ENDORO

Convegno di
Gastroenterologia ed
Endoscopia Digestiva

Rovigo, 15 maggio 2025

La terapia avanzata delle IBD tra nuove evidenze e sostenibilità

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Sistema Socio Sanitario
Regione Lombardia

DISCLOSURES

	Maurizio Vecchi
Receipt of honoraria or consultation fees	Abbvie, MSD, Takeda, Janssen, Roche, Bristol-Meyers Squibb, Pfizer, Mundipharma, Galapagos, Biogen, Ferring, Eli-Lilly, Sofar, Giuliani.
Participation in a company sponsored speaker's bureau	Abbvie, Ferring, Takeda, Janssen, Pfizer, Biogen, Amgen, Galapagos
Stock shareholder	None
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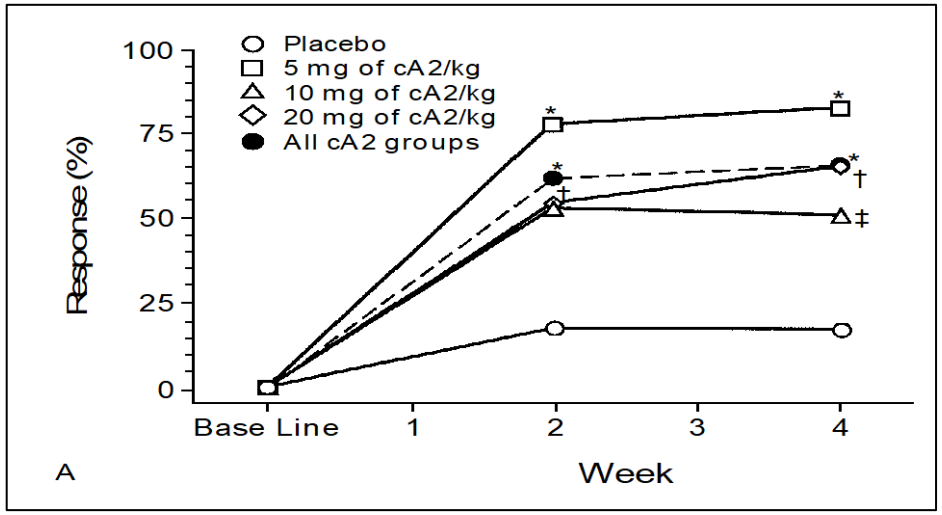
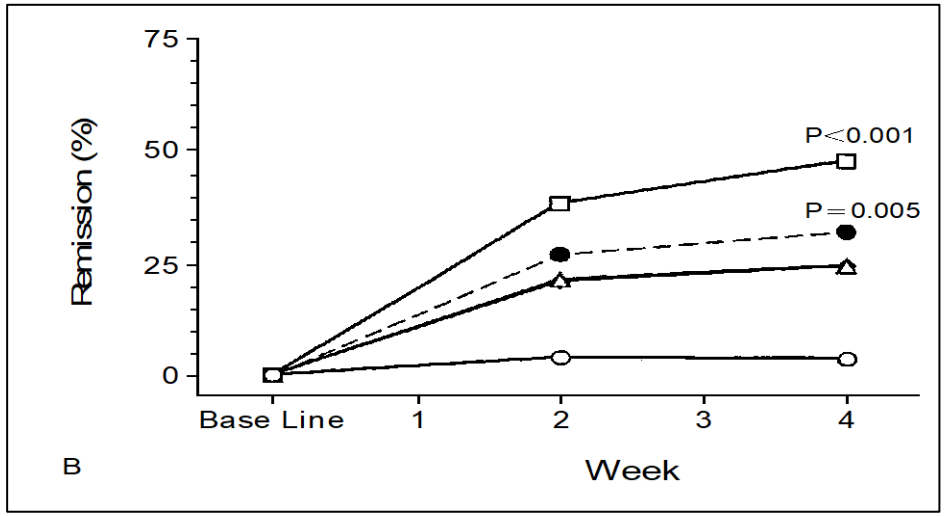
1997: the beginning of a new era in the treatment of IBD

A SHORT-TERM STUDY OF CHIMERIC MONOCLONAL ANTIBODY cA2 TO TUMOR NECROSIS FACTOR α FOR CROHN'S DISEASE

STEPHAN R. TARGAN, M.D., STEPHEN B. HANAUER, M.D., SANDER J.H. VAN DEVENTER, M.D., PH.D., LLOYD MAYER, M.D., DANIEL H. PRESENT, M.D., TANJA BRAAKMAN, M.D., KIMBERLY L. DEWOODY, M.S., THOMAS F. SCHAIBLE, PH.D., AND PAUL J. RUTGEERTS, M.D., PH.D., FOR THE CROHN'S DISEASE cA2 STUDY GROUP



