *et al. J Clin Med* 2022;11:doi: 10.3390/jcm11072004

Dual Biologic or Small Molecule Therapy in Refractory Pediatric Inflammatory Bowel Disease (DOUBLE-PIBD): A Multicenter Study from the Pediatric IBD Porto Group of ESPGHAN

- 62 pacientes, 14 centros (56.5% EC, 43.5% CU)
- Edad media al dx 10.6a (8-13); al inicio TDA 15.5 (13.1-16.8)
- 88.7% uso previo IS; 75% con > 1 biológico



- Remisión clínica 35% (3m), 50% (6m), 65% (12m)



Yerushalmy-Feler A, *et al*. *Inflamm Bowel Dis* 2023 (Epub ahead of print)

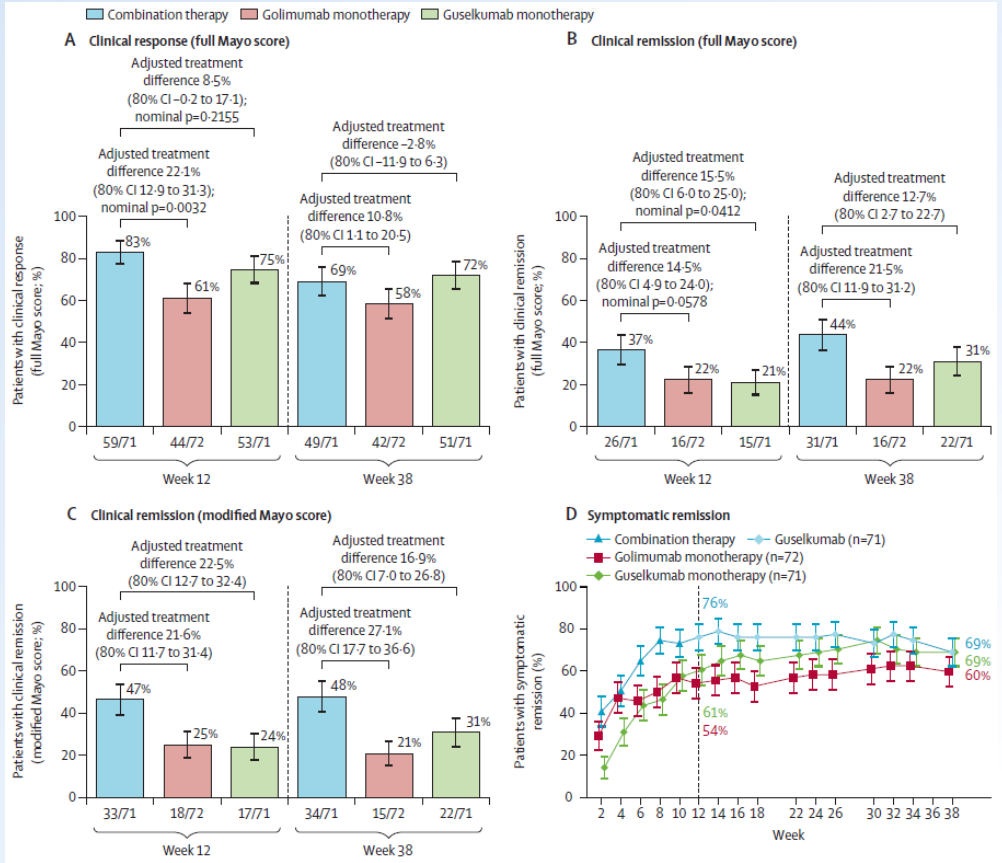
Dual Biologic or Small Molecule Therapy in Refractory Pediatric Inflammatory Bowel Disease (DOUBLE-PIBD): A Multicenter Study from the Pediatric IBD Porto Group of ESPGHAN

