Kombinációs kezelések

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Semmelweis Egyetem

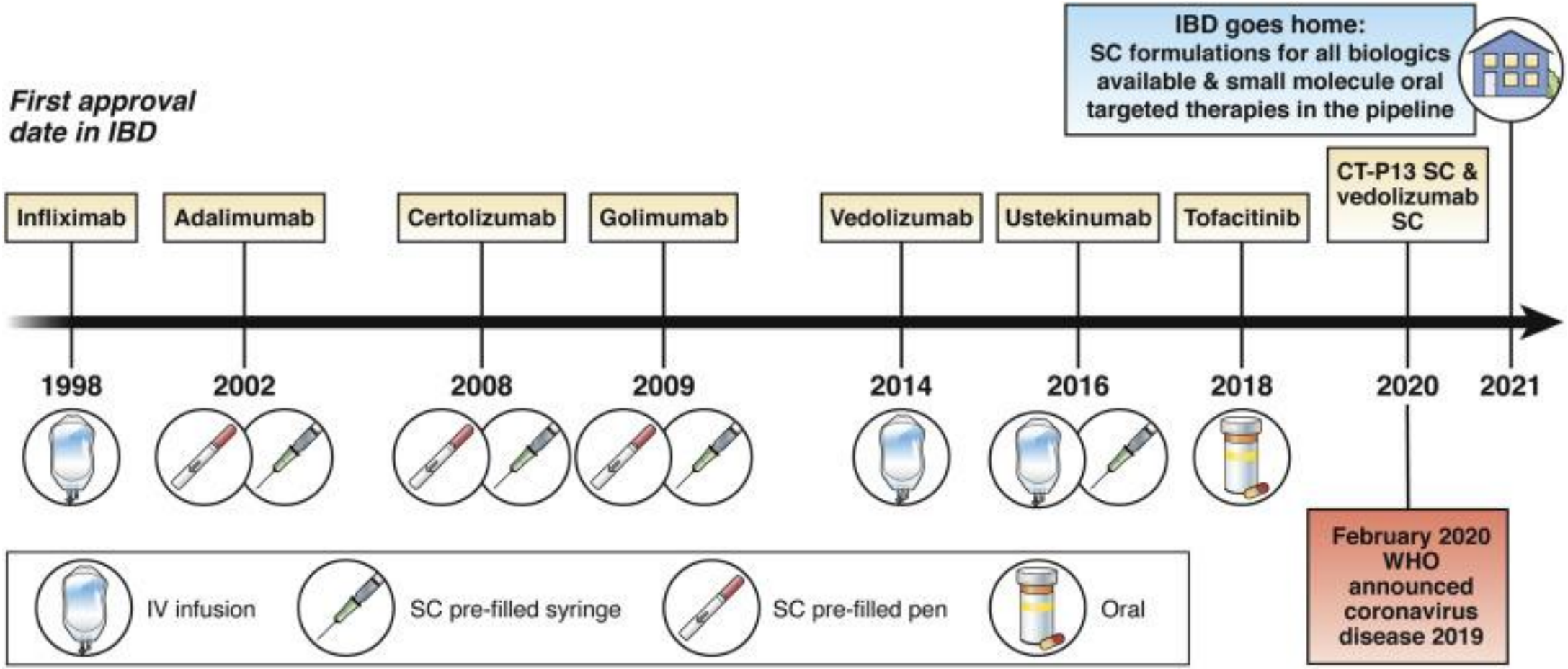
SEMMELWEIS
EGYETEM 1769

Kezdetben vala…

- Sulphasalazyn
- Mesalazin
- Azathioprin

- Corticosteroidok
- Cyclosporin

Biológiai kezelés evolúciója IBD-ben



Solitano V et al. Gastroenterology. 2021 Jun;160(7):2244-2247.

Terápiás elégtelenség

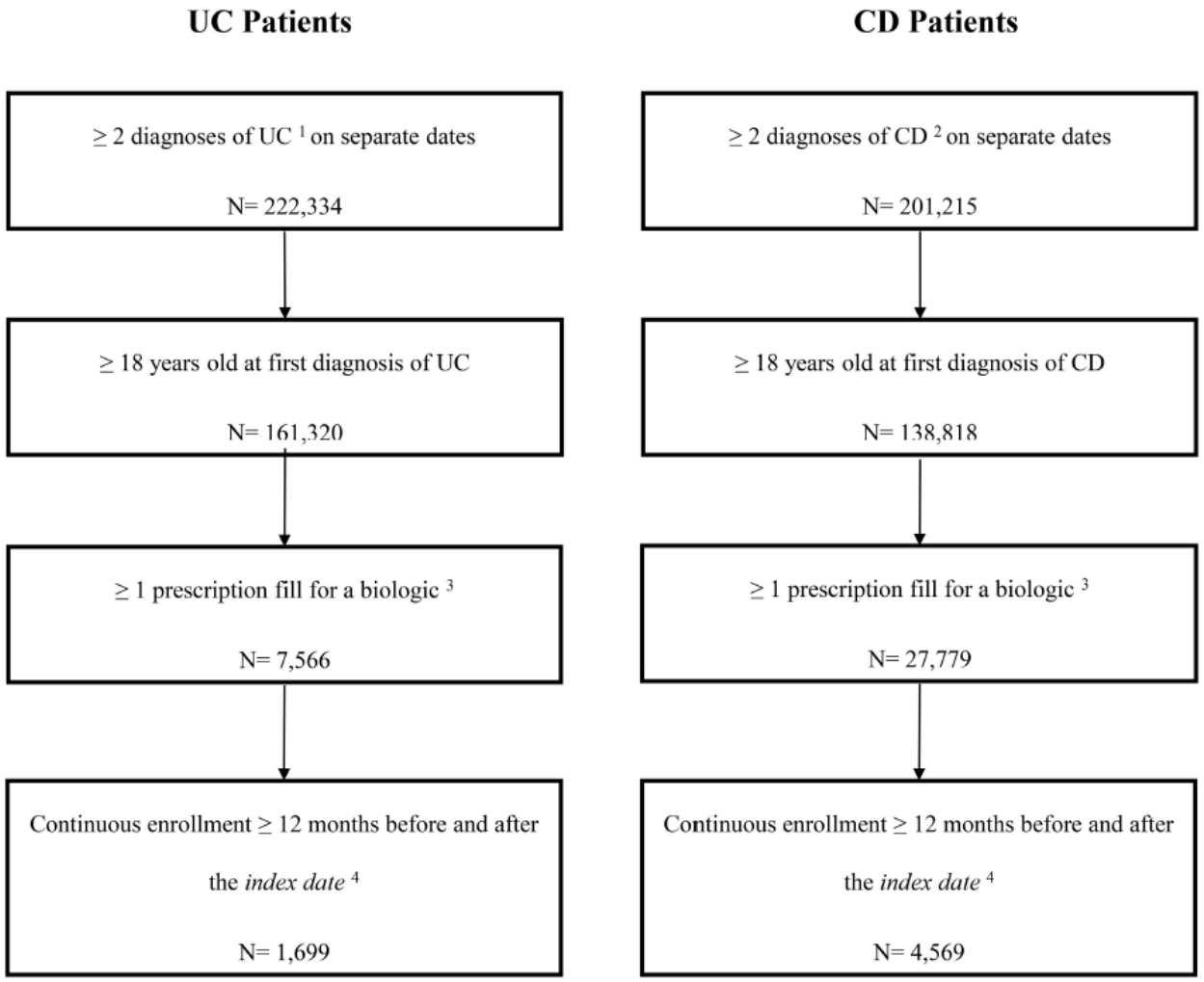
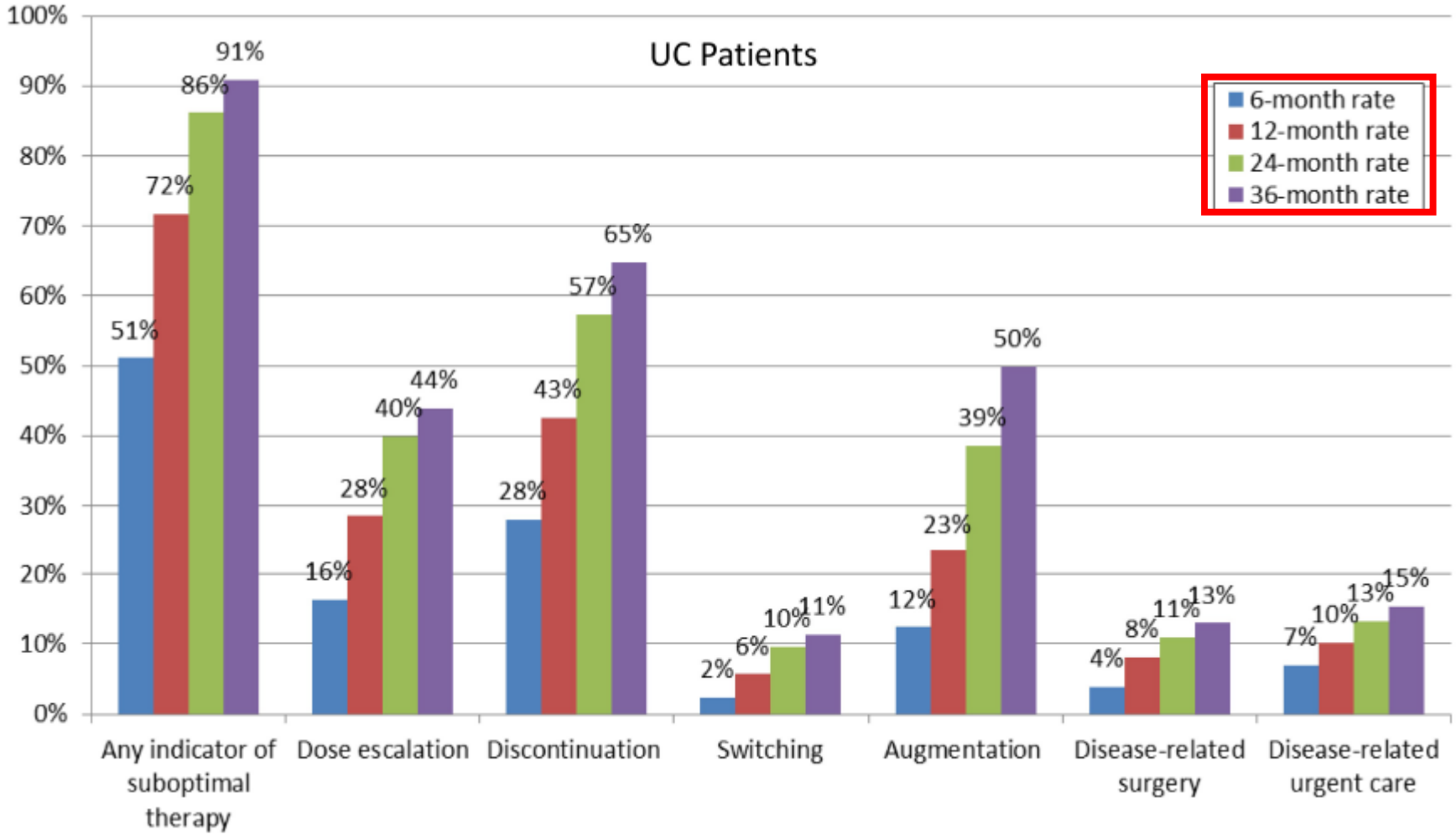


Table 1. Patient characteristics.