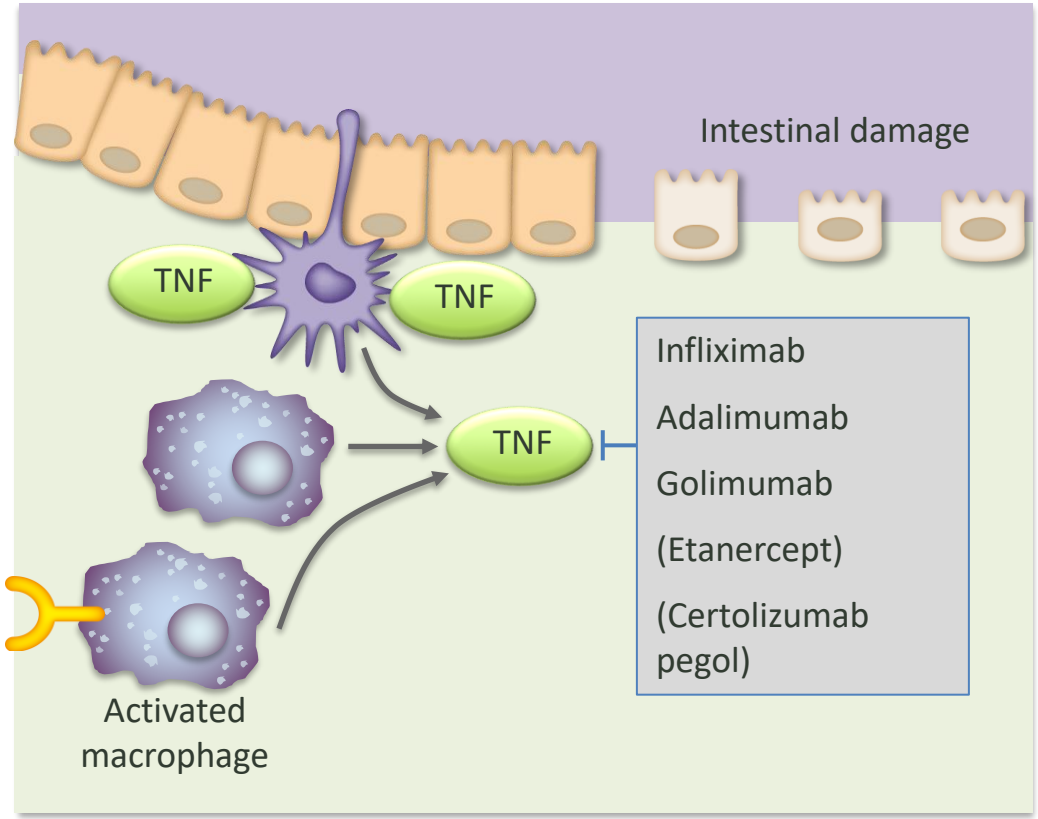
EMA 1999



NEJM 1997

Mechanism of action of anti-TNFs

TNFα is released after intestinal damage. It is a key cytokine involved in production of further inflammatory mediators and adhesion molecules



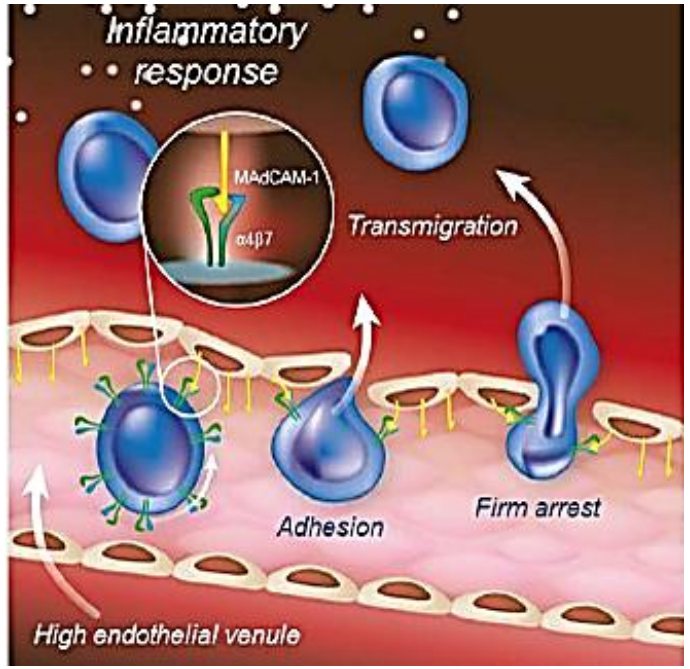
- TNF-inhibitors reduce inflammation by:
  - Binding membrane-bound and soluble (free) TNFα
  - Preventing TNFα binding to its receptors
  - Apoptosis of inflammatory cells
- … Resulting in top clinical efficacy and top rapidity of action in the treatment of both active UC and CD (with rare exceptions!!!!)

Image: Danese S, *et al. Nat Rev Gastroenterol Hepatol*. 2015;12:537–45
With permission

1. *Adapted from Danese S et al. Nat Rev Gastroenterol Hepatol. 2015;12:537–45*
2. *Tracey D, et al. Pharmacol Ther. 2008;117:244–79*

Mechanism of action of anti-integrins

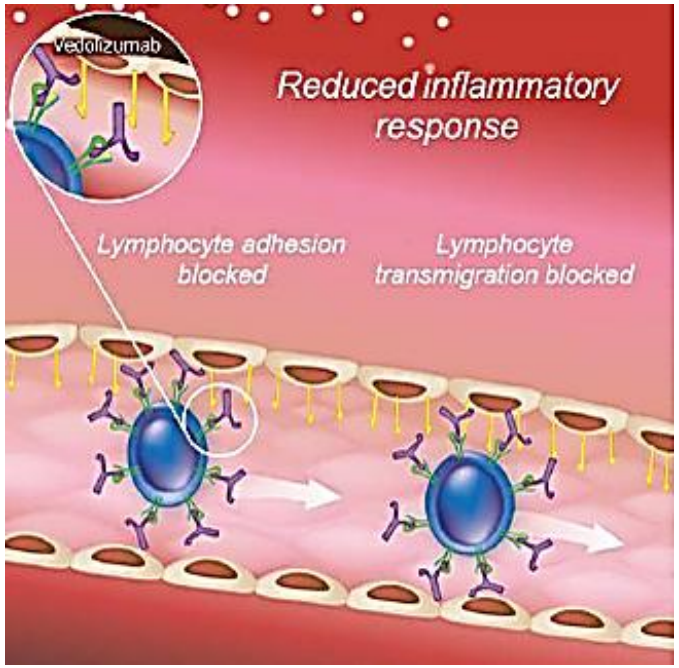
IBD



- Lymphocytes expressing a4b7 integrin:
  - Home to inflamed gut tissue
  - Adhere to MAdCAM-1 on endothelial cells
  - Migrate into the tissue
- Continuous lymphocyte recruitment increases chronic inflammation