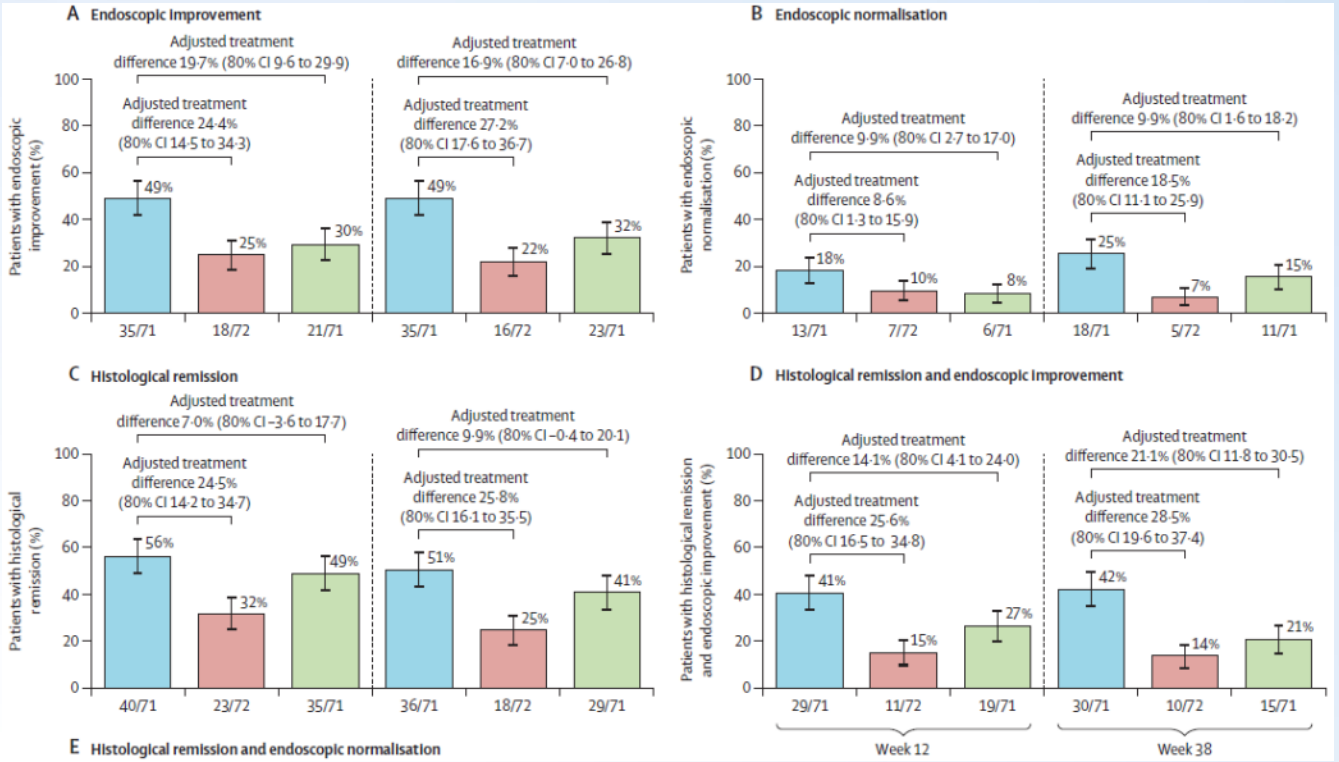
TABLE 3. Adverse events

Combination	Serious adverse events	Other adverse events
Infliximab + vedolizumab	Infusion reaction to infliximab, fatigue and headache after vedolizumab infusion, eczema (n = 2)	COVID-19 infection, mycoplasma upper respiratory tract infection, influenza-like disease, *Clostridioides difficile* infection, sinusitis, headache, elevated liver enzymes (n = 2)
Adalimumab + vedolizumab		Fever, COVID-19 infection (n = 3), impetigo, folliculitis, psoriasis
Infliximab + ustekinumab	Cellulitis and skin abscess, nonspecific rash	External otitis (n = 2), cellulitis, psoriasis (n = 2), urticaria
Adalimumab + ustekinumab	Elevated liver enzymes	COVID-19 infection, influenza-like disease, folliculitis, nonspecific rash, headache
Vedolizumab + ustekinumab	—	Influenza-like disease, acne
Tofacitinib + biologic agent	Deep vein thrombosis	Elevated liver enzymes
Other	—	Psoriasis, blepharitis

Yerushalmy-Feler A*, et al*. *Inflamm Bowel Dis* 2023 (Epub ahead of print)

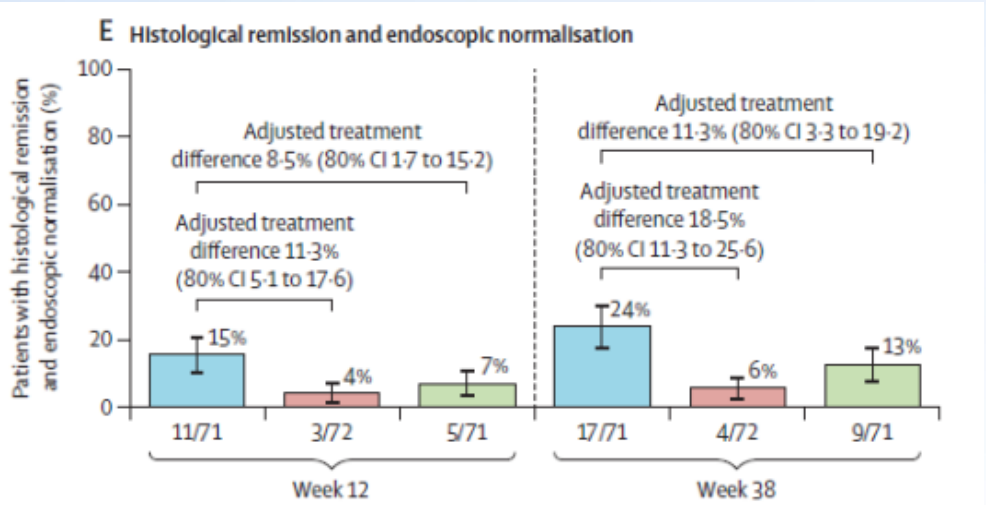
Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial





Feagan B, *et al*. *Lancet Gastroenterol Hepatol* 2023; 8: 307–20

Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial



	Combination therapy induction until week 12			Therapy until week 50		
	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)
Duration of follow-up, weeks	12·4 (0·84)	12·0 (0·92)	12·1 (1·74)	48·8 (9·70)	45·8 (12·91)	48·6 (9·00)
Any adverse event	29 (41%)	38 (53%)	31 (44%)	45 (63%)	55 (76%)	46 (65%)
Common adverse events*						
Ulcerative colitis	4 (6%)	9 (13%)	1 (1%)	10 (14%)	17 (24%)	4 (6%)
Upper respiratory tract infection	1 (1%)	4 (6%)	5 (7%)	6 (8%)	5 (7%)	6 (8%)
Headache	4 (6%)	2 (3%)	3 (4%)	5 (7%)	4 (6%)	6 (8%)
Anaemia	4 (6%)	5 (7%)	6 (8%)	4 (6%)	7 (10%)	10 (14%)
Nasopharyngitis	2 (3%)	3 (4%)	2 (3%)	4 (6%)	5 (7%)	3 (4%)
Neutropenia	2 (3%)	2 (3%)	4 (6%)	3 (4%)	3 (4%)	5 (7%)
Pyrexia	1 (1%)	2 (3%)	0	2 (3%)	5 (7%)	1 (1%)
Infections†	10 (14%)	16 (22%)	10 (14%)	22 (31%)	23 (32%)	17 (24%)
Opportunistic infections	0	0	0	2 (3%)	0	0
Serious adverse events	1 (1%)	1 (1%)	2 (3%)	4 (6%)	4 (6%)	4 (6%)
Serious infections†	1 (1%)	0	0	2 (3%)	2 (3%)	2 (3%)
Adverse events leading to discontinuation of study treatment	2 (3%)	3 (4%)	1 (1%)	7 (10%)	4 (6%)	1 (1%)
Malignancies	0	0	0	0	0	1 (1%)
Deaths	0	0	0	1 (1%)	0	1 (1%)
Adverse events associated with an injection site reaction	1 (1%)	0	1 (1%)	1 (1%)	0	1 (1%)
Adverse events temporally associated with an infusion	1 (1%)	2 (3%)	2 (3%)	1 (1%)	2 (3%)	2 (3%)
Adverse events associated with COVID-19 infection	1 (1%)	0	0	2 (3%)	2 (3%)	3 (4%)

Data are mean (SD) or n (%). *Reported by at least 5% of patients in any group. †As assessed by the investigator.