Patient Characteristics	UC Patients (N = 1,699)	CD Patients (N = 4,569)
Age, Mean ± SD	47.5 ± 14.7	43.4 ± 14.7
18–39, n (%)	533 (31.4)	1,899 (41.6)
40–49, n (%)	384 (22.6)	1,044 (22.8)
50–64, n (%)	589 (34.7)	1,312 (28.7)
≥65, n (%)	193 (11.4)	314 (6.9)
Female, n (%)	867 (51.0)	2,644 (57.9)
Region, n (%)		
South	691 (40.7)	1,785 (39.1)
North-Central	451 (26.5)	1,401 (30.7)
West	332 (19.5)	763 (16.7)
North-East	225 (13.2)	620 (13.6)
Insurance Plan Type, n (%)		
Point of Service (POS) or Exclusive Provider Organization (EPO)	211 (12.4)	559 (12.2)
Preferred Provider Organization (PPO)	928 (54.6)	2,579 (56.4)
Health Maintenance Organization (HMO) or POS with capitation	321 (18.9)	831 (18.2)
Consumer-directed Health Plan (CDHP) or High-deductible Health Plan (HDHP)	56 (3.3)	163 (3.6)
Basic or Comprehensive Coverage	183 (10.8)	437 (9.6)
Biologic Agent Initiated on the Index Date, n (%)		
Adalimumab	498 (29.3)	2,226 (48.7)
Certolizumab	25 (1.5)	369 (8.1)
Infliximab	1,162 (68.4)	1,943 (42.5)
Golimumab	7 (0.4)	7 (0.2)
Natalizumab	7 (0.4)	24 (0.5)
CD location, n (%)		
Ileum	-	752 (16.5)
Colon	-	486 (10.6)
Ileum/Colon	-	347 (7.6)
Multiple sites	-	333 (7.3)
Not Specified	-	2,651 (58.0)

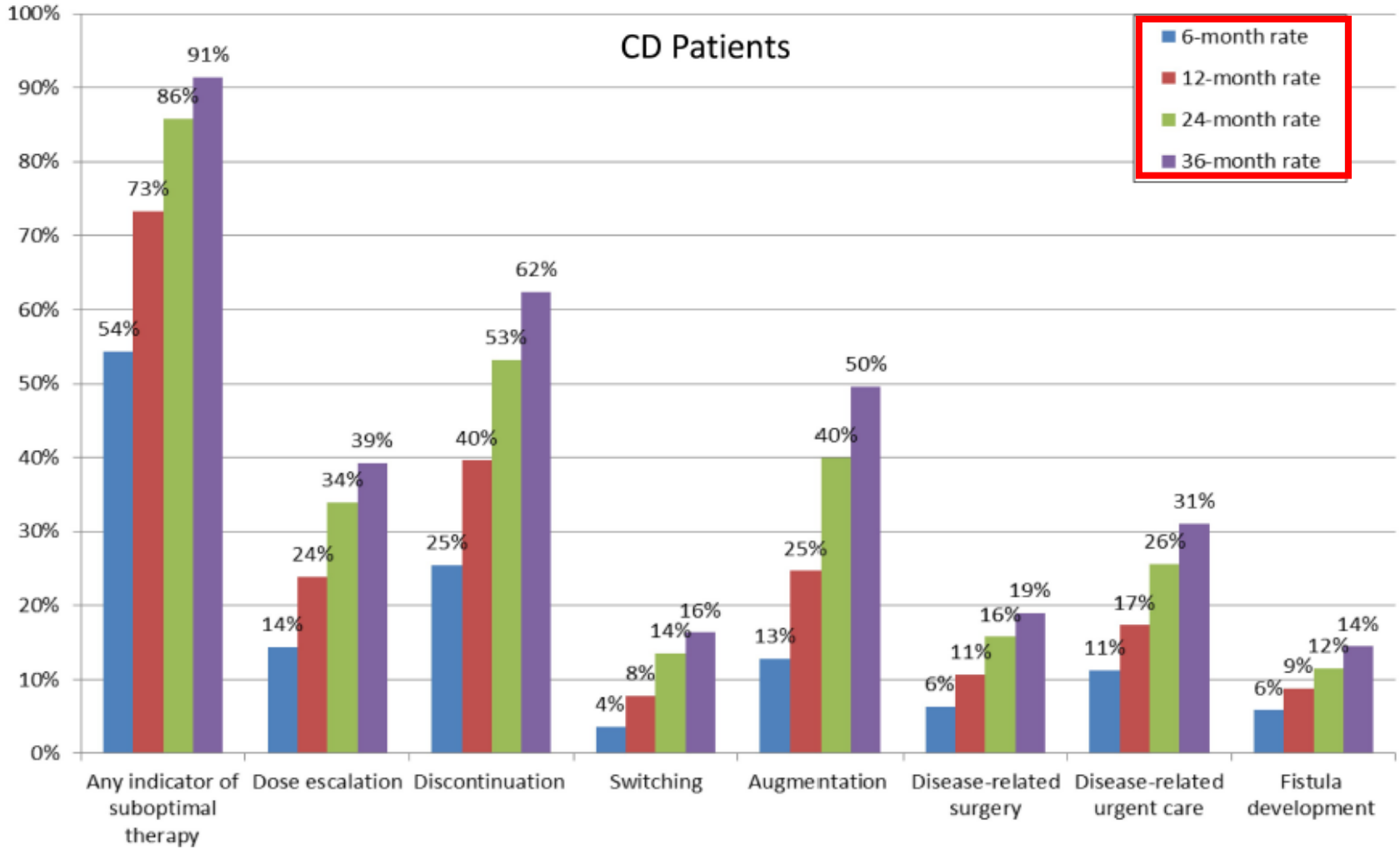
Patel H et al. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS One. 2017 Apr 20;12(4)

Terápiás elégtelenség – colitis ulcerosa



Patel H et al. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS One. 2017 Apr 20;12(4)

Terápiás elégtelenség - Crohn-betegség



Patel H et al. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS One. 2017 Apr 20;12(4)

Terápiás elégtelenség

Nincs kitüntetett körülmény

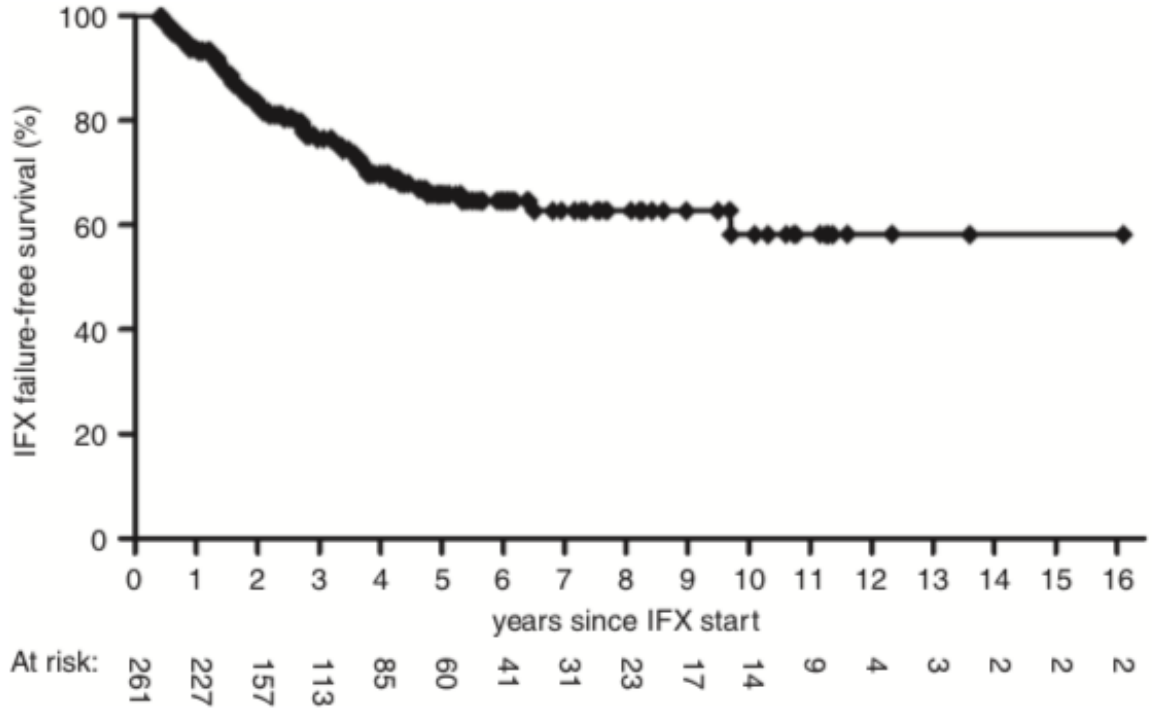
Table 2. Factors associated with indicators of suboptimal therapy for UC and CD patients.

	UC Patients (N = 1,699)	CD Patients (N = 4,569)
	HR (95% CI)	HR (95% CI)
Age		
18–39	*Reference*	*Reference*
40–49	1.08 (0.94; 1.25)	0.98 (0.91; 1.07)
50–64	1.02 (0.89; 1.16)	0.94 (0.87; 1.01)
≥65	1.13 (0.92; 1.40)	0.98 (0.84; 1.14)
Female *(Reference = Male)*	*1.12 (1.01; 1.24)**	*1.19 (1.12; 1.27) **
Insurance Plan Type		
Point of Service (POS) or Exclusive Provider Organization (EPO)	*Reference*	*Reference*
Preferred Provider Organization (PPO)	1.00 (0.85; 1.18)	0.95 (0.86; 1.04)
Health Maintenance Organization (HMO) or POS with capitation	1.11 (0.92; 1.33)	1.05 (0.93; 1.17)
Consumer-directed Health Plan (CDHP) or High-deductible Health Plan (HDHP)	1.13 (0.81; 1.56)	0.97 (0.81; 1.18)
Basic or Comprehensive Coverage	0.84 (0.66; 1.06)	1.00 (0.86; 1.15)
Region *(reference = South)*		
North-Central	1.03 (0.91; 1.18)	0.90 (0.84; 0.97)
North-East	0.98 (0.83; 1.16)	0.97 (0.88; 1.07)
West	0.98 (0.85; 1.13)	0.94 (0.86; 1.03)
CCI	*1.05 (1.01; 1.10)**	*1.06 (1.02; 1.09)**
CD location *(reference = ileum)*		
Colon	NA	0.95 (0.84; 1.07)
Ileum/Colon	NA	0.95 (0.83; 1.09)
Multiple sites	NA	0.92 (0.80; 1.06)
Not Specified	NA	0.99 (0.90; 1.07)

Patel H et al. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS One. 2017 Apr 20;12(4)

Anti-TNF - hosszú távú hatékonyság - CD

Belga tanulmány (Leuven-i centrum)
1031 beteg, 261 volt megfelelő a vizsgálathoz
5 éves infliximab hatásvesztés-mentes lefolyás 65.9% (95% CI 58.3-73.5).



Billiet T et al.: Prognostic factors for long-term infliximab treatment in Crohn's disease patients: a 20-year single centre experience. Aliment Pharmacol Ther. 2016 Oct;44(7):673-83.

Anti-TNF - hosszú távú hatékonyság - CD

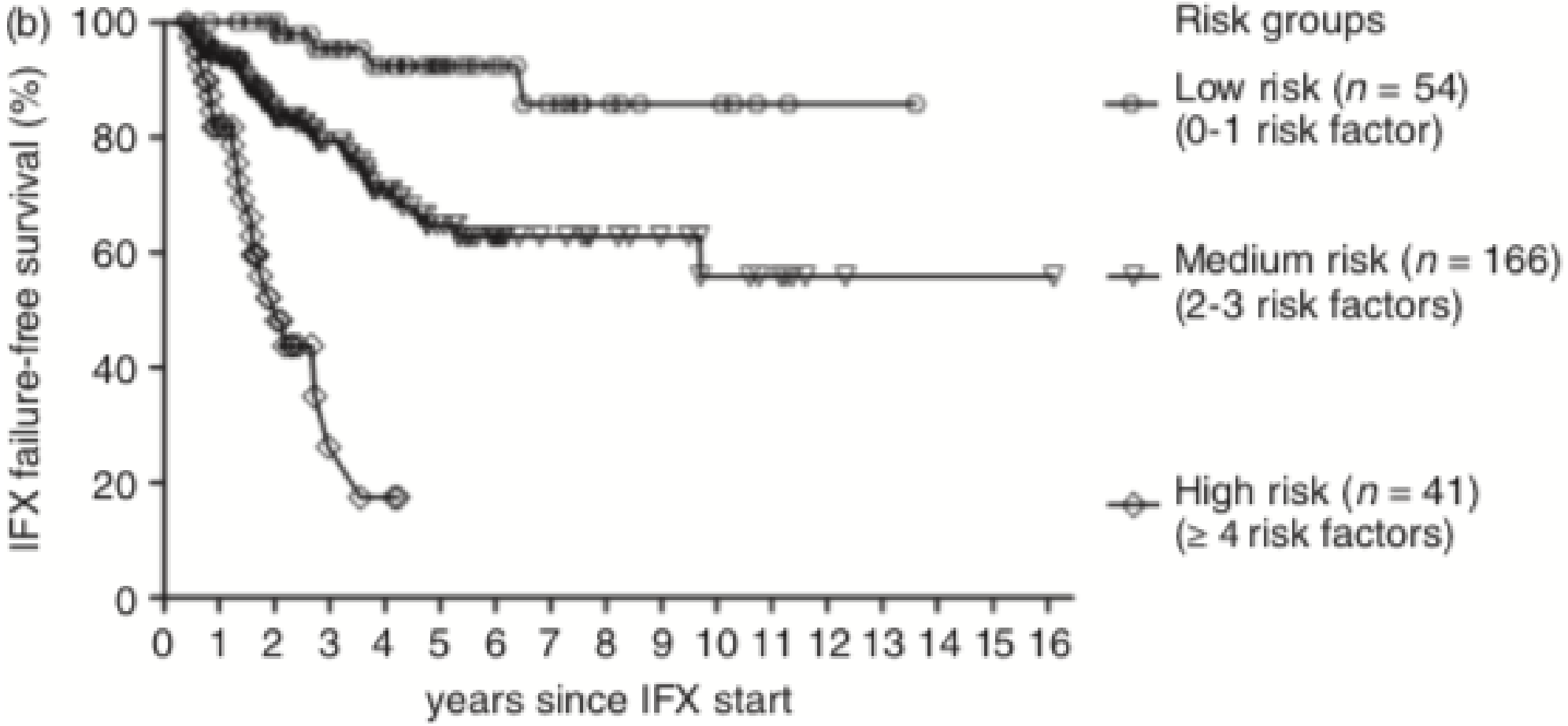
Mely tényezők befolyásolják a hosszú távú anti-TNF kezelés sikerét?