MAdCAM-1=mucosal addressin cell adhesion molecule-1

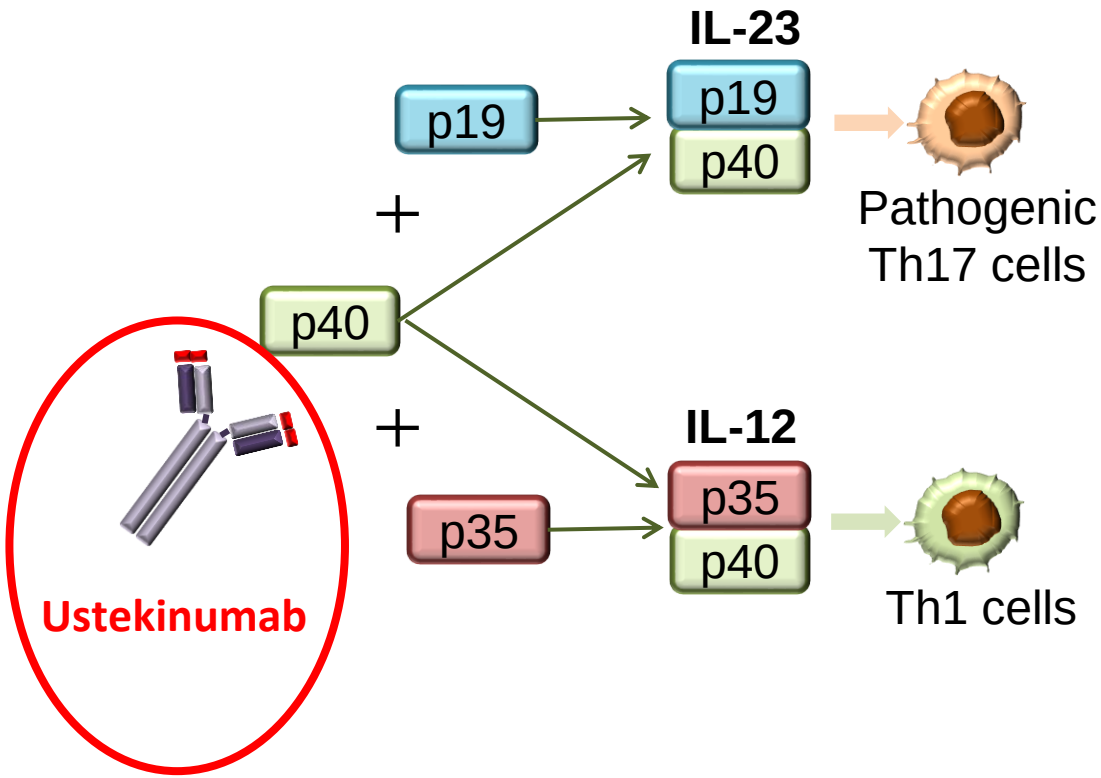
IBD with vedolizumab



- Vedolizumab:
  - Specifically binds a4b7 integrin
  - Blocks adhesion to MAdCAM-1
  - Inhibits lymphocytes migration to tissue
- Inhibition of lymphocytes migration reduces inflammation

Peyrin-Biroulet L, et al. Lancet. 2008;372:67–81
Briskin M, et al. Am J Pathol. 1997;151:97–110

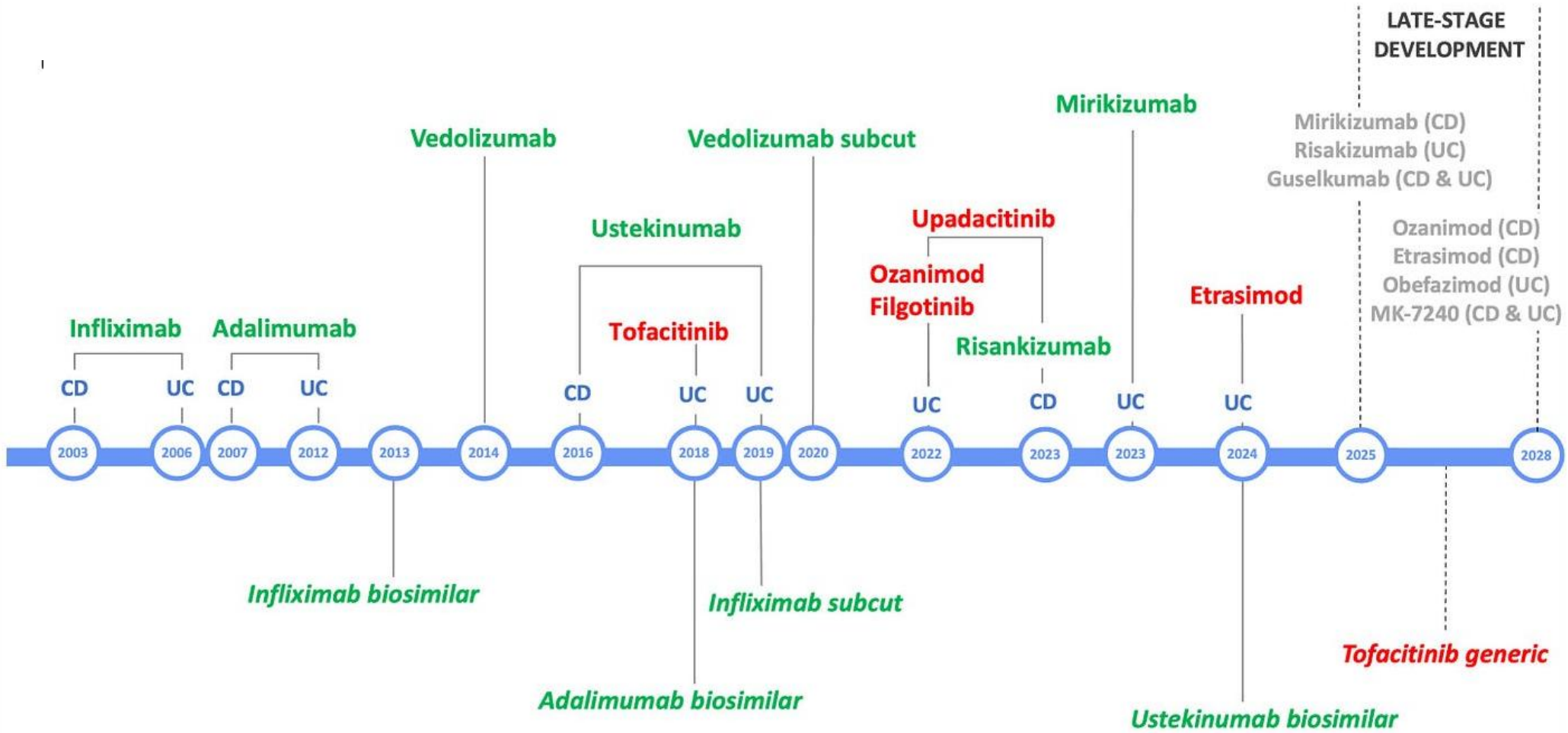
Drugs targeting T cell differentiation in IBD