Table 3: **Adverse events**

Feagan B, *et al*. *Lancet Gastroenterol Hepatol* 2023; 8: 307–20

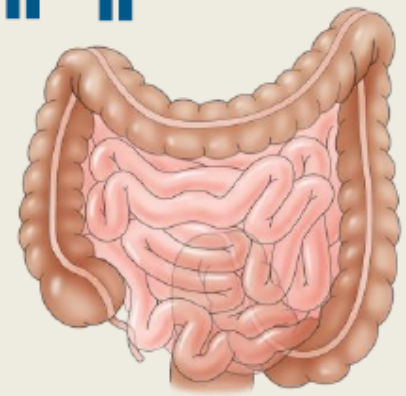
Vedolizumab, Adalimumab, and Methotrexate Combination Therapy in Crohn's Disease (EXPLORER)

Phase 4, open-label study of vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease

Journal Preproof

Patients

N = 55



Biologic naïve patients with newly diagnosed, moderate to high risk CD

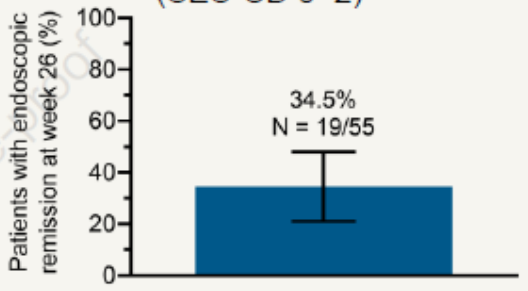
Treatment

Triple combination therapy

- IV vedolizumab 300 mg at weeks 0, 2, and 6 and every 8 weeks until week 102
- SC adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks until week 26
- Oral methotrexate 15 mg weekly until week 34

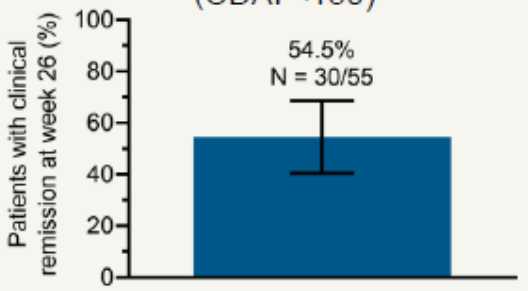
Primary end point

Endoscopic remission at week 26 (SES-CD 0–2)



Secondary end point

Clinical remission at week 26 (CDAI <150)



Post hoc Bayesian analysis[a]

Probability that triple combination therapy produces higher endoscopic remission than benchmark rates for…

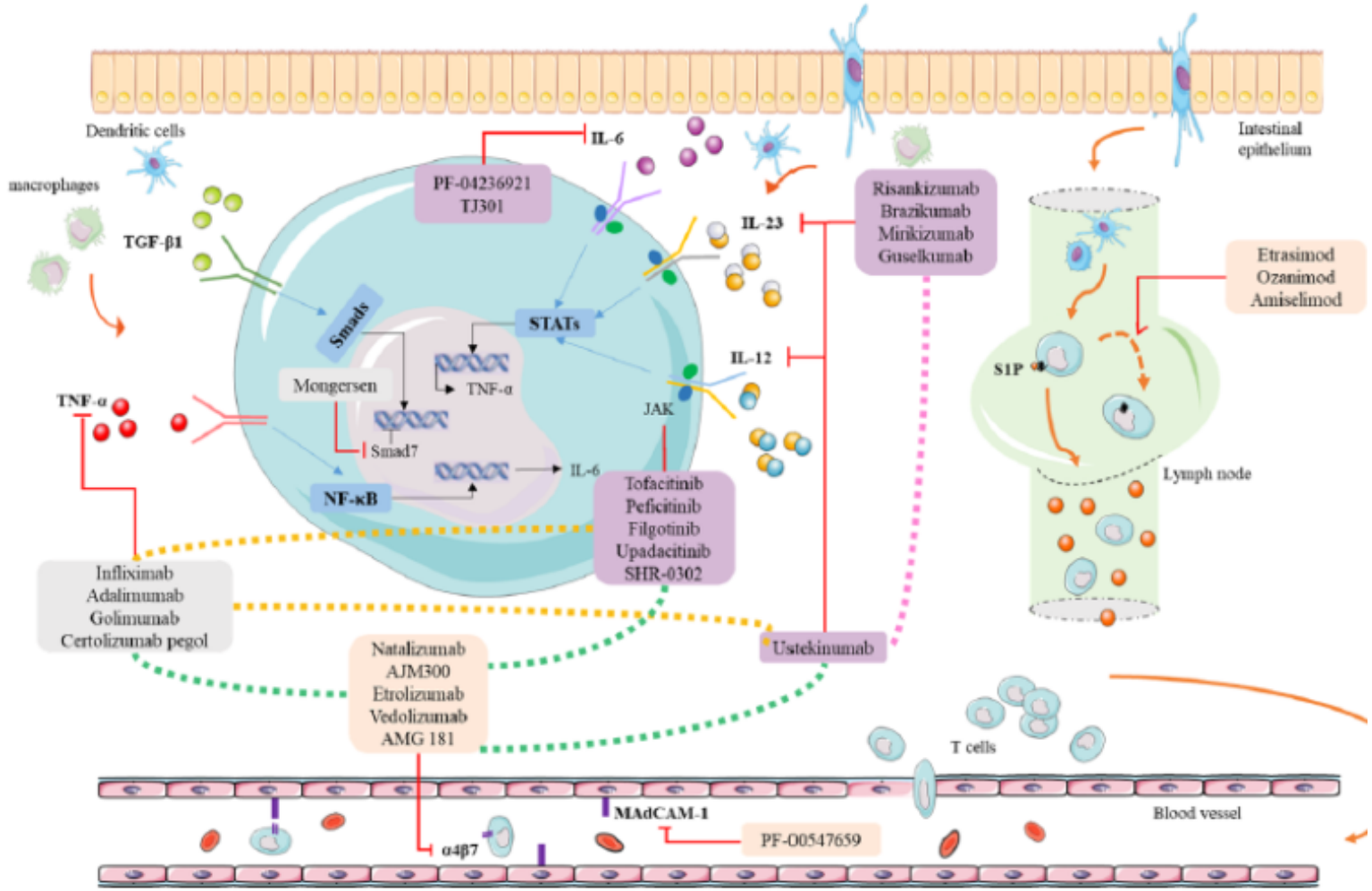
- …placebo ≥99.9%
- …vedolizumab monotherapy = 86.3%
- …adalimumab monotherapy = 71.4%

[a]*Beta*(1.667, 5) prior. Posterior mean endoscopic remission rate = 33.5% (95% credible interval: 22.4, 45.7).
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease

Clinical Gastroenterology and Hepatology

Colombel JF, *et al*. *Clin Gastroenterol Hepatol* 2023 (*Epub ahead of print*)