Table 3 | Univariate and multivariate Cox regression showing only significant factors associated with infliximab failure-free survival

Variables	Univariate analysis *P* value	Multivariate analysis Hazard ratio (95% CI)	*P* value
Female gender	0.03		
Duration of disease (years) (> 1 év)	0.003	1.03 (1.01–1.06)	0.02
BMI (kg/m²)	0.02		
L1 location	0.008	2.20 (1.20–4.02)	0.01
B1 behaviour	0.007		
B3 behaviour	0.002		
Prior anti-TNF use	0.04	2.38 (1.15–4.94)	0.02
Haemoglobin (g/dL) <13.5g/dl	0.046	0.82 (0.69–0.98)	0.03
CRP drop below normal	0.02		
Therapeutic drug monitoring use	2×10^{-10}	0.19 (0.10–0.37)	9×10^{-7}
Time until 1st optimisation (days)	3×10^{-5}	0.99 (0.98–0.99)	6×10^{-5}

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein.

Anti-TNF - hosszú távú hatékonyság - CD



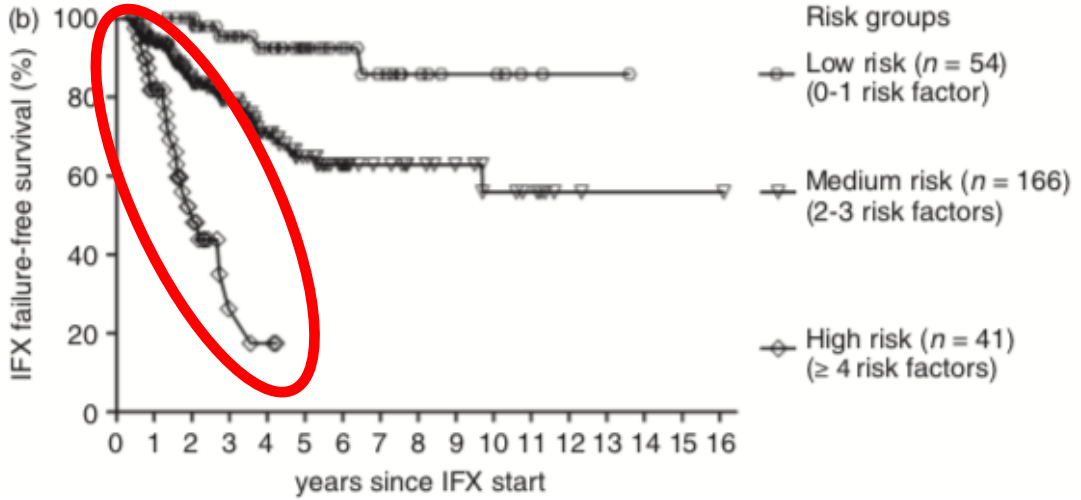
Anti-TNF - hosszú távú hatékonyság - CD

Saját beteganyag:

- Betegeinknél a biológiai kezelésig eltelt átlagos idő: 2-3 év (korábban 7 év volt)
- Vékonybél lokalizáció: 70%
- Vérképük többnyire a kezelésmegkezdésekor nem jó (Hgb <13.5g/dl)
- Gyógyszer szint mérés rutinszerűen nem elérhető
- Optimalizálás lassú, nem is mindig engedélyezet

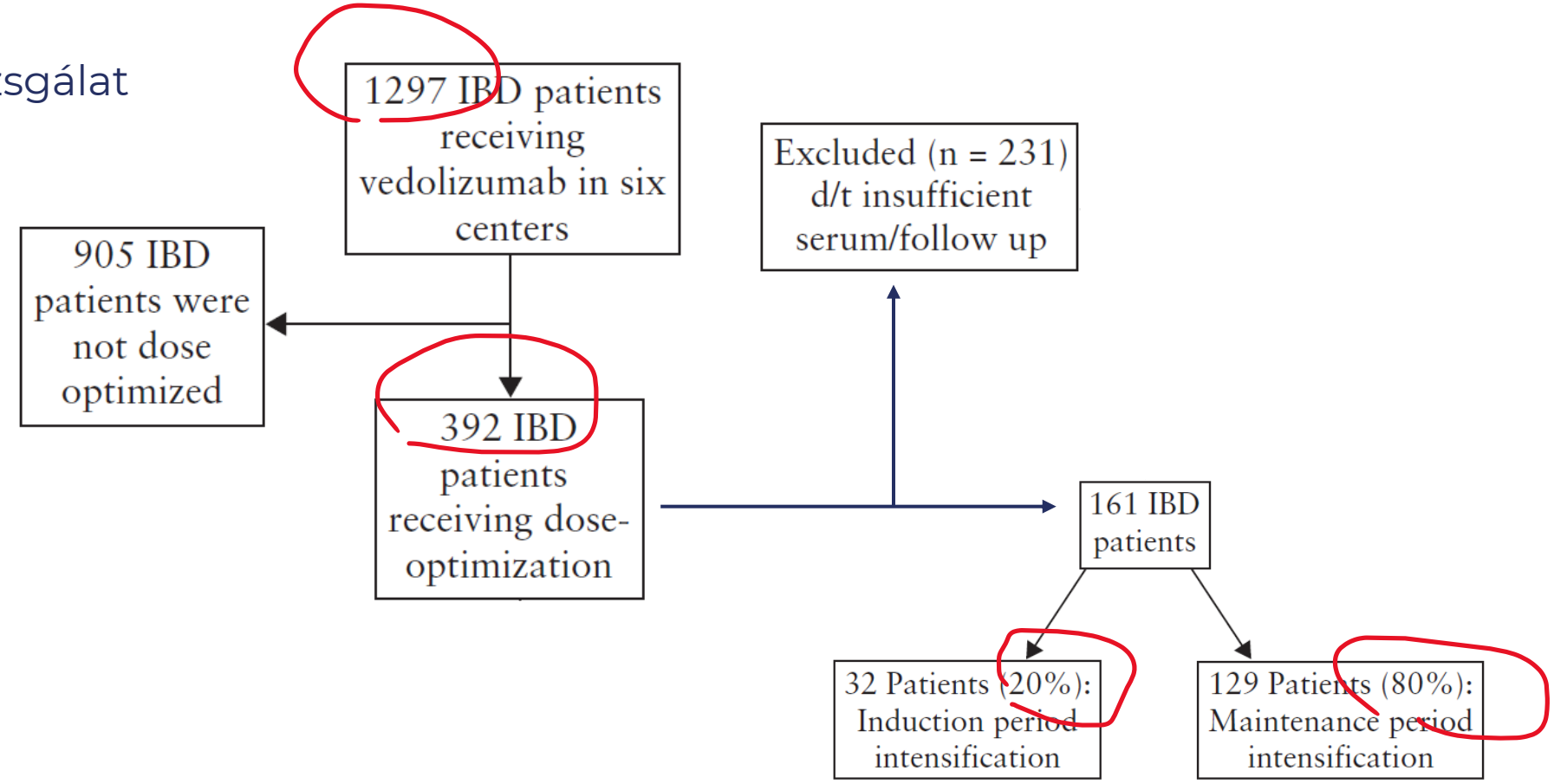
∑: betegeink többsége >4 kockázati tényezővel bír

Esélyük: <20% a 3 éves sikeres IFX kezelésre



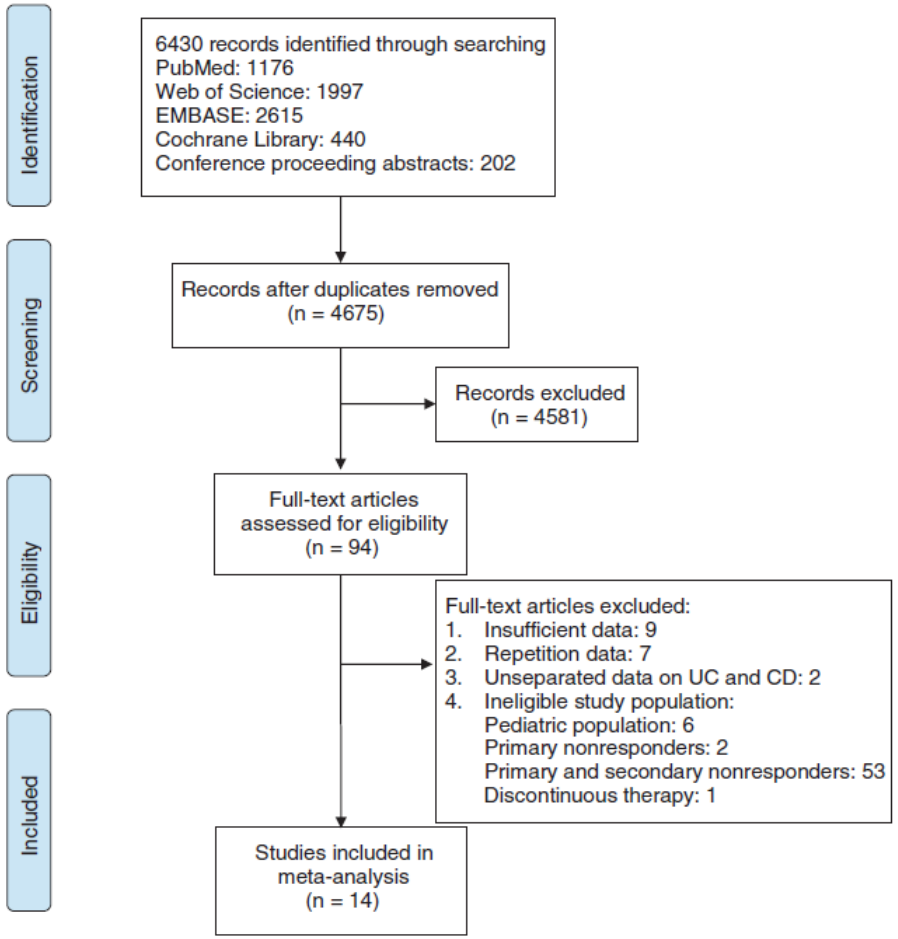
Vedolizumab

Izraeli vizsgálat



Ungar B et al.: Dose optimisation for Loss of Response to Vedolizumab- Pharmacokinetics and Immune Mechanisms. J Crohns Colitis. 2021 Oct 7;15(10):1707-1719.

Ustekinumab



Biologic-experienced (%)	Induction regimen (%)	Maintenance regimen (mg, %)	Concomitant therapies (%)
Anti-TNF (89), Natalizumab (17)	45–270 mg SC (100)	90 q8w (most)	NA
100	~6 mg/kg IV or SC induction	NA	Steroids (29), IMM (22)
96	≥1 dose of UST IV (100)	90 q8w (91)	IMM (35)
Anti-TNF (40)	~6 mg/kg or 130 mg IV	90 q8w (50), 90 q12w (50)	Steroid (46), IMM (36), 5-ASA (36)
98	~6 mg/kg IV	90 q8w (100)	Steroids (7), IMM (38)
Anti-TNF (62)	~6 mg/kg or 130 mg IV	90 q8w (75), 90 q12w (25)	IMM (32), 5-ASA (36)
95	~6 mg/kg IV (100)	90 q8/12w	Steroids (35), IMM (5)
100	~6 mg/kg IV (100)	90 q8w (100)	NA
Anti-TNF (90)	NA	NA	NA
100	SC induction: 90 mg Week 0/1/2/3 (46), 90 mg Week 0/2 (17), 90 mg week 0 (21)	90 q8w (75)	Steroid (32), IMM (36)
Anti-TNF (92)	IV (88) or SC (12) induction	90 q8w (84), 90 q12w (15), 90 q6w (1)	Steroids (39), IMM (42)
88	~6 mg/kg IV (100)	90 q8/12w	Steroids (37)
Anti-TNF (100)	SC induction: 90 mg Week 0/4 (48), 90 mg Week 0 (20), 45 mg Week 0/4 (7)	90 q8w (51), 90 q6w (18), 90 q4w (14)	Steroids (15), IMM (15)
NA	130 mg or ~6 mg/kg IV	90 q8w (51), 90 q12w (49)	NA