Major features of «traditional biologics» in IBD therapy

- Effectiveness (Infliximab > adalimumab ≈ ustekinumab ≈vedolizumab) (primary non response 40 % in RTC, 20 % in RWE)
- Rapidity of action (Infliximab >> others, the only drug for severe UC)
- I.V. and s.c.
- Very low cost of anti-TNFs biosimilars (adalimumab costs around 1000 Euros/yr)
- Overall good safety (choose the right patient!!)
- Loss of response (Infliximab > others, probably immune-mediated)
- Persistence (Vedolizumab, Ustekinumab)

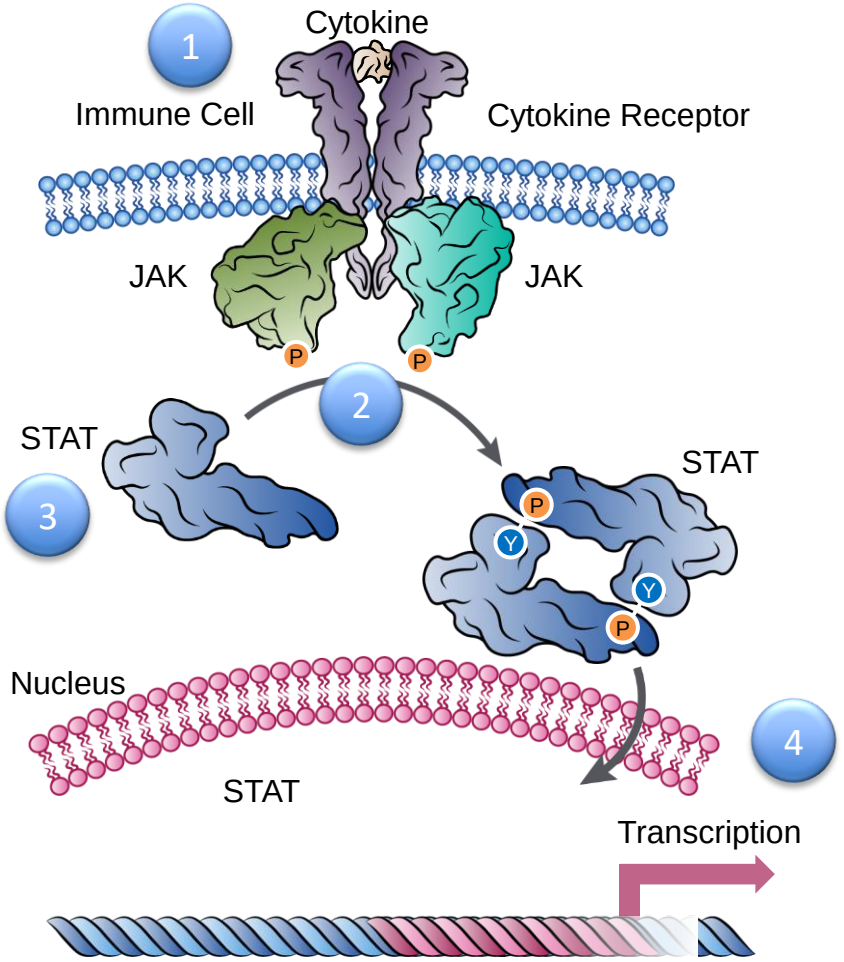
Drugs for IBD: 2024 and beyond



Monoclonal antibodies. **Small molecules**

JAKs pair together to facilitate signalling of specific cytokines

1. JAK proteins form homo- or heterogeneous pairs and associate with specific cytokine receptors
2. Receptor engagement induces activation of the JAK complex via phosphorylation of specific tyrosine residues on each JAK
3. JAK activation leads to the phosphorylation and dimerisation of Signal Transducer and Activator of Transcription (STAT) proteins
4. STAT proteins bind to DNA and regulate gene transcription of proteins required for key physiological processes, e.g. immune modulators



EMA 2021

- O'Shea JJ, *et al. Annu Rev Med* 2015; 66:311–328.