Breaking through the therapeutic ceiling of inflammatory bowel disease: Dual-targeted therapies



Agentes terapéuticos categorizados en:

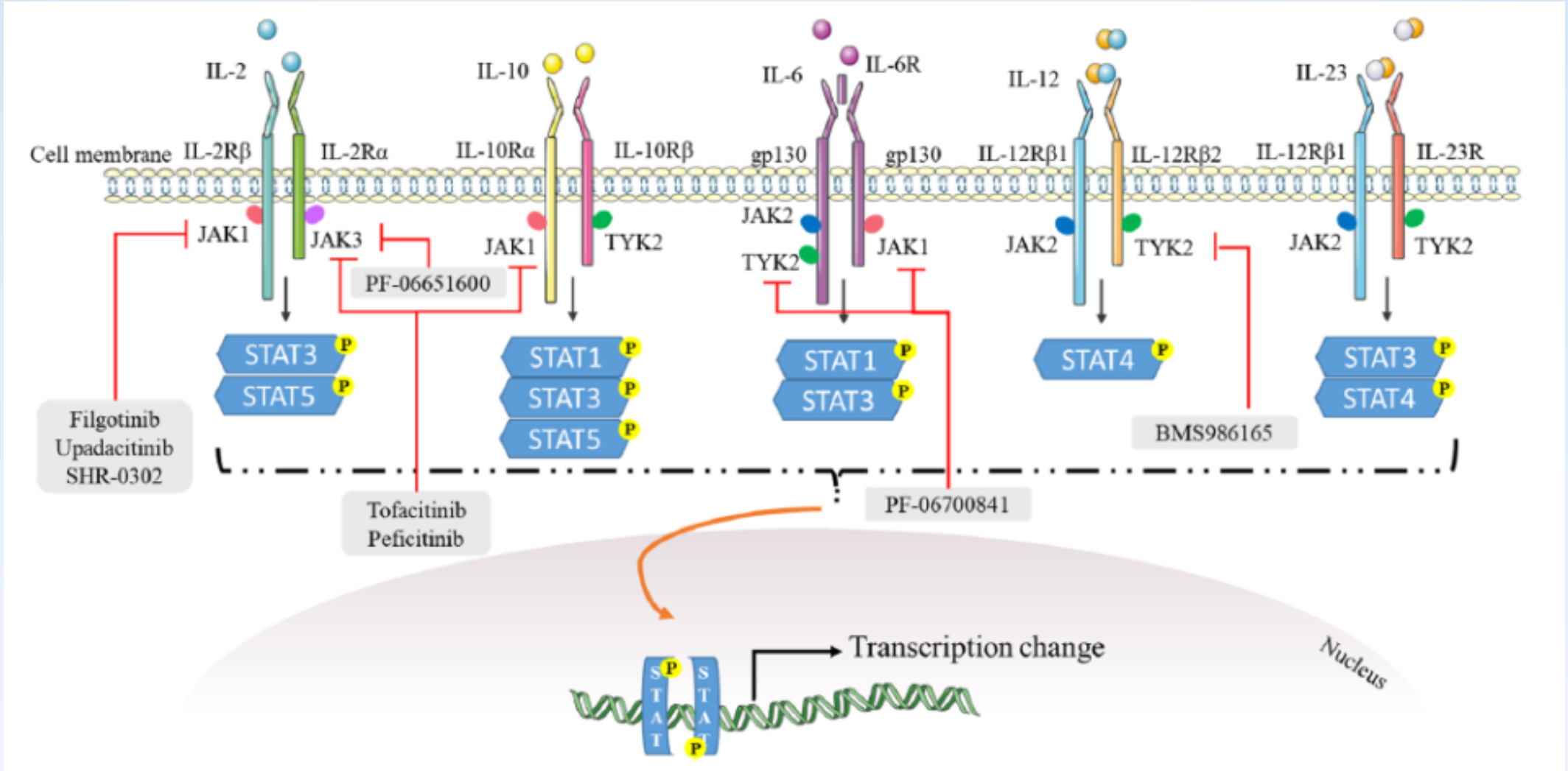
1. dirigidos a vías de señalización celular
   - JAK dependientes
   - JAK independientes
2. dirigidos al tráfico leucocitario

Tres categorías de combinación según efecto:

- de superposición
- sinergístico
- complementario

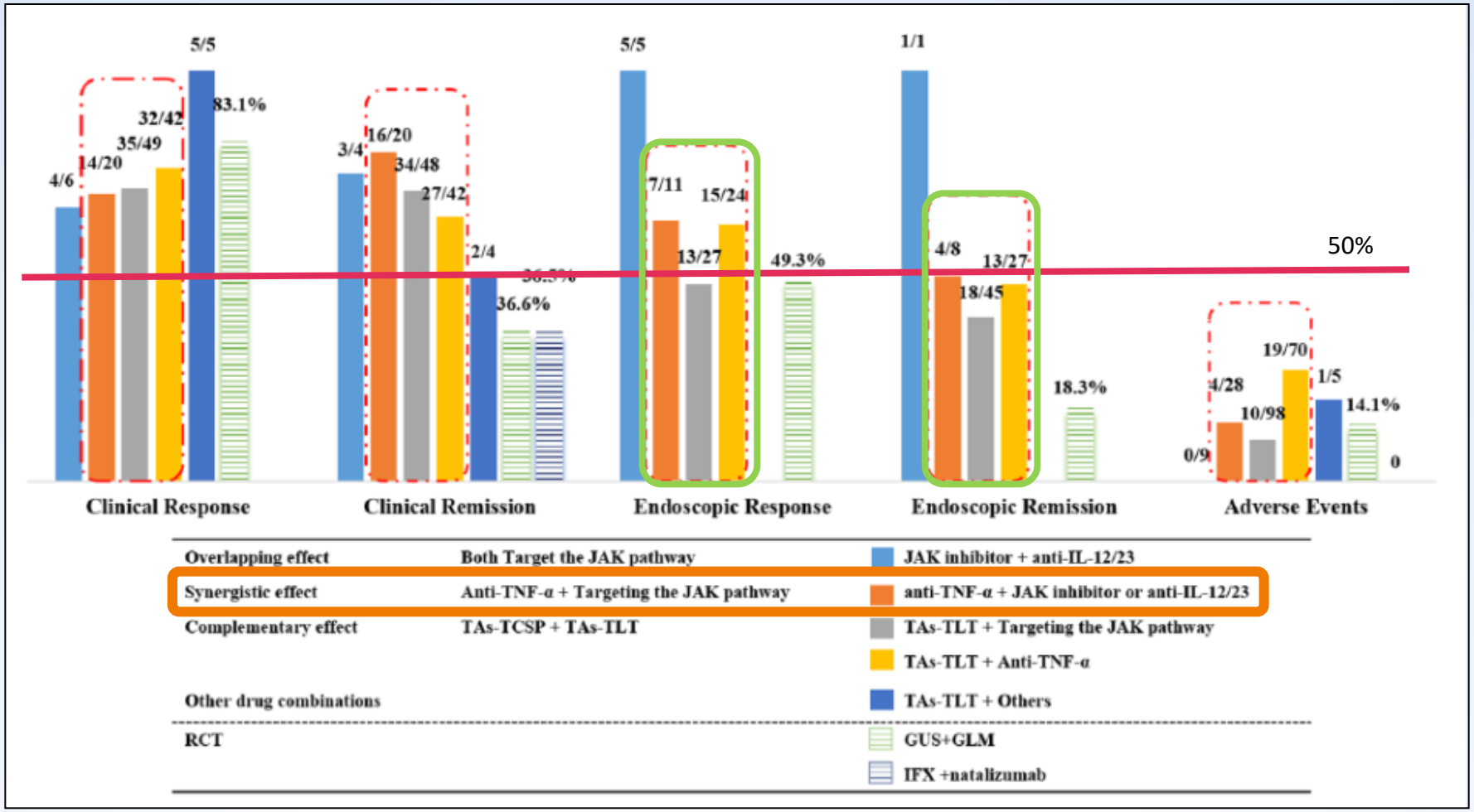
Feng Z, *et al*. Biomed Pharmather2023 doi: 10.1016/j.biopha.2022.114174