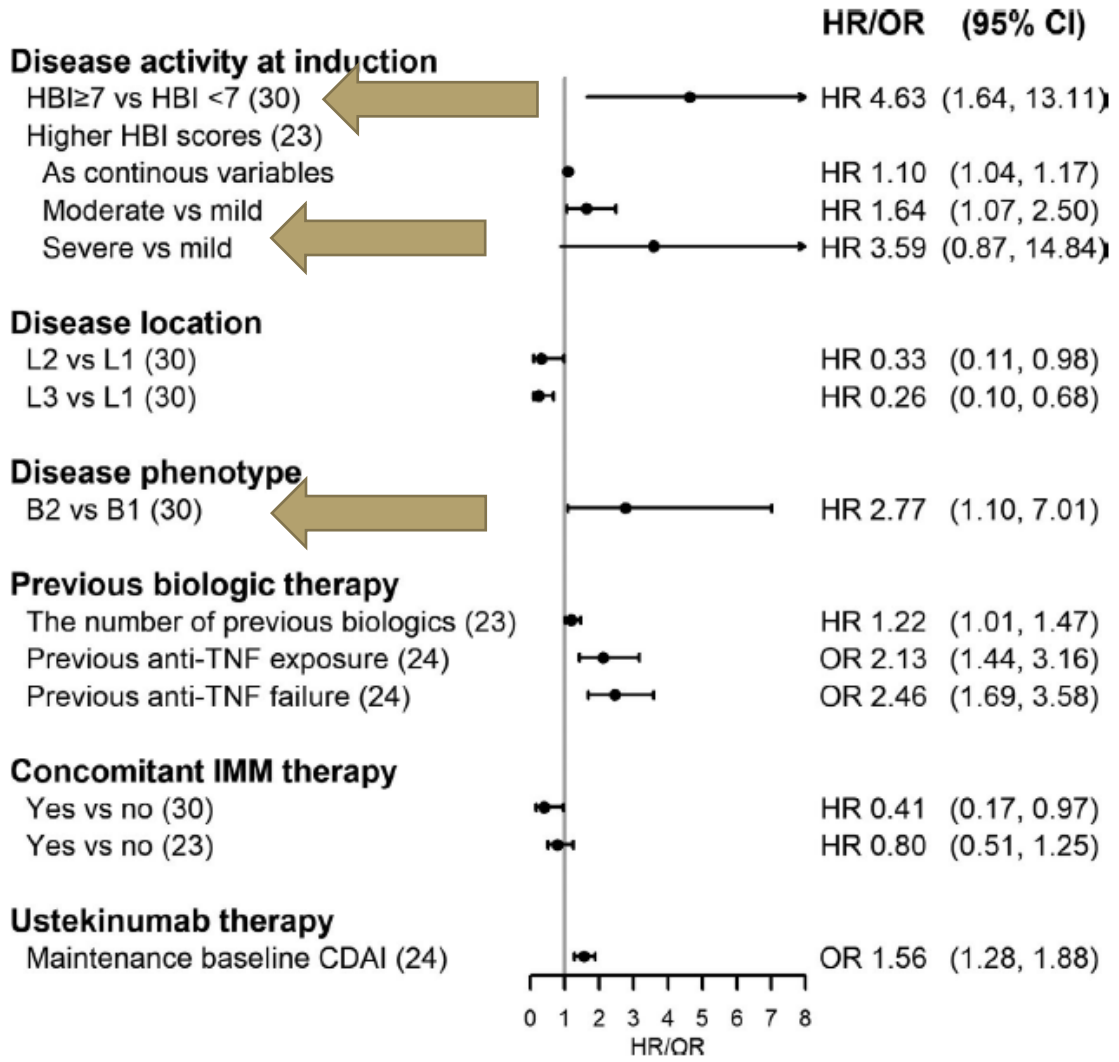
Yang H et al.: **Systematic review with meta-analysis: loss of response and requirement of ustekinumab dose escalation in inflammatory bowel diseases**. Aliment Pharmacol Ther. 2022 Apr;55(7):764-777.

Ustekinumab

Éves LOR arány: CD (n71133) 21%
Ismételt klinikai válasz dózisemelésre: 58%

Megf. idő: 26hét-36 hónap

Éves LOR arány UC (1 vizsg.): 35%
Ismételt klinikai válasz dózisemelésre: 58%



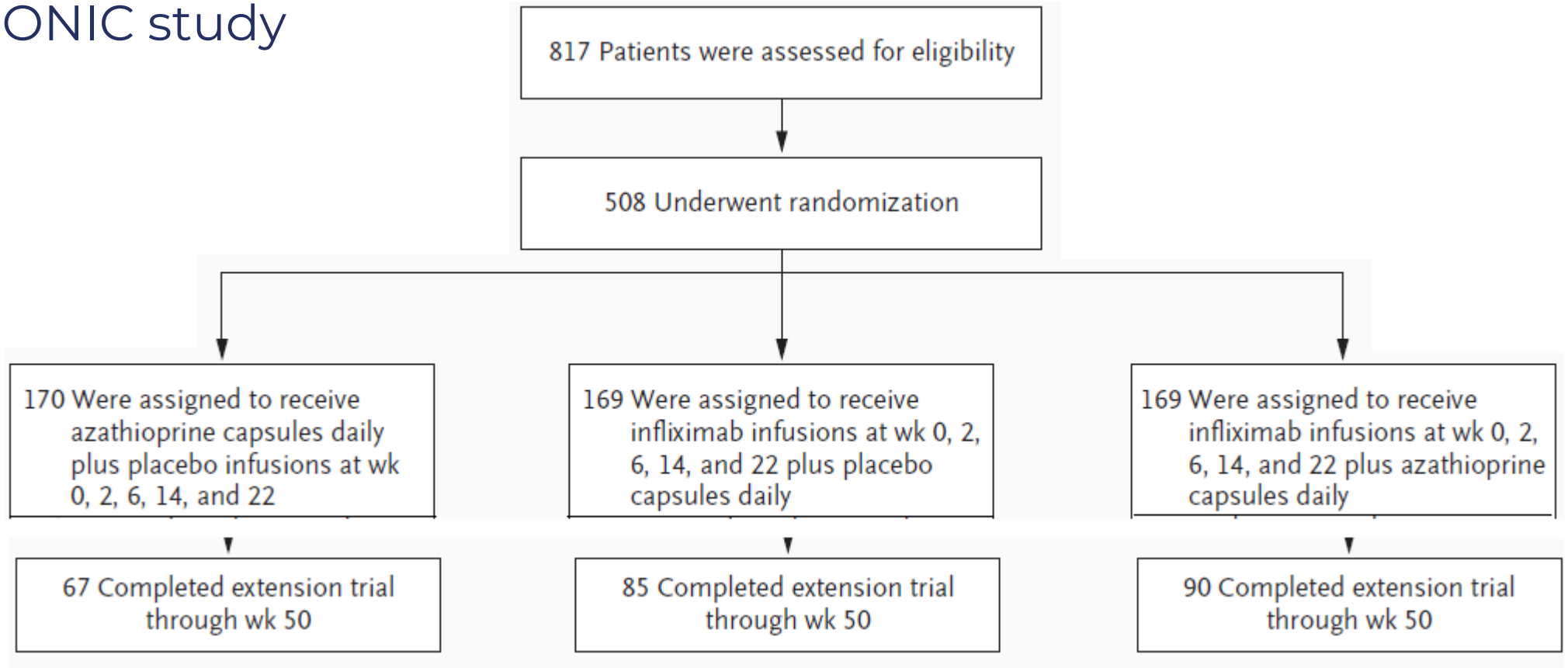
Yang H et al.: Systematic review with meta-analysis: loss of response and requirement of ustekinumab dose escalation in inflammatory bowel diseases. Aliment Pharmacol Ther. 2022 Apr;55(7):764-777.

Kombinációk

Biológiai kezelés + immunszupresszió

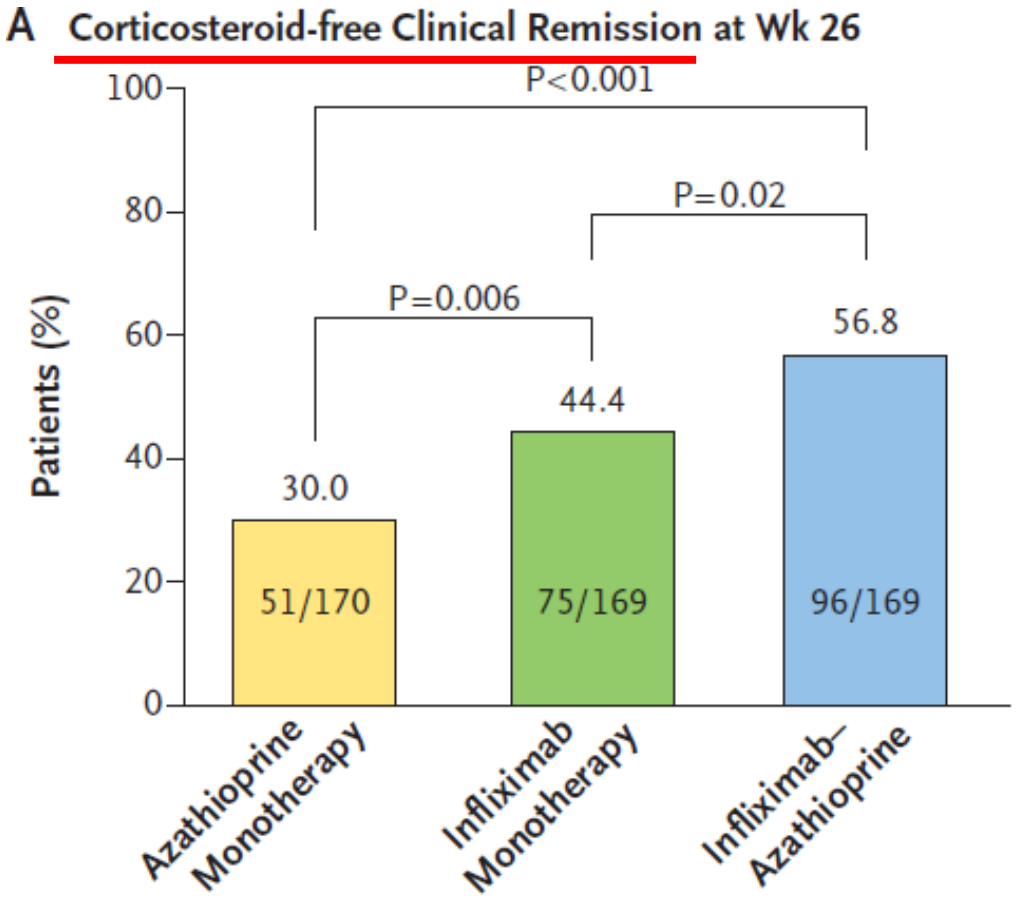
Infliximab + azathioprine -CD

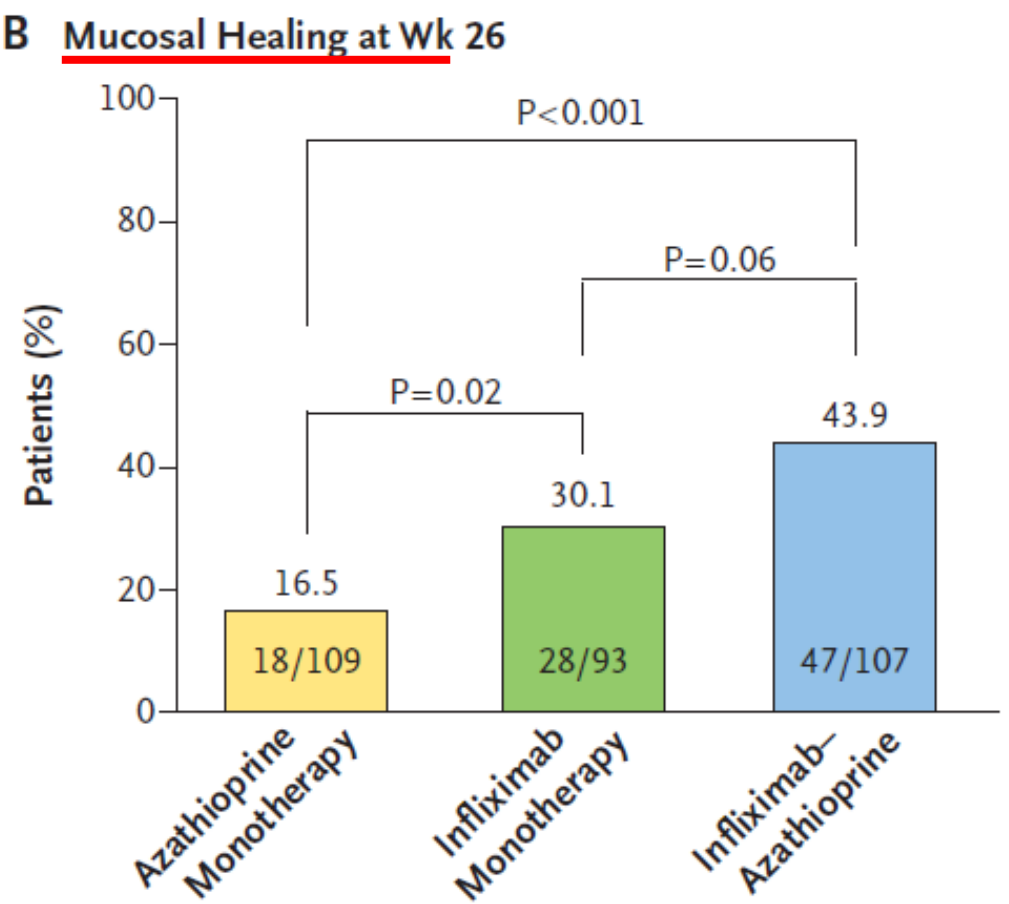
SONIC study



Colombel JF et al. SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383-95.