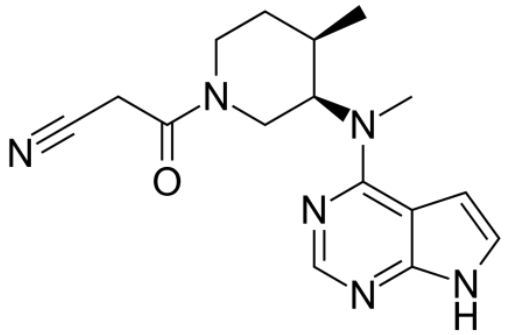
Many IBD-relevant cytokines converge on JAK pathways for their action

Cytokines	JAKs
IL-2	1 3
IL-7	1 3
IL-15	1 3
IL-21	1 3
IL-6	1 2 T2
IL-13	1 2 T2
IFN-γ	1 2
IL-22	1 T2

Cytokines	JAKs
IL-12	2 T2
IL-23	2 T2
IL-5	2 2
IL-1β	—
IL-8	—
IL-17	—
IL-18	—
TNF-α	—

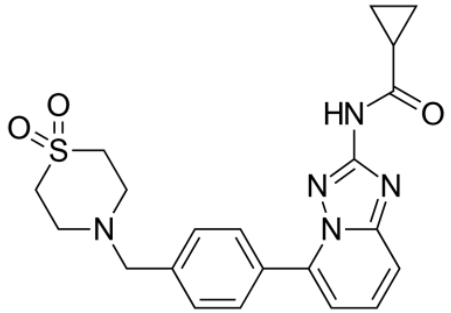
Available JAK Inhibitors for IBD

Tofacitinib



FDA/EMA approval for UC: 2018

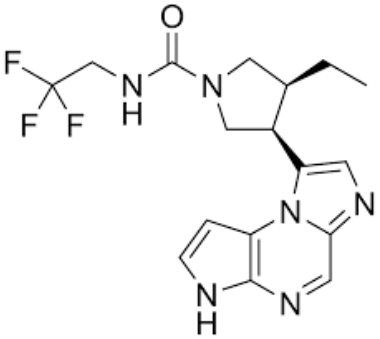
Filgotinib



FDA approval for UC: NA