Breaking through the therapeutic ceiling of inflammatory bowel disease: Dual-targeted therapies



Feng Z, *et al*. Biomed Pharmather2023 doi: 10.1016/j.biopha.2022.114174

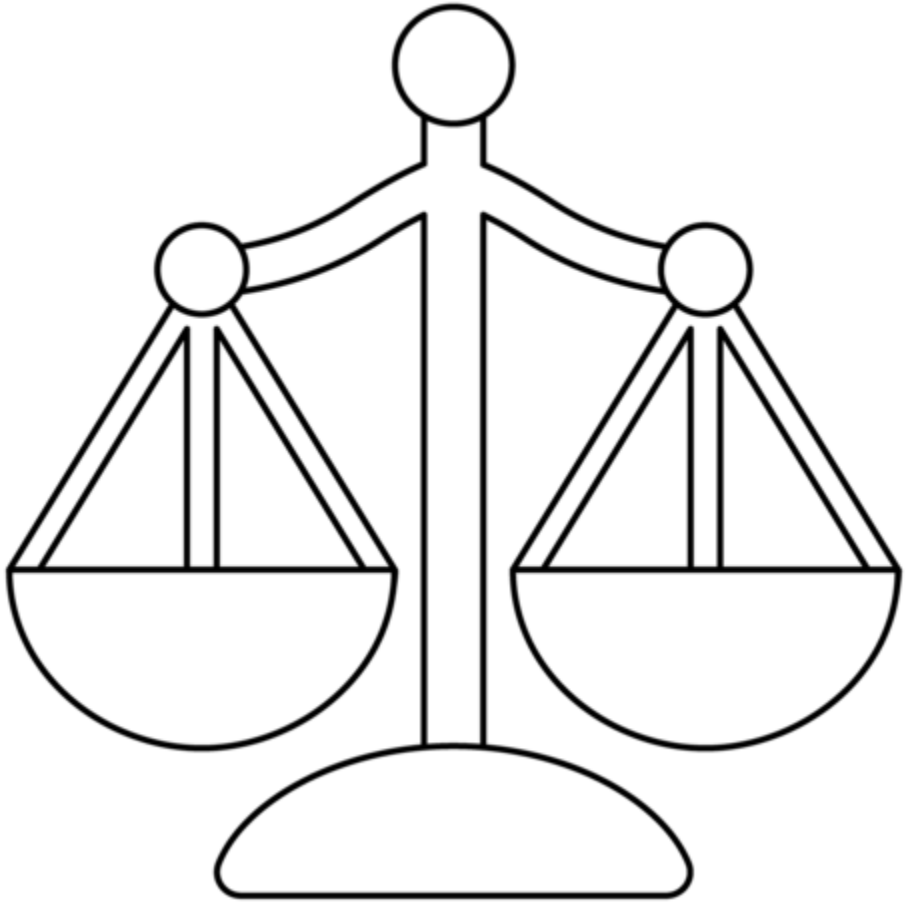
Breaking through the therapeutic ceiling of inflammatory bowel disease: Dual-targeted therapies



Feng Z, *et al*. Biomed Pharmather2023 doi: 10.1016/j.biopha.2022.114174

Limitaciones a la nueva estrategia (*concern*)