Infliximab + azathioprine - CD

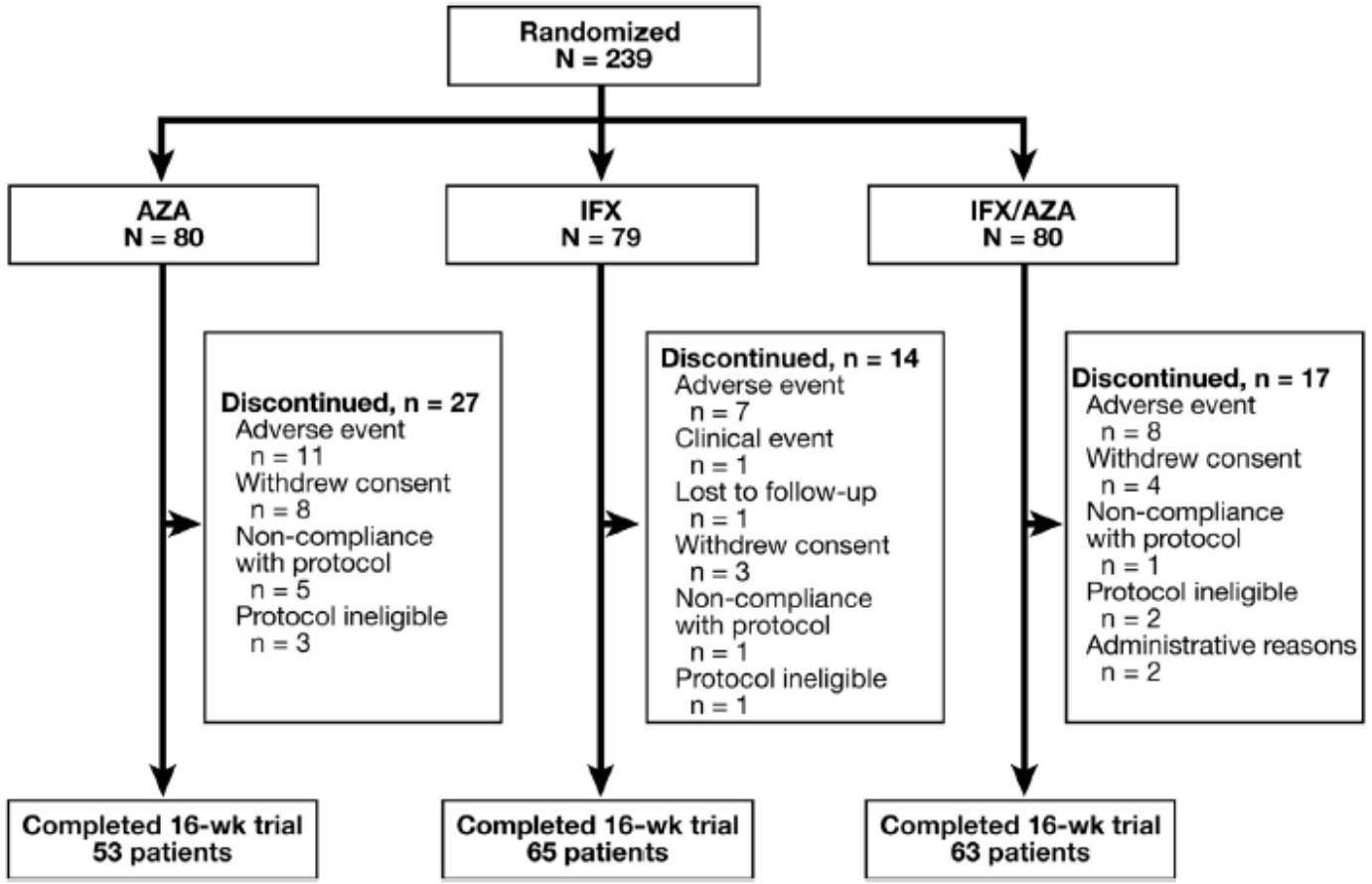




Colombel JF et al. SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383-95.

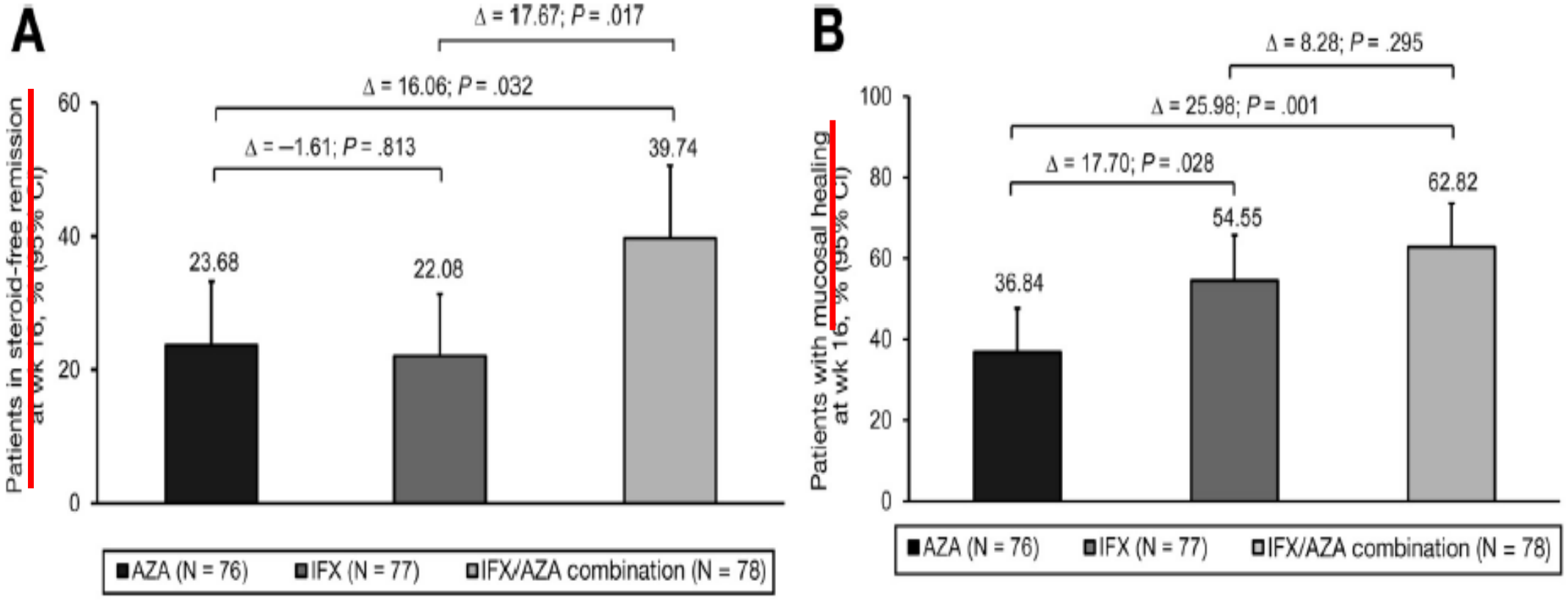
Infliximab + azathioprine - UC

UC SUCCESS



Panaccione R et al.: Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014 Feb;146(2):392-400.

Infliximab + azathioprine



Anti-TNF + azathioprine - milyen hosszan?

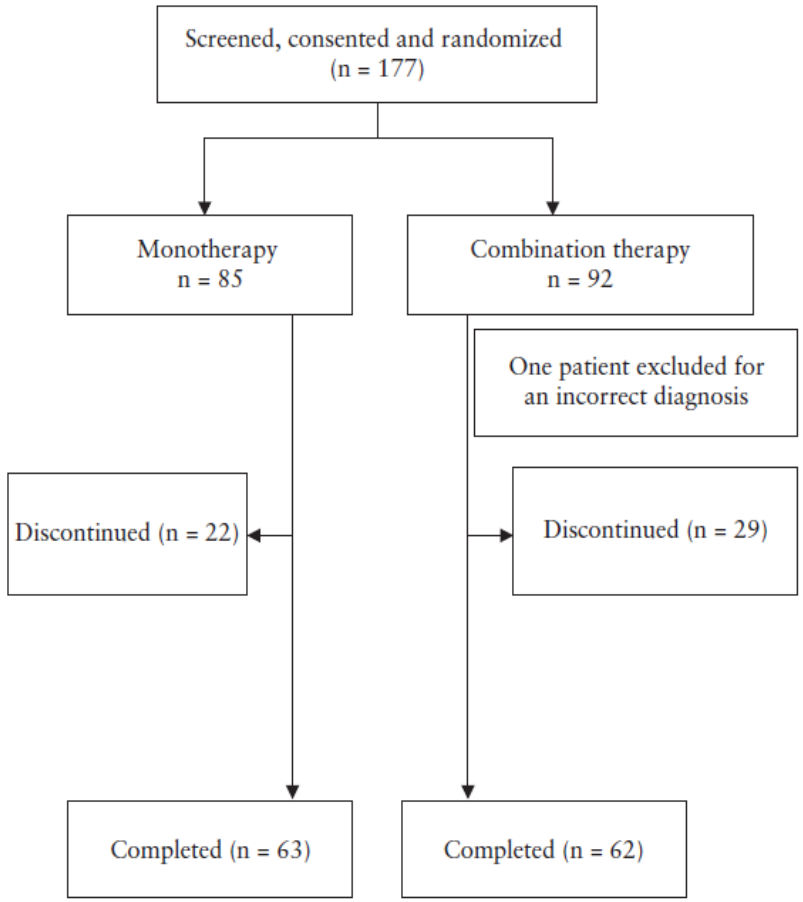
Farmakokinetikai előny: kevesebb antitest képződés

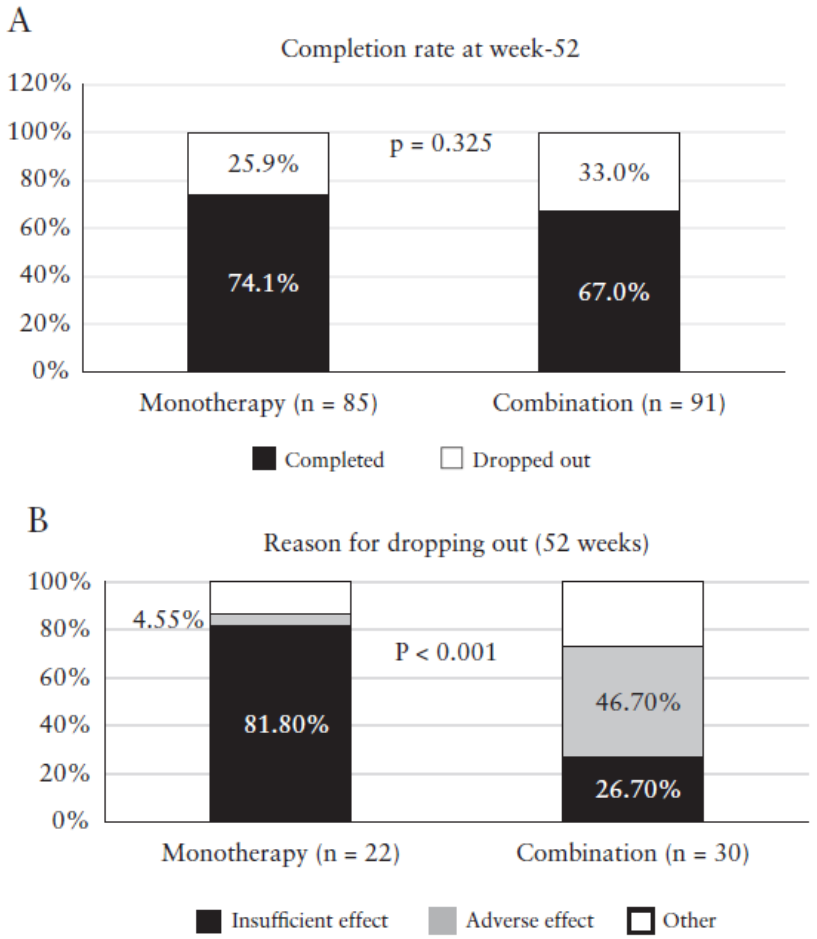
6. Hónap után kombináció előnye elvész ?

1610 betegen végzett prospektív obszervációs vizsgálat:
Kombinált immunomodulator (AZT vagy MTX) védett az immunogenicitás ellen:
IFX - HR=0.39 (95% CI 0.32 to 0.46), p<0.0001,
ADAlimumab - HR=0.44 (95% CI 0.31 to 0.64),

Kennedy NA et al: UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353.

Adalimumab+ azathioprin





Hisamatsu T et al.: Concerns and Side Effects of Azathioprine During Adalimumab Induction and Maintenance Therapy for Japanese Patients With Crohn's Disease: A Subanalysis of a Prospective Randomised Clinical Trial [DIAMOND Study]. J Crohns Colitis. 2019 Sep 19;13(9):1097-1104.

Anti-TNF + azathioprin

Infliximabhoz kell
Adalimumabhoz nem kell

De:
- HSTC lymphoma
- EBV status?

Vedolizumab + azathioprin

SWIBERG study
147 CD, 92 UC and 7 IBD-U
86% TNF-antagonist hatásvesztett
48% CD beteg legalább egy műtét volt

17 hónap utánkövetési idő:
58% maradt VDZ-n, 54% CD és 64% UC beteg maradt klinikai remisszióban

Megelőző anti-TNF kezelés (HR: 4.03; 95% CI: 0.96-16.75) és emelkedtet kezdeti CRP (HR: 2.22; 95% CI: 1.10-4.35) hatástalanságot prediktáló tényező.
Párhuzamosan adott immunszupresszió nem !

Eriksson C et al: Long-term effectiveness of vedolizumab in inflammatory bowel disease: a national study based on the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG). Scand J Gastroenterol. 2017 Jun-Jul;52(6-7):722-729.

Vedolizumab + azathioprin

Dulai PS et al.: The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe **Crohn's Disease**: Results From the US VICTORY Consortium. Am J Gastroenterol. 2016 Aug;111(8):1147-55.