EMA approval for UC: 2021

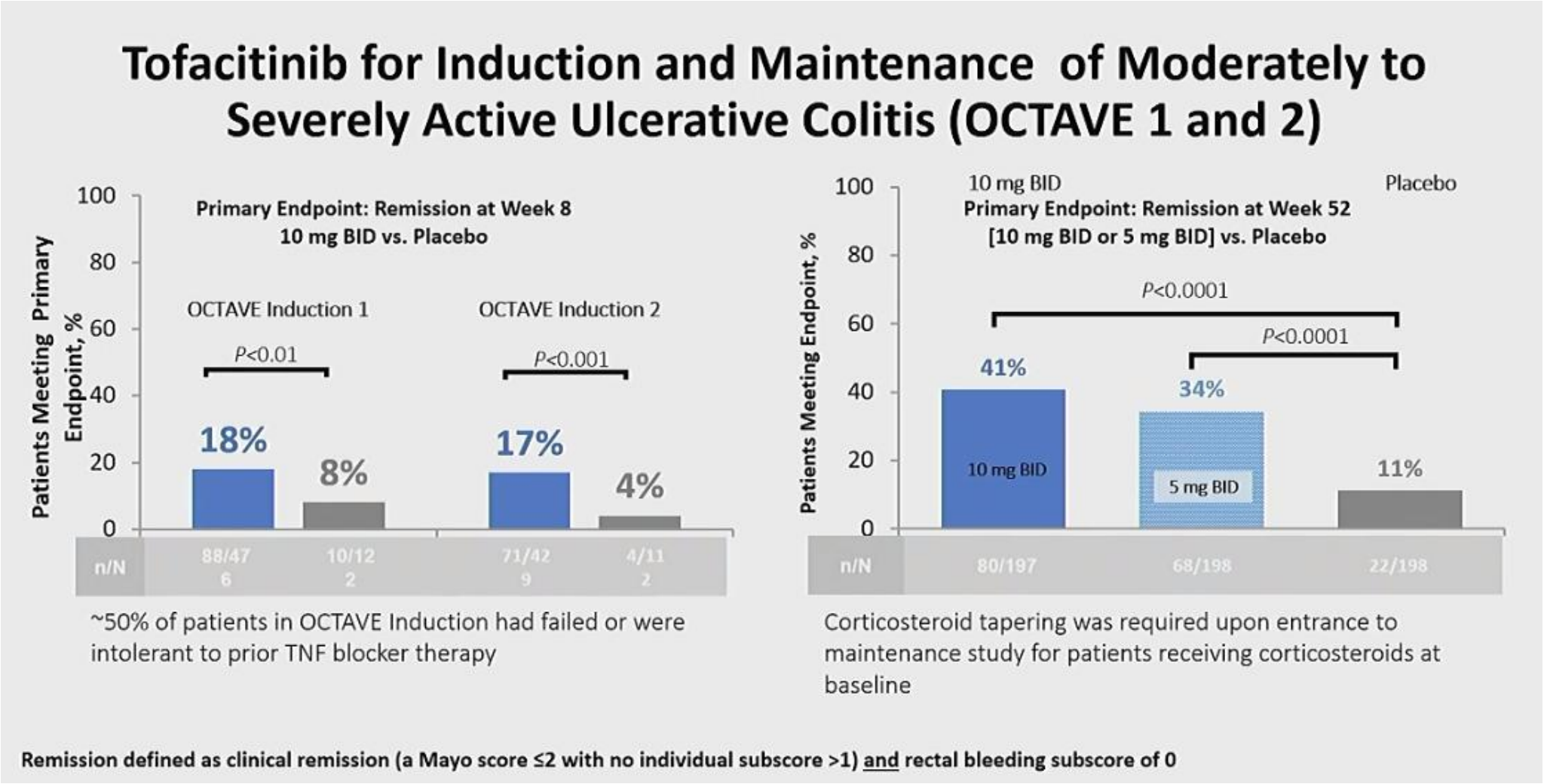
Upadacitinib



FDA/EMA approval for UC: 2022

FDA/EMA approval for CD: 2023

Tofacitinib: OCTAVE program

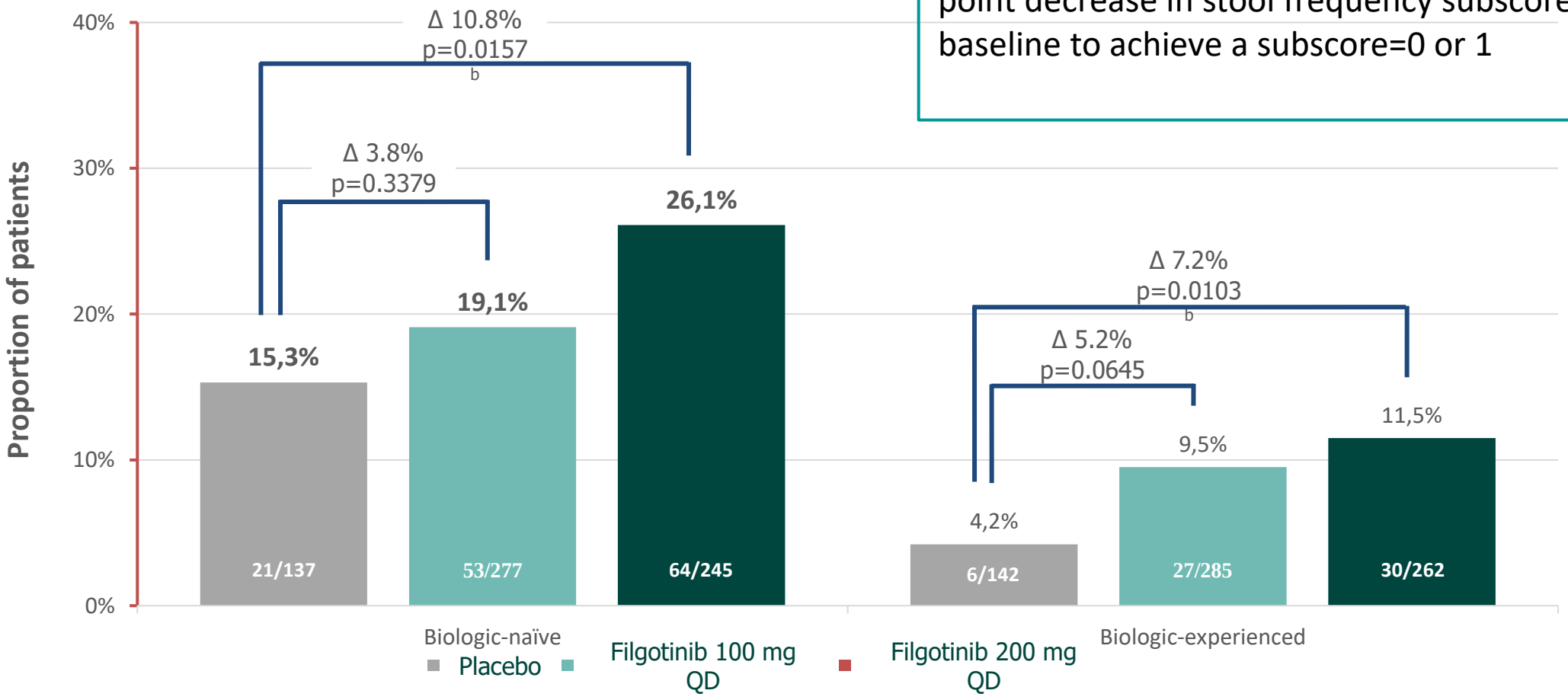


Sandborn WJ et al. N Engl J Med 2017

Filgotinib: SELECTION trials

Clinical Remission at Week 10

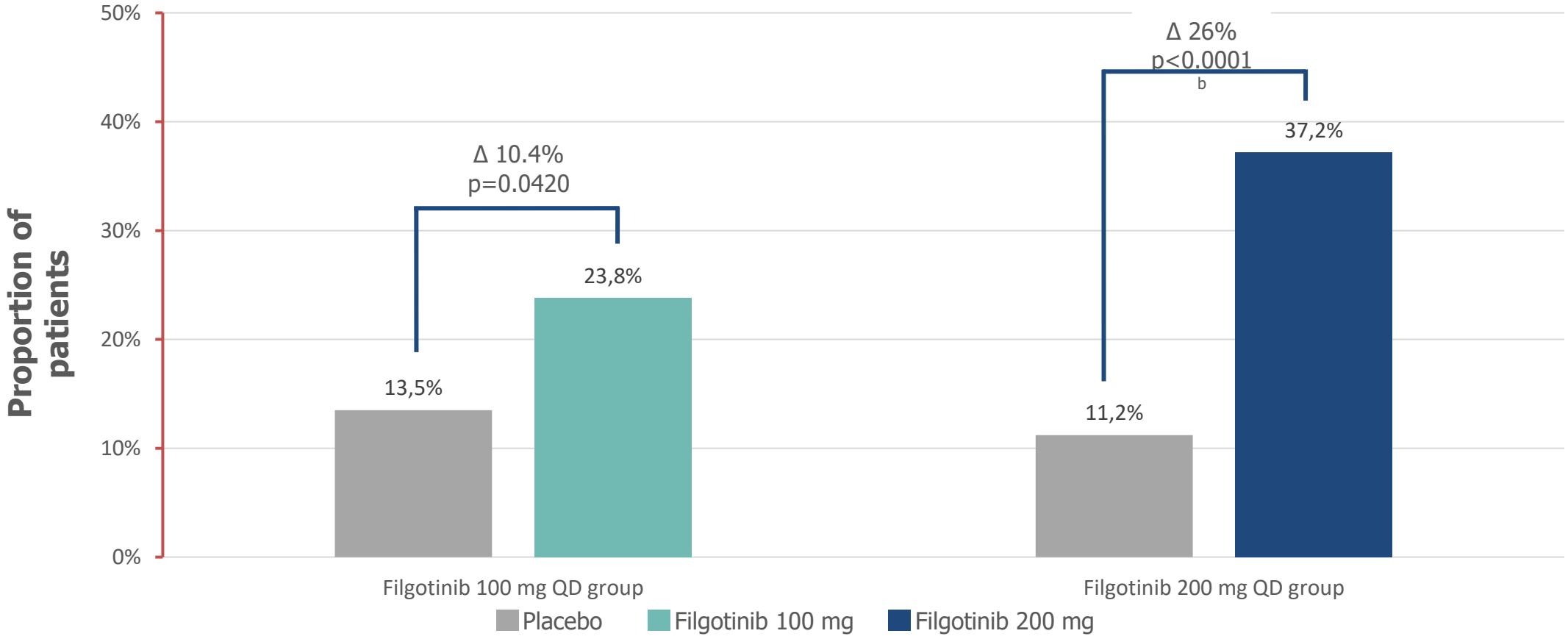
CR: MES=0 or 1, rectal bleeding subscore=0, and ≥1-point decrease in stool frequency subscore from baseline to achieve a subscore=0 or 1