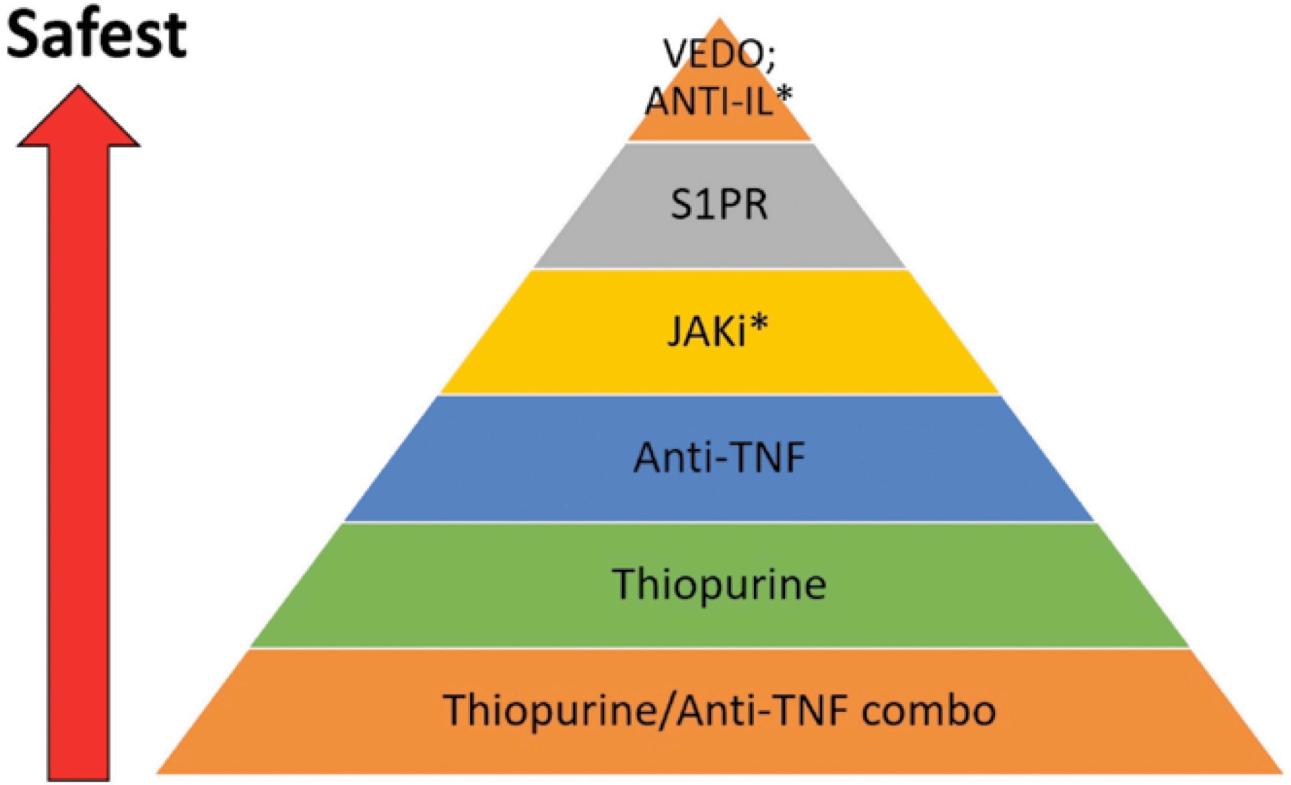
Eficacia



Seguridad

Costes

Safety and Monitoring of Inflammatory Bowel Disease Advanced Therapies



Patient-specific considerations influencing safety profile

- Age
- Disease classification
- Disease presentation
- Disease phenotype & inflammatory burden
- Comorbidities
- Concurrent medications (drug-interactions)
- Conception plans

Inadequate treatment of Crohn's disease and ulcerative colitis is an adverse event and should be balanced with risks of therapies on an individual basis.

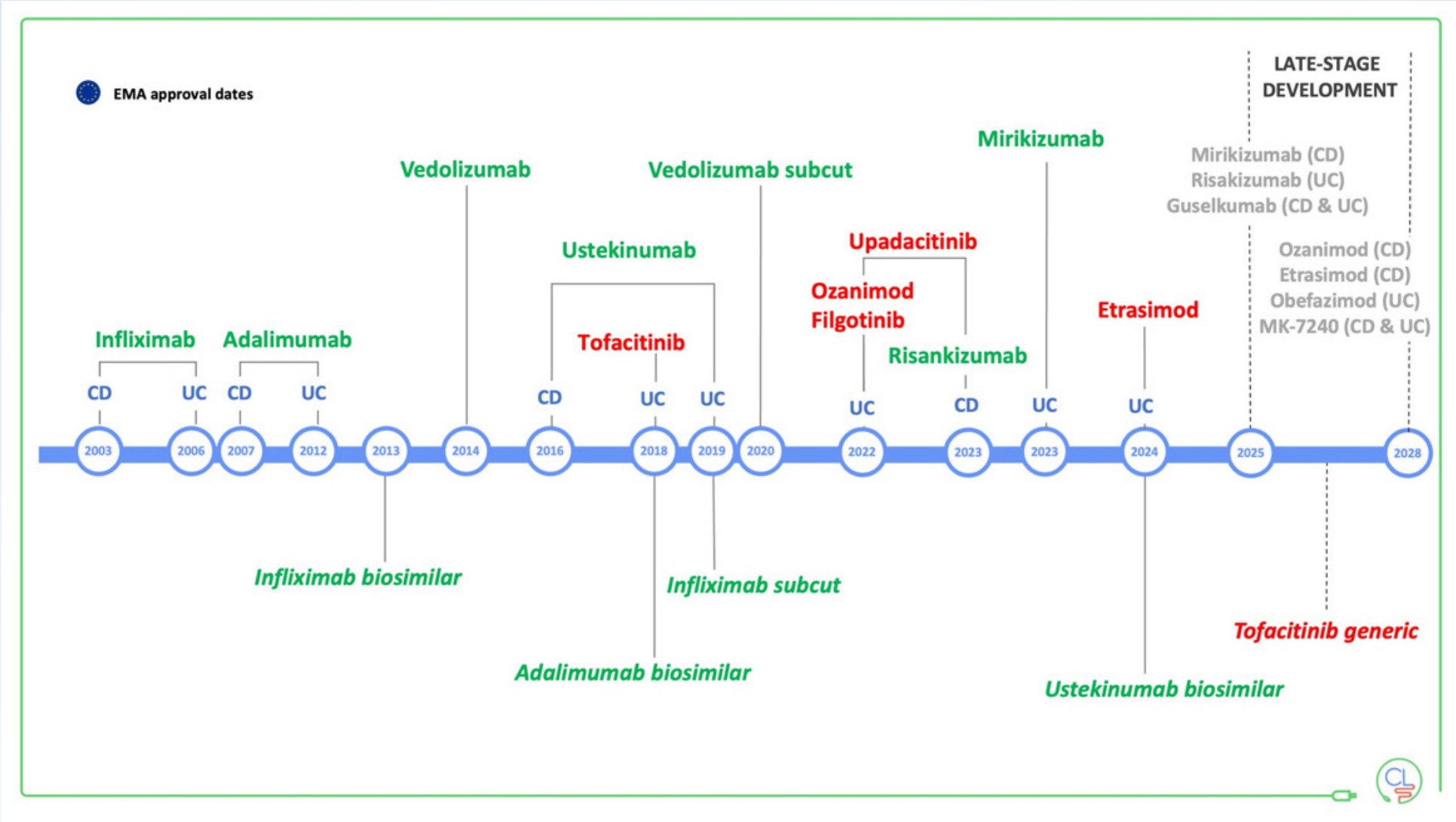
Bhat S, *et al*. *Inflamm Bowel Dis* 2023 (Epub ahead of print)