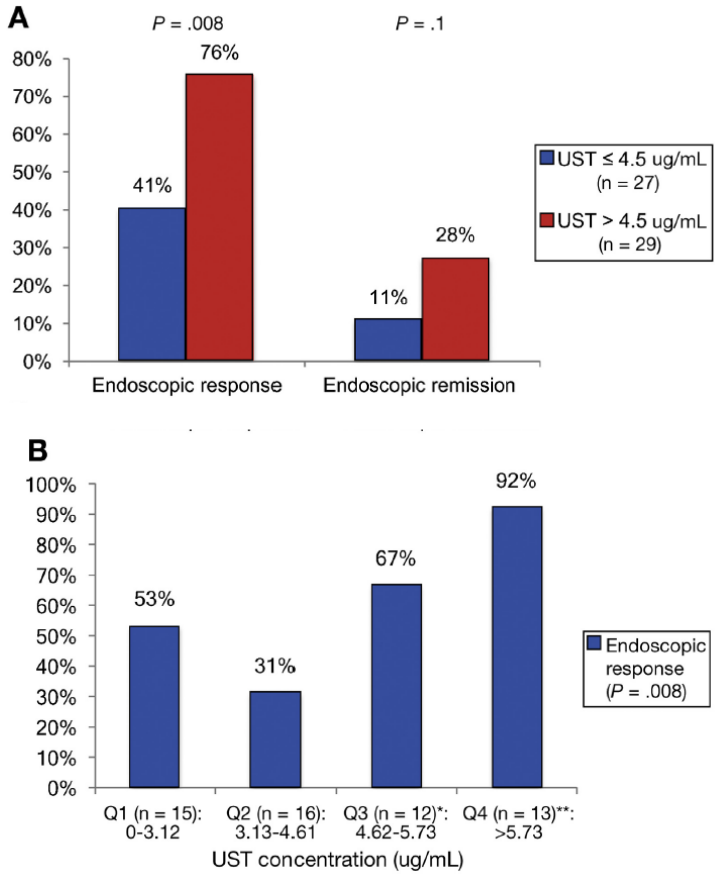
Stallmach A et al.: Vedolizumab provides clinical benefit over 1 year in patients with active **inflammatory bowel disease** - a prospective multicenter observational study. Aliment Pharmacol Ther. 2016 Dec;44(11-12):1199-1212.

Ustekinumab + azathioprin

Szteroid mentes klinikai remisszió egyforma volt a kombinált és a monoterápián lévőkben (50.0% vs 50.0%)

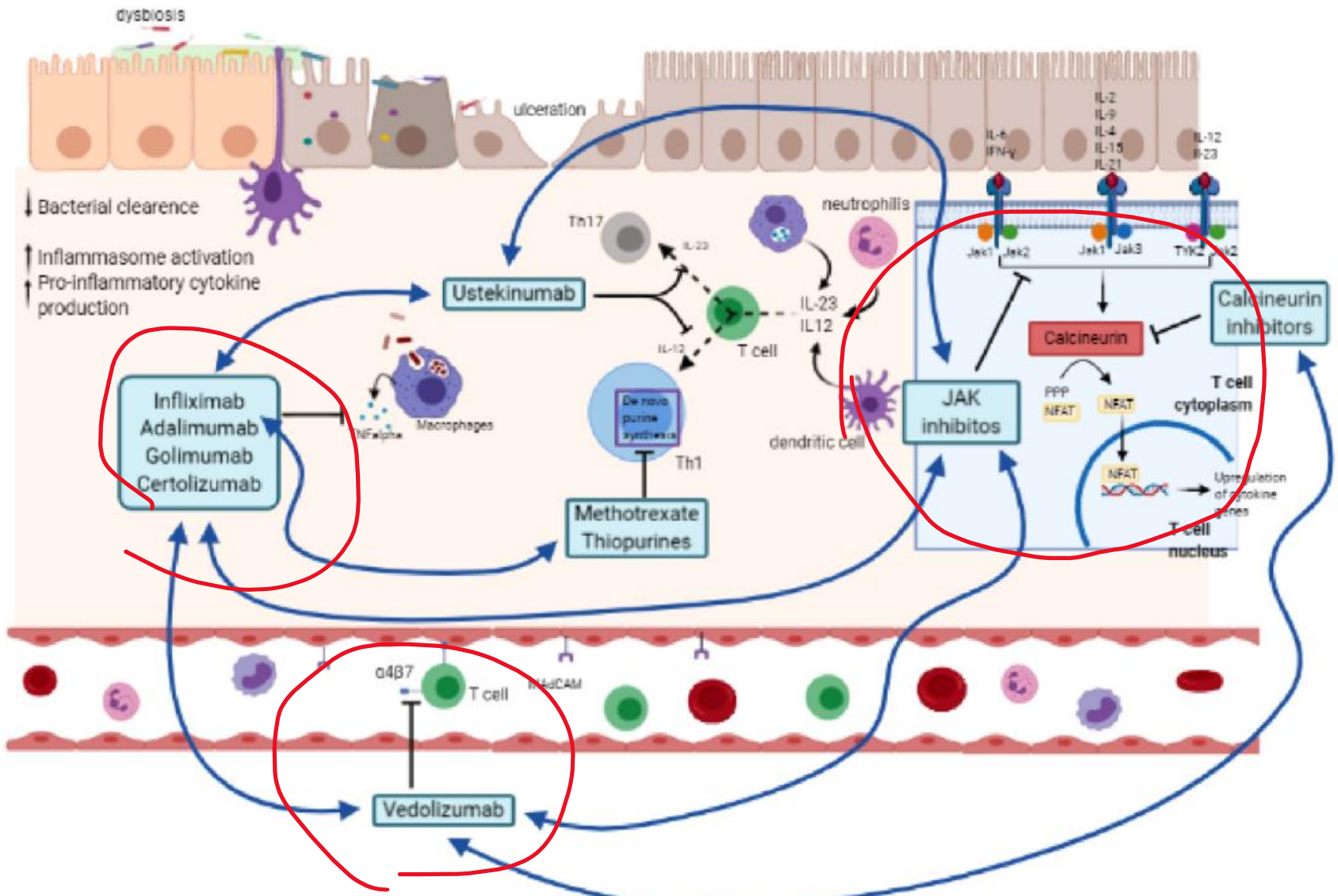
Endoszkópos válasz (58.5% vs 60.0%) és az endoszkópos remisszió is (14.6% vs 33.3% , NS)

Átlagos szérum koncentráció is megegyező volt a 10. héten (2.7 ±1.0 vs 3.7 ± 2.4ug/ml) és 26. héten 3.8±1.9 vs 4.7 ± 2.0ug/ml)



Battat R et al.: Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2017 Sep;15(9):1427-1434.e2.

2 biológiai/SMD kezelés

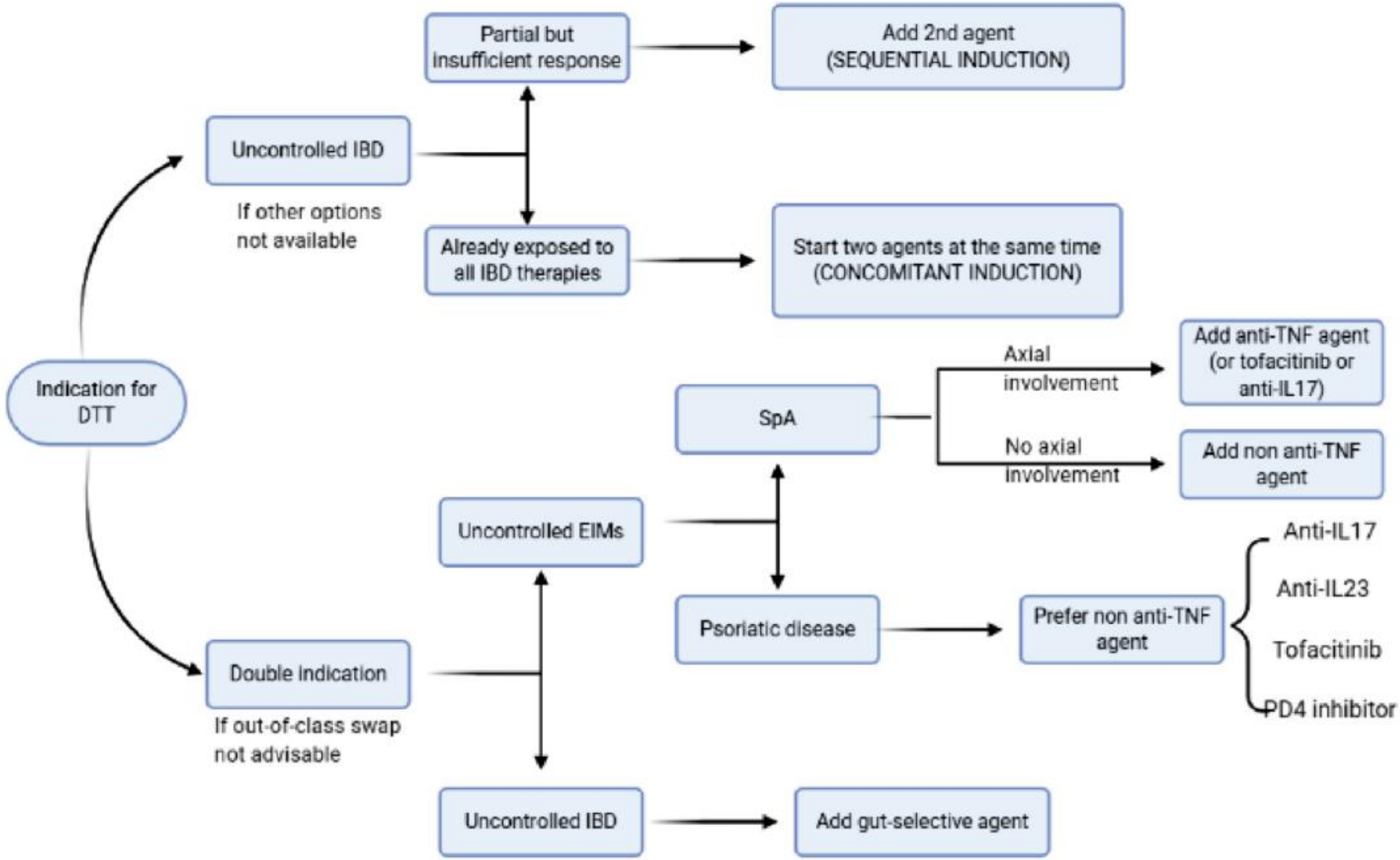


Anti-citokinek

Migráció gátlók

Kis molekulák

Privitera G. et al.: Combination therapy in inflammatory bowel disease - from traditional immunosuppressors towards the new paradigm of dual targeted therapy. Autoimmun Rev. 2021 Jun;20(6):102832.


Indication for DTT
Uncontrolled IBD
If other options not available
Partial but insufficient response
Add 2nd agent (SEQUENTIAL INDUCTION)
Already exposed to all IBD therapies
Start two agents at the same time (CONCOMITANT INDUCTION)
Double indication
If out-of-class swap not advisable
Uncontrolled EIMs
SpA
Axial involvement
Add anti-TNF agent (or tofacitinib or anti-IL17)
No axial involvement
Add non anti-TNF agent
Psoriatic disease
Prefer non anti-TNF agent
Anti-IL17
Anti-IL23
Tofacitinib
PD4 inhibitor
Uncontrolled IBD
Add gut-selective agent

Kombinációk hatóanyag szerint

Anti cytokinek
- Anti-TNF alfa
- IL12/23

Kis molekulák
- JAK gátlók
- ?

Migráció gátlók
- Anti integrinek
- ~~S1P gátlók~~

Reumatológia – modellekben

Etanercept (aTNF) + tacrolymus (calcyneurin inh) – arthritis egérmodellben gyulladást csökkentette

„Dual kinase inhibitor” – JAK és lép tyrosine kinaz – osteoclast aktivitás csökkentése RA-ban

Bruton’s tyrosine kinase + aTNF – csontbontás csökkent

Bispecifikus antitestek (BsAb) - két epitóp ellen aTNF – CXCL10

Tapasztalatok – reumatológia – valós élet

Table 1 Key randomised controlled trials on advanced combination treatment (ACT) in rheumatological patients

Author (year)	Study design	Population enrolled	Combination arm	Control arm	Safety outcomes	Efficacy outcomes
Genovese (2004)[28]	RCT	Active RA despite MTX therapy	Etanercept plus anakinra	Etanercept monotherapy	Serious infections, injection-site reactions and neutropenia increased with combo	Lack of clinical benefit
Weinblatt (2006)[29]	RCT	Active RA receiving ≥1 traditional nonbiological and/or biological DMARDs	Abatacept plus anti-TNF Abatacept plus anakinra	Abatacept or anti-TNF plus placebo	Serious AE increased with combo	Lack of clinical benefit
Weinblatt (2007)[30]	RCT	Active receiving a stable dose of MTX and stable dose of anti-TNF	Abatacept plus etanercept	Etanercept plus placebo	Serious AE increased with combo	No clear evidence of efficacy
Greenwald (2011)[31]	RCT	Active RA receiving a stable dose of MTX and stable dose of anti-TNF	Anti-TNF plus rituximab	Anti-TNF plus placebo	No safety signals	No clear evidence of efficacy
Van Vollenhoven (2015)[32]	RCT	Active RA receiving rituximab retreatment	Rituximab plus atacicept	Rituximab plus placebo	No safety signals	No clear evidence of efficacy

AE, adverse events; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomised controlled trial.

aTNF+aIL1

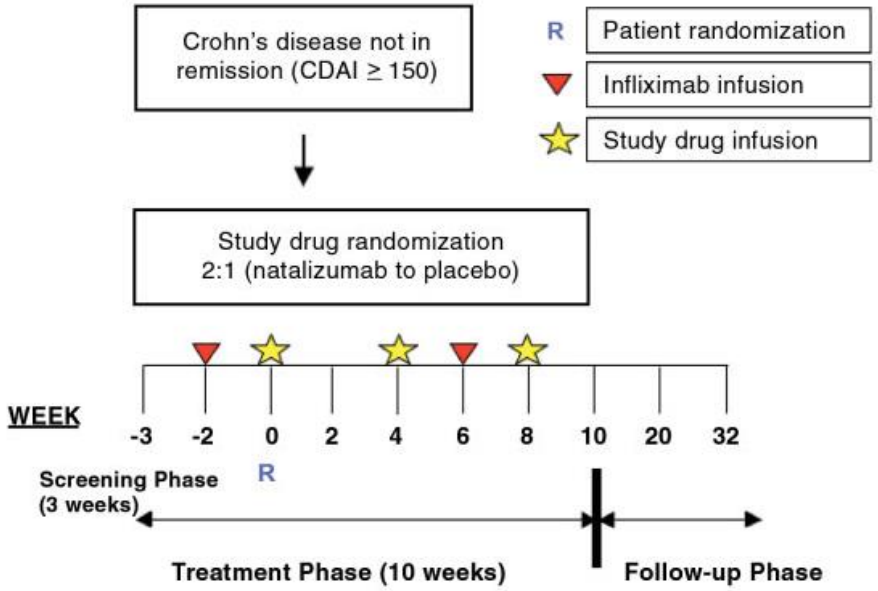
DMARD

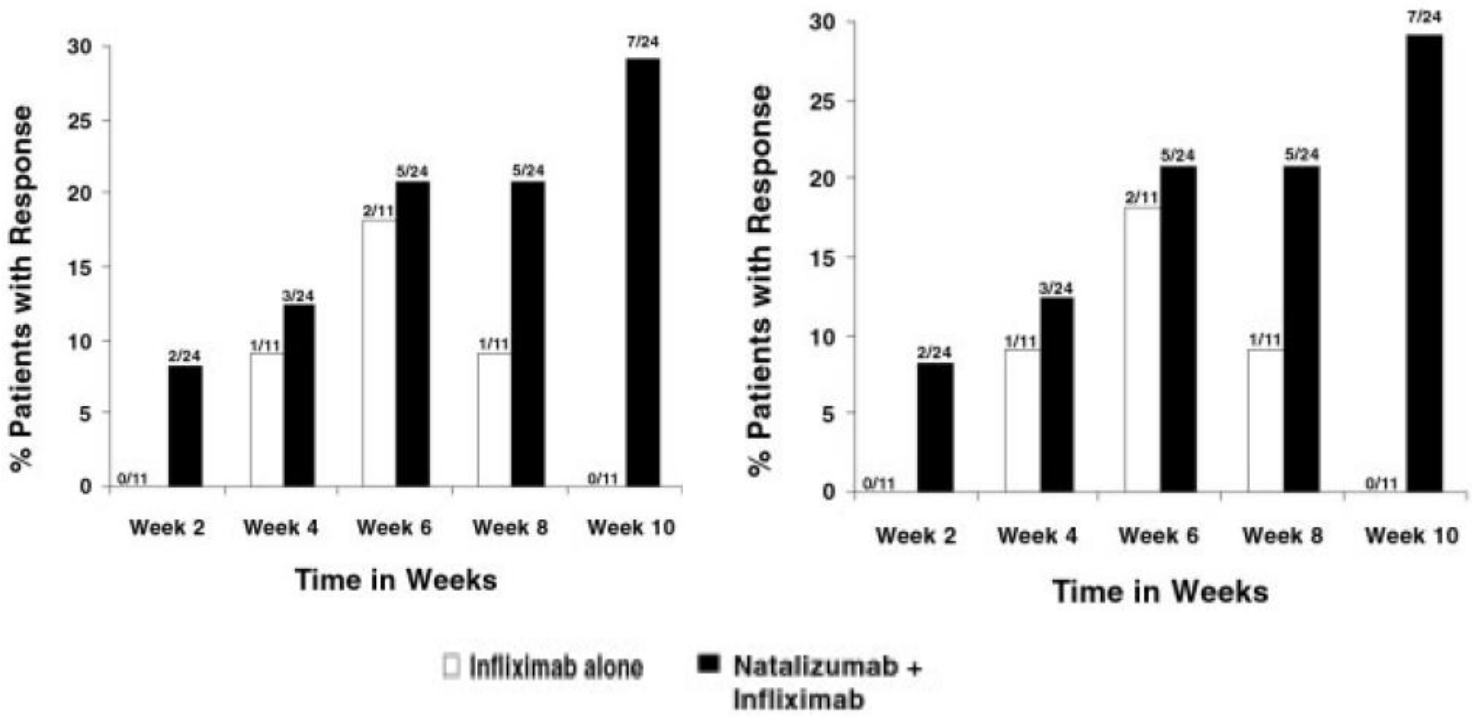
aTNF+aCD20

aCD20+B sejt gátló

Gyulladásos bélbetegségekben - első

Anti-TNF és natalizumab/placebo – pozitív trendek





Bruce E. Sands, MD, MS and others, Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab, *Inflammatory Bowel Diseases*, Volume 13, Issue 1, 1 January 2007, Pages 2–11

Gyulladásos bélbetegségekben

TABLE 1 Baseline characteristics of patients with inflammatory bowel disease (IBD) on combination biologic therapy

Characteristics	IBD (N = 50)	CD (n = 31)	UC (n = 18)	IBD-U (n = 1)*
Age, y (mean ± SD)	36.7 ± 13.2	38.7 ± 13.9	34.1 ± 11.8	23
Male sex (n, %)	16 (32)	7 (23)	8 (44)	1 (100)
Disease duration, y (mean ± SD)	14.8 ± 11.1	17.8 ± 11.7	10.2 ± 8.1	4
Prior bowel resection (n, %)	20 (40)	20 (65)	0 (0)	0 (0)
Previous biologics, n (median [IQR])	2 (1–2)	2 (1.5–2.5)	2 (1–2)	1
Disease location				
Montreal classification (n, %)		L1: 2 (6)	E1: 1 (6)	L1: 0
		L2: 8 (26)	E2: 4 (22)	L2: 0
		L3: 21 (68)	E3: 13 (72)	L3: 1 (100)
		L4: 7 (23)		L4: 0
		P: 12 (39)		P: 0
Clinical disease activity at baseline (n, %)		HBI (n = 29)	Partial Mayo (n = 15)	HBI (n = 1)
		<5: 5 (17)	0-1: 3 (20)	<5: 0
		5-7: 9 (31)	2-4: 2 (13)	5-7: 1 (100)
		8-16: 11 (38)	5-6: 9 (60)	8-16: 0
		>16: 4 (14)	7-9: 1 (7)	>16: 0
Concomitant rheumatologic/dermatologic disease (n, %)				
Total	10 (20)			
Psoriasis	5 (10)	4 (13)	1 (6)	0 (0)
Psoriatic arthritis	2 (4)	2 (6)	0 (0)	0 (0)
AS	2 (4)	2 (6)	0 (0)	0 (0)
RA	1 (2)	0 (0)	1 (6)	0 (0)

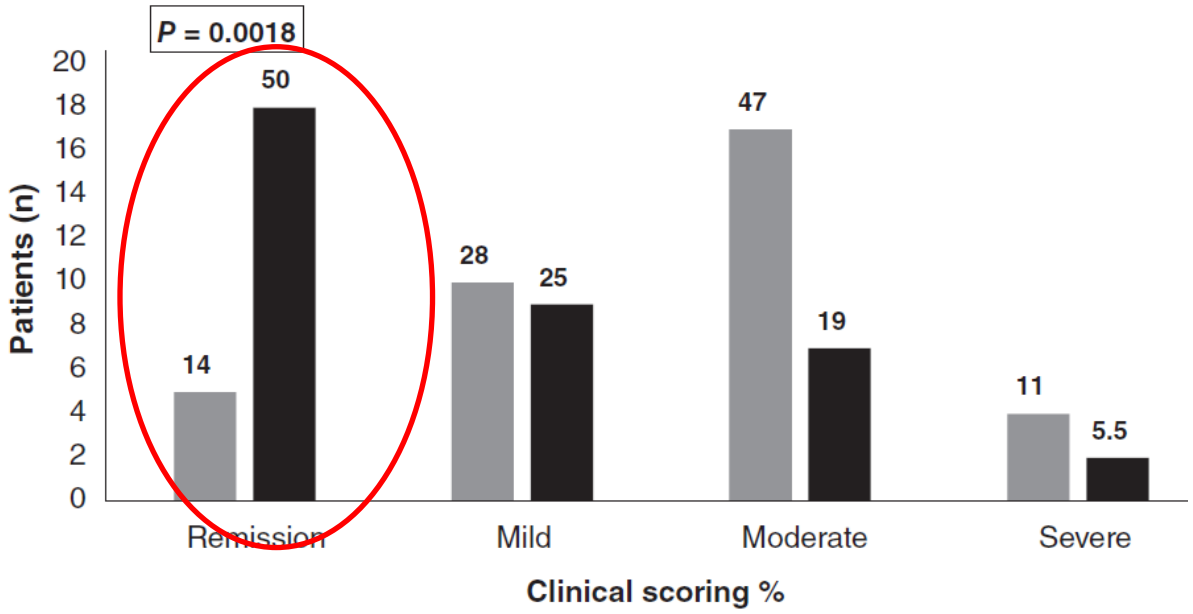
Glassner K, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. J Dig Dis. 2020 May;21(5):264-271.

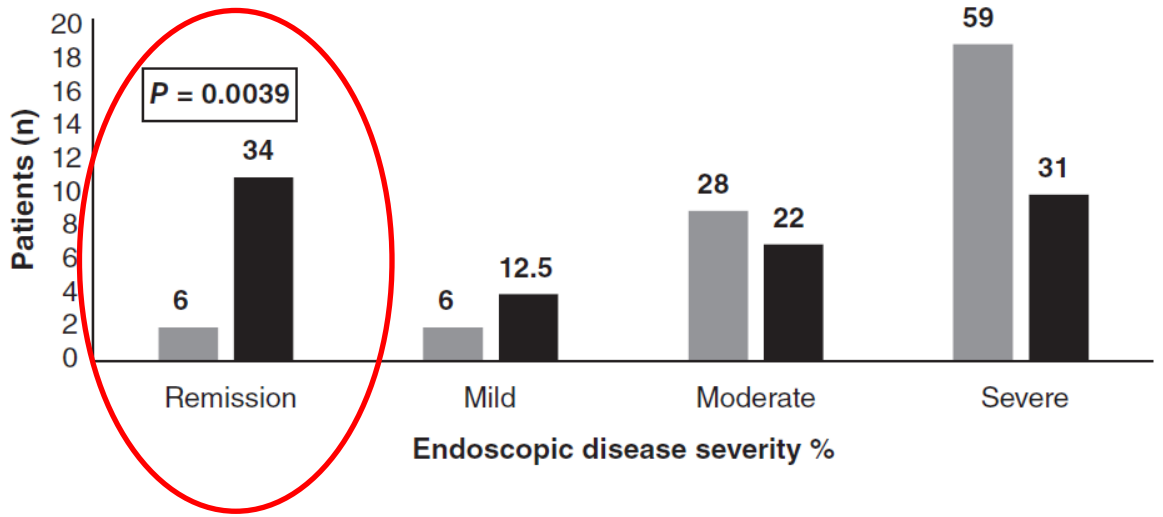
Gyulladásos bélbetegségekben

Combinations	IBD (N = 53)	CD (n = 34)	UC (n = 18)	IBD-U (n = 1)
Vedolizumab + tofacitinib	8 (15.1)	0 (0)	8 (44.4)	0
Vedolizumab + ustekinumab	25 (47.2)	23 (67.6)	1 (5.6)	1 (100)
Vedolizumab + adalimumab	3 (5.7)	2 (5.9)	1 (5.6)	0 (0)
Vedolizumab + certolizumab	2 (3.8)	2 (5.9)	0 (0)	0 (0)
Vedolizumab + golimumab	2 (3.8)	1 (2.9)	1 (5.6)	0 (0)
Tofacitinib + infliximab	4 (7.5)	1 (2.9)	3 (16.7)	0 (0)
Tofacitinib + golimumab	4 (7.5)	0 (0)	4 (22.2)	0 (0)
Tofacitinib + certolizumab	1 (1.9)	1 (2.9)	0 (0)	0 (0)
Tofacitinib + ustekinumab	3 (5.7)	3 (8.8)	0 (0)	0 (0)
Adalimumab + apremilast	1 (1.9)	1 (2.9)	0 (0)	0 (0)

Glassner K, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. J Dig Dis. 2020 May;21(5):264-271.