Costes terapia avanzada

Paciente Peso medio 30 kg	Inducción	Mantenimiento 1 año	Total
Infliximab biosimilar	1.464,12€	2.928,24-3.416,28€	4.392,36-4.880,4€
Adalimumab biosimilar	1.267,49€	4.707,82€	5.975,31 €
Vedolizumab	4.008,39€	8.016,78 - 9.352,91€	12.025,17-13.361,3€
Ustekinumab	4.448,1€	13.344,3 - 15.568,35 €	17.792,4-20.016,45€
Tofacitinib	1.505,28€	4.892,16€	6.397,44€

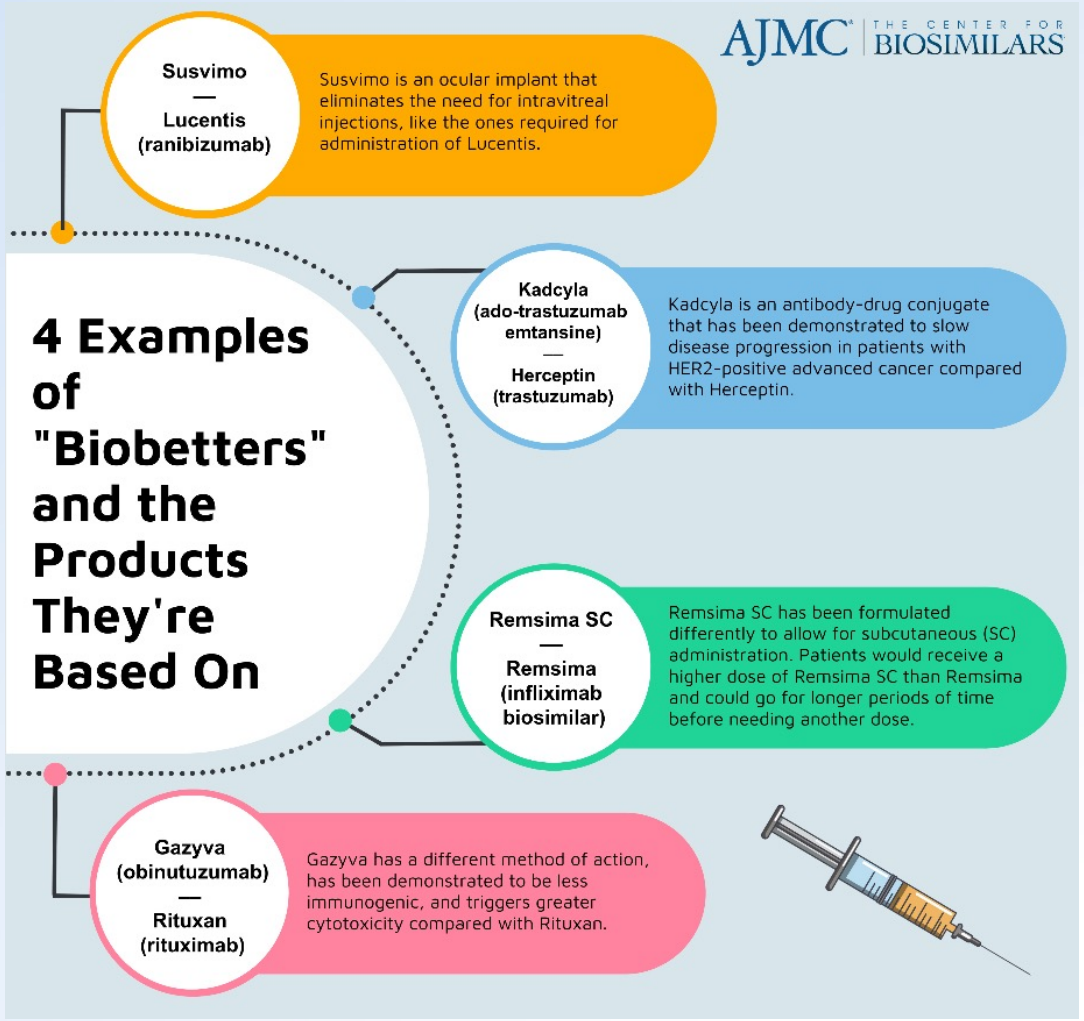
Agradecimiento a Cristina Latre, Servicio de Farmacia SJD

¿Hacia la sostenibilidad?

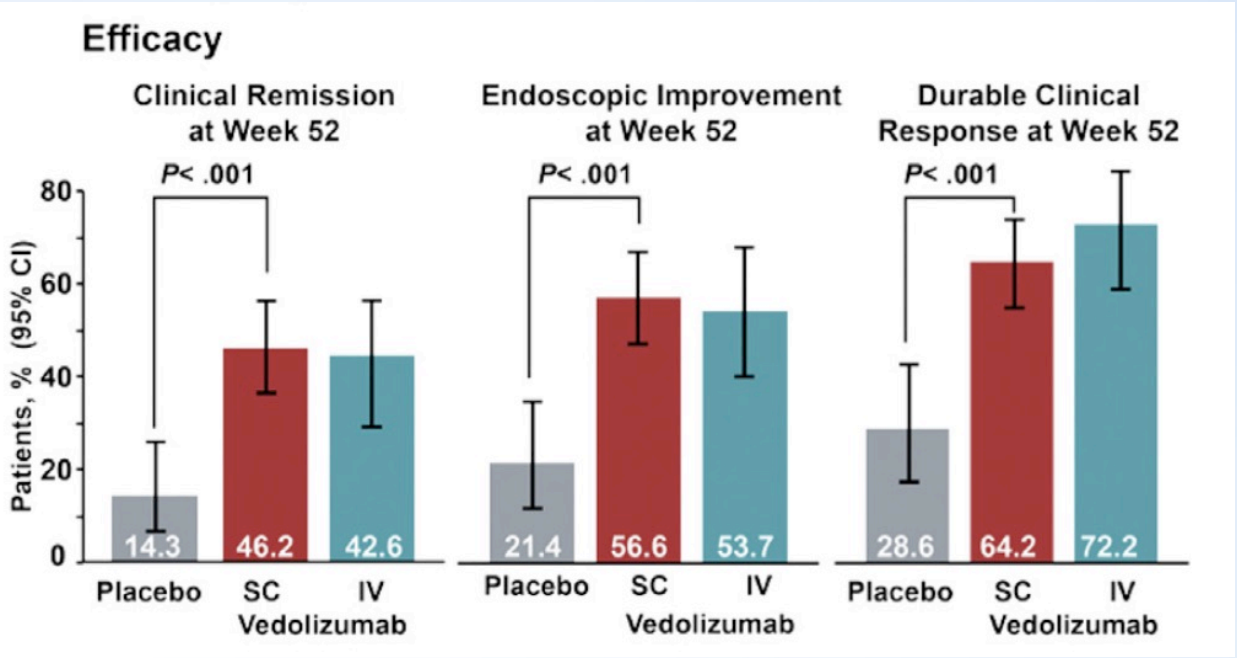


Cortesía Dr. Charlie Lees

Cambios actuales pueden ayudar...



Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis



Sandborn WJ, *et al*. *Gastroenterology* 2020;158:562-72

¿Cómo podemos imaginar el futuro?

How could nanobiotechnology improve treatment outcomes of anti-TNF-α therapy in inflammatory bowel disease? Current knowledge, future directions

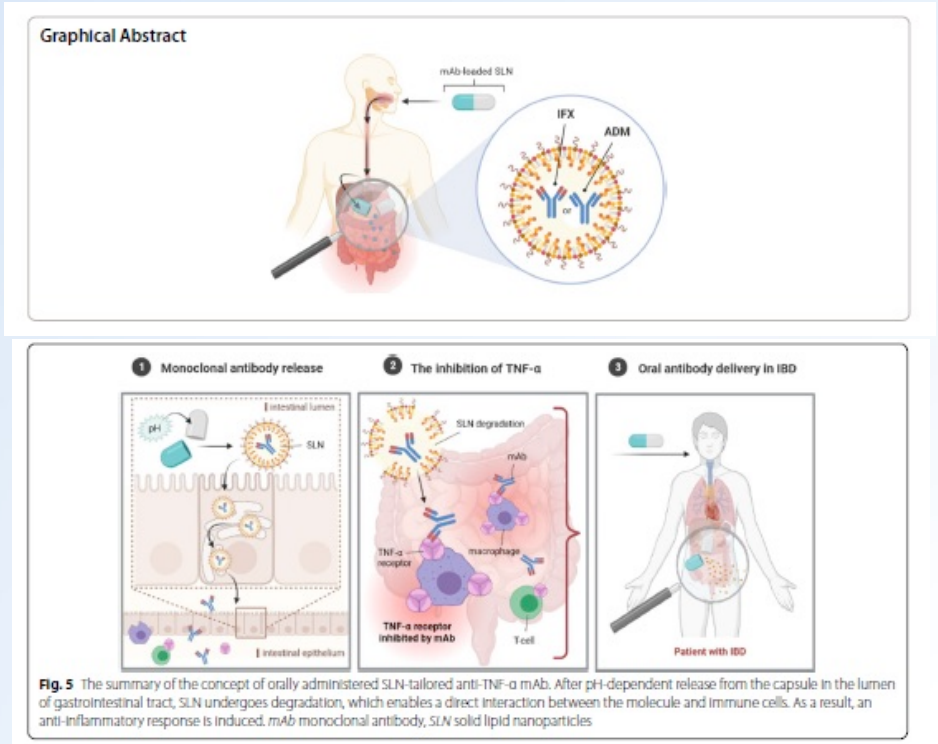
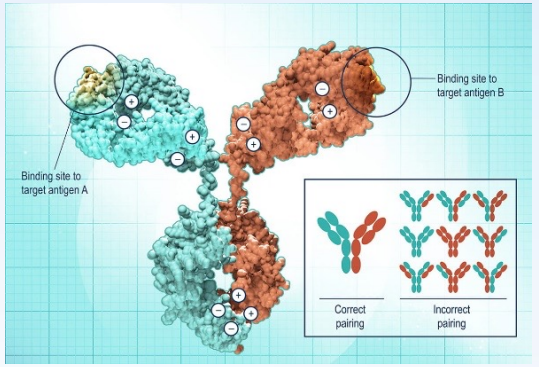


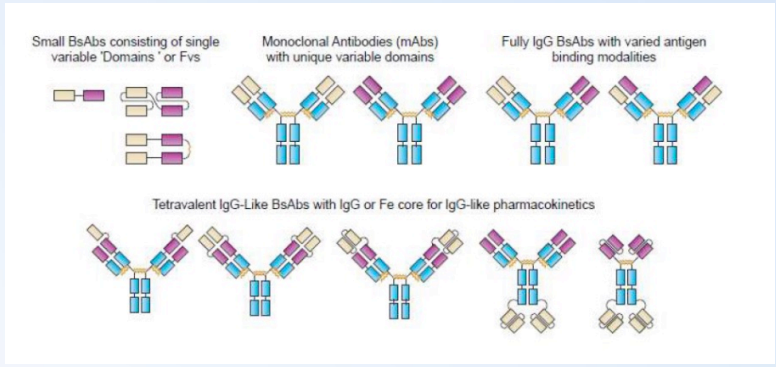
Fig. 5 The summary of the concept of orally administered SLN-tailored anti-TNF-α mAb. After pH-dependent release from the capsule in the lumen of gastrointestinal tract, SLN undergoes degradation, which enables a direct interaction between the molecule and immune cells. As a result, an anti-inflammatory response is induced. *mAb* monoclonal antibody, *SLN* solid lipid nanoparticles

Eder P, *et al*. *J Nanobiotechnology* 2021;19:346

Bispecific antibodies for the treatment in inflammatory bowel disease: an avenue worth exploring?

Caron B, *et al*. *J Nanobiotechnology* 2022;22:951-3





Preclinical development of a bispecific TNFα/IL-23 neutralising domain antibody as a novel oral treatment for inflammatory bowel disease

Roberts KJ, *et al*. *Sci Rep* 2021 doi: 10.1038/s41598-021-97236-0

Conclusiones

- Pese a disponer de nuevos fármacos eficaces, la falta de respuesta primaria y la pérdida secundaria de la misma sigue constituyendo una limitación importante en el tratamiento de la EII
- La combinación de las denominadas terapias avanzadas (biológicos, moléculas pequeñas) ha demostrado ser una estrategia beneficiosa en un subgrupo de pacientes con enfermedad especialmente refractaria
- La combinación anti-TNFα + JAKi/anti-IL12-23/anti-IL23 parece ser la TDA más efectiva (eficacia/seguridad)
- El uso de terapia avanzada dual debe ser valorada de manera individualizada en cada paciente, en función de la situación clínica, grado de respuesta a los diferentes fármacos y seguridad de la combinación

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