Gyulladásos bélbetegségekben





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Gyulladásos bélbetegségekben

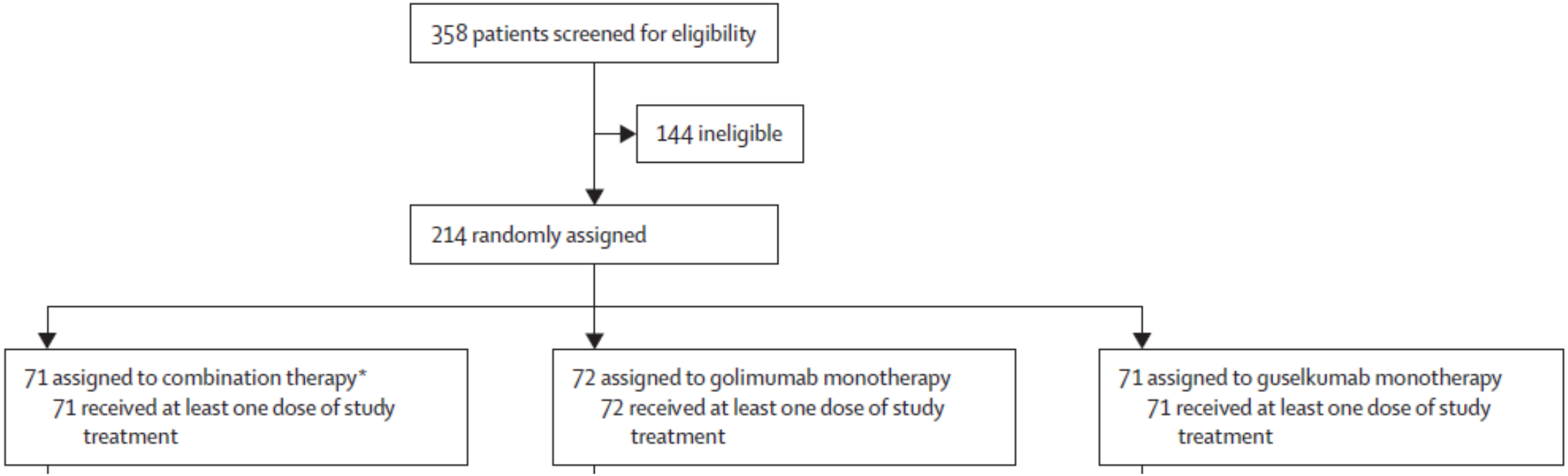
Leading article

Table 3 Possible ACT combinations in IBD

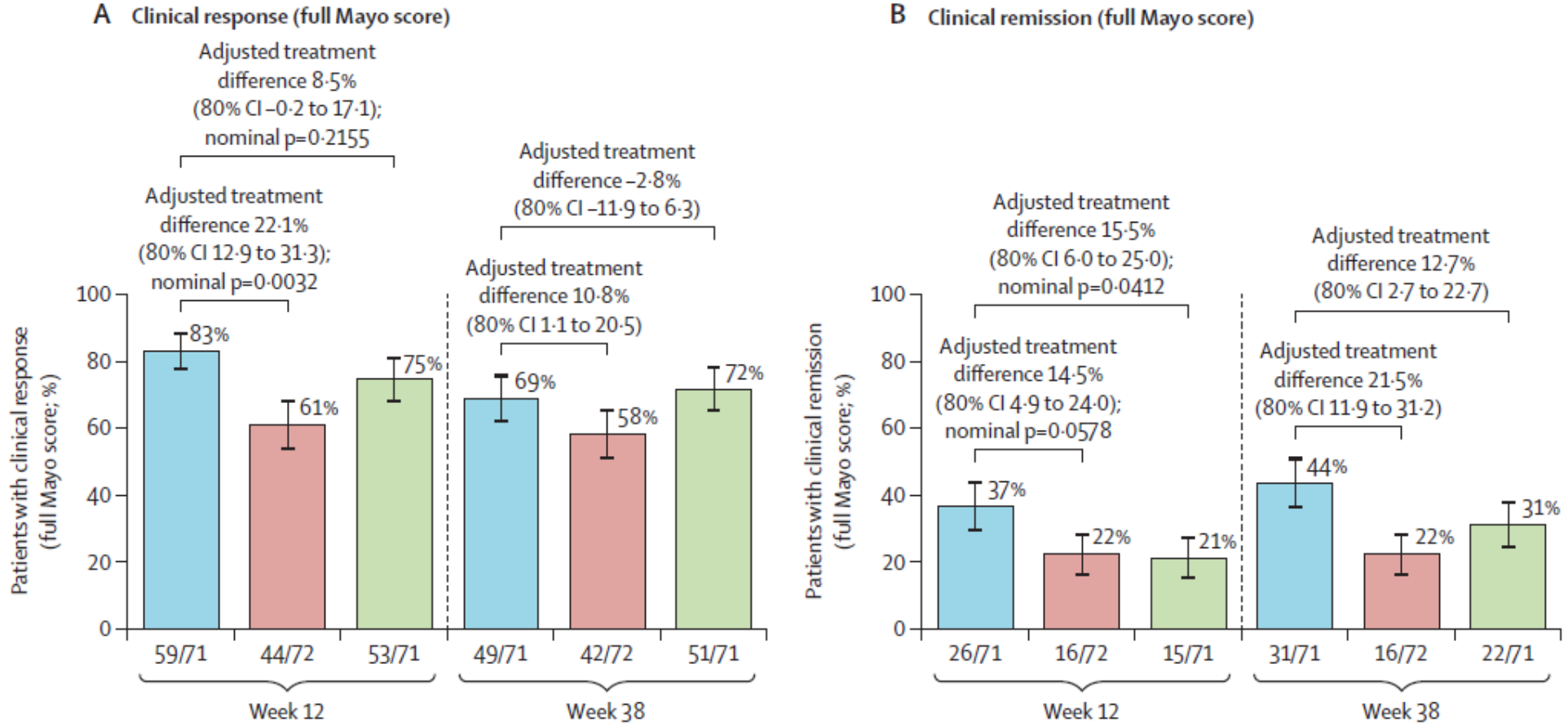
	Anti-TNF	Vedolizumab	Ustekinumab	Anti IL-23 (eg, guselkumab)	JAK inhibitors (eg, tofacitinib)
Anti-TNF	---	Yes	Yes	Yes	Too little evidence
Vedolizumab	Yes	---	Yes	Yes	Yes
Ustekinumab	Yes	Yes	---	Very similar MOA	Yes
Anti IL-23 (eg, guselkumab)	Yes	Yes	Very similar MOA	---	Too little evidence
JAK inhibitors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

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

Feagan BG et al.: **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. Lancet Gastroenterol Hepatol. 2023 Apr;8(4):307-320



Feagan BG et al.: **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. Lancet Gastroenterol Hepatol. 2023 Apr;8(4):307-320



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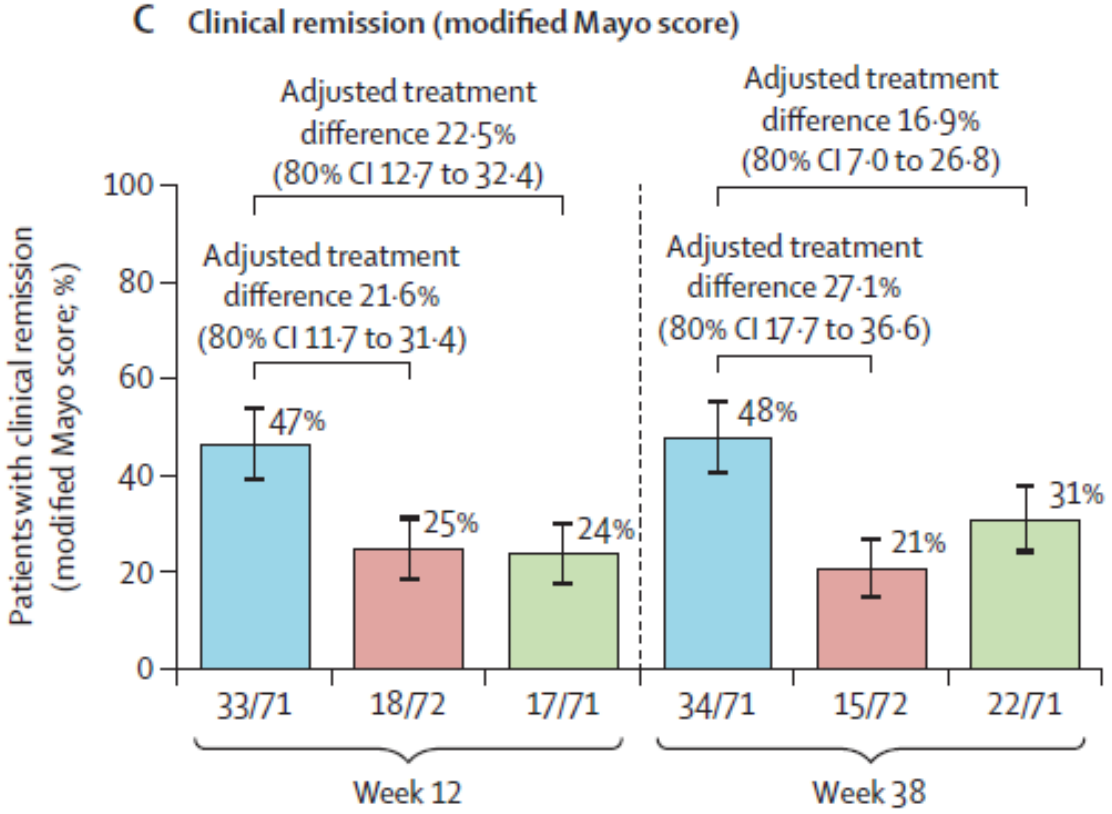

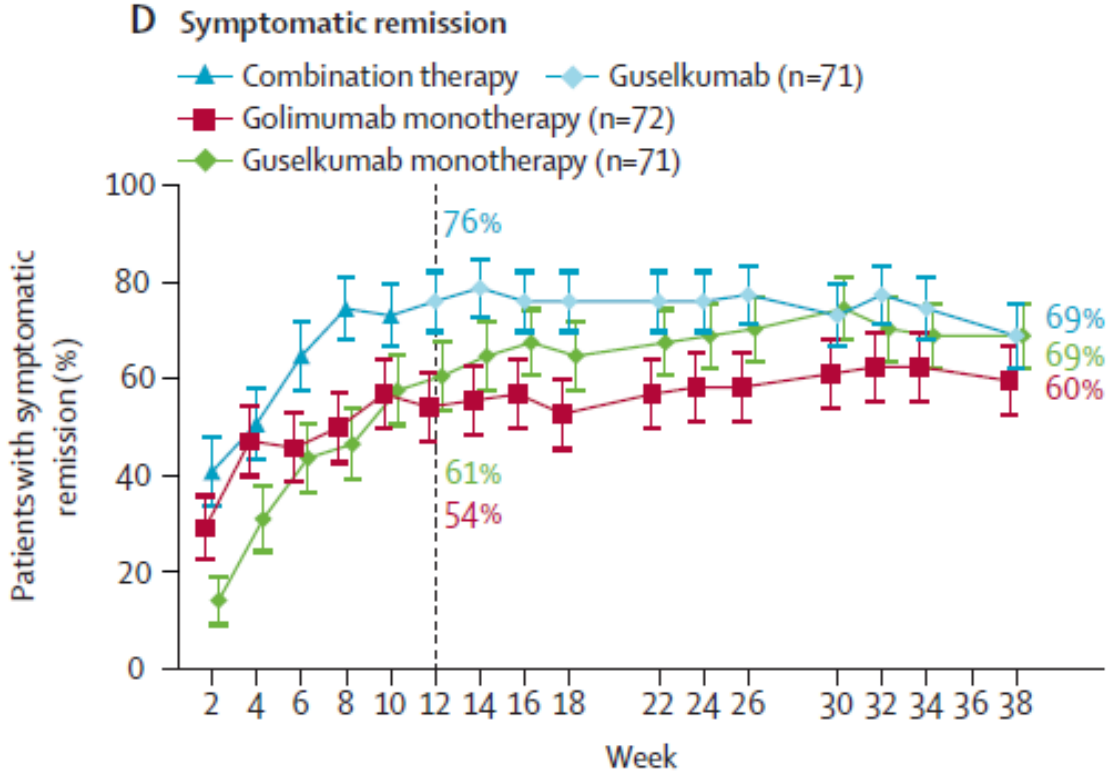

Gyulladásos bélbetegségekben

Table 2 Clinical practice recommendations on ACT in 2022

Who	**Patients with refractory IBD, patients who are at high risk of developing complications or patients with a concomitant uncontrolled IMID**
When	The risk of doing nothing (eg, uncontrolled disease) is higher than the risk of adding combination molecule
Where	Centres with clinical expertise and multidisciplinary teams
Why	The existence of a therapeutic ceiling through use of single agents and multiple pathways driving the immunemediated inflammatory process
How	Preference is for agents with the most favourable safety profile (eg, vedolizumab and ustekinumab), especially in frail or elderly patients
	Preference for anti-TNF in CD, especially in ileal CD
	Preference for vedolizumab in UC patients
	Preference for anti-TNF or ustekinumab (or anti-IL-23 blocker when approved) or a JAK inhibitor in patients with concomitant EIM or IMID
	Preference for anti-TNF in CD patients with bowel damage (eg, strictures, fistulas)

ACT, advanced combination treatment; CD, Crohn's disease; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; JAK, Janus kinase; UC, ulcerative colitis.

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