Feagan et al. Lancet 2021

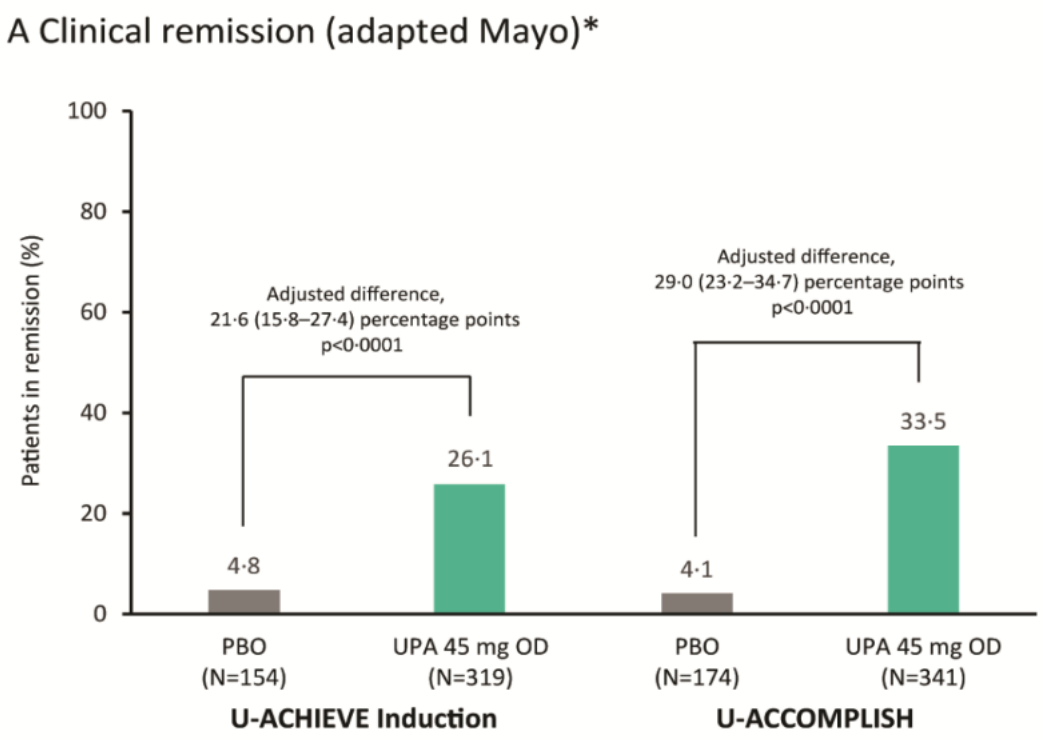
Filgotinib: SELECTION trials

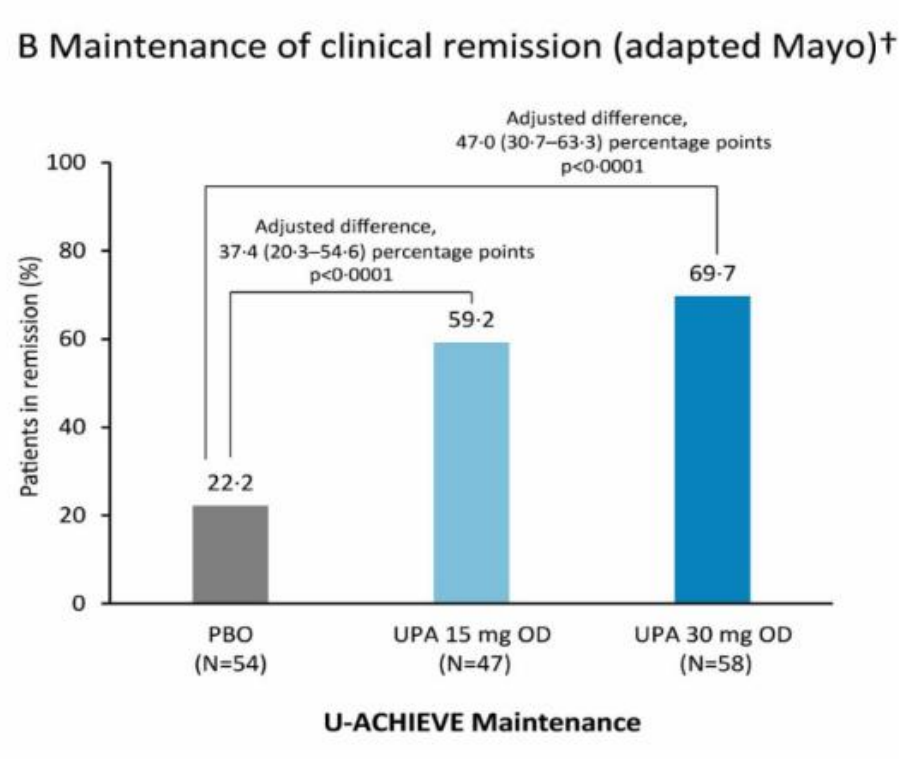
Clinical Remission at Week 58



Feagan et al. Lancet . 2021

Upadacitinib: ACCOMPLISH/ACHIEVE trials

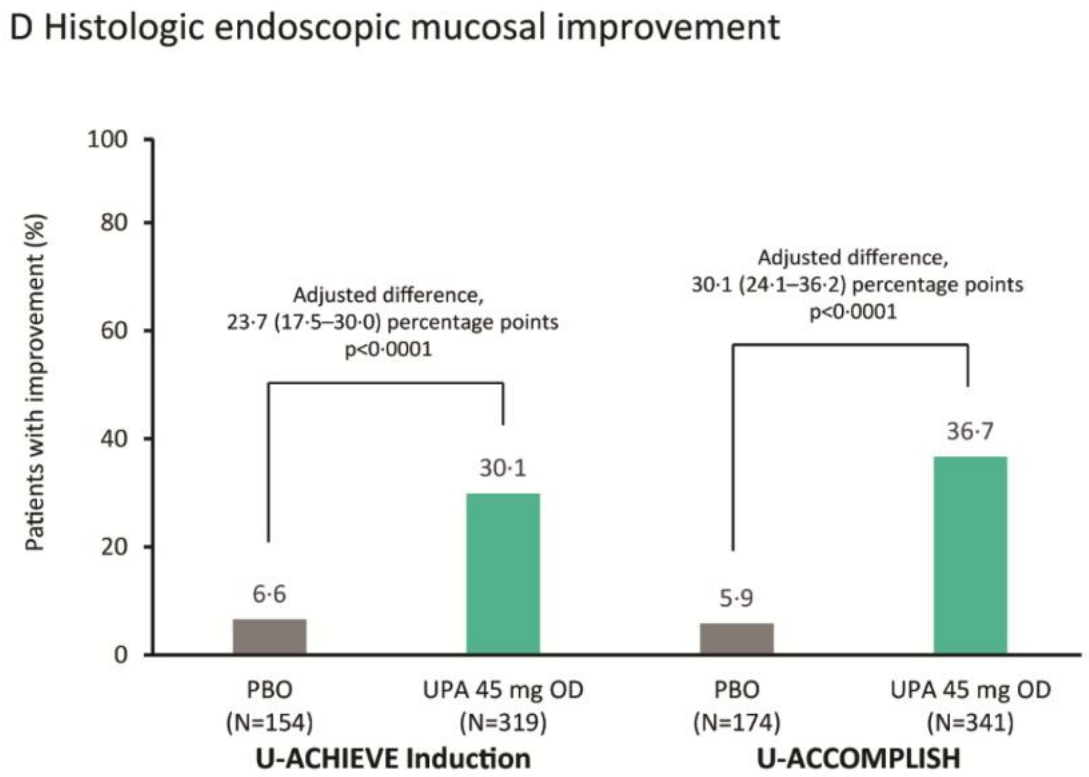


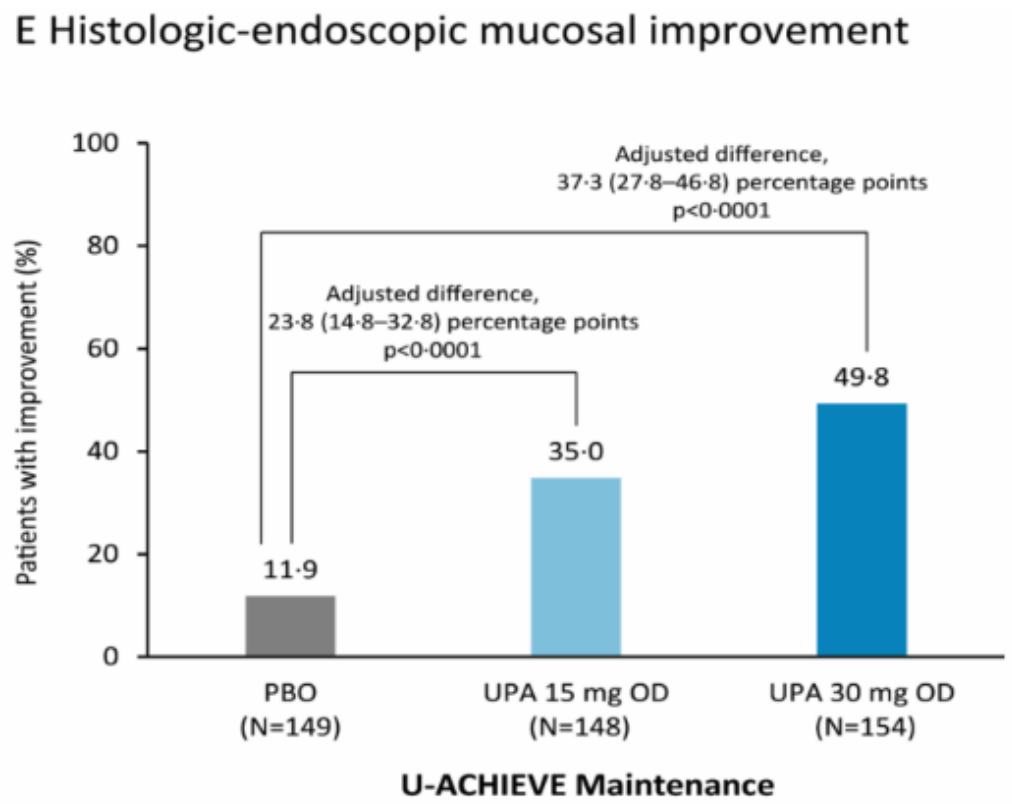


CLINICAL REMISSION: SF ≤1 and not greater than baseline, RB of 0

Danese et al. Lancet . 2022

Upadacitinib: ACCOMPLISH/ACHIEVE trials





HEMI defined as endoscopic subscore of 0 or 1 and Geboes score ≤3·1

Danese et al. Lancet . 2022

Real-world Effectiveness Studies

RCTs generate a relatively small amount of initial high-quality data, collected over a short time-frame. They remain the 'gold standard' in assessing safety and efficacy[1,2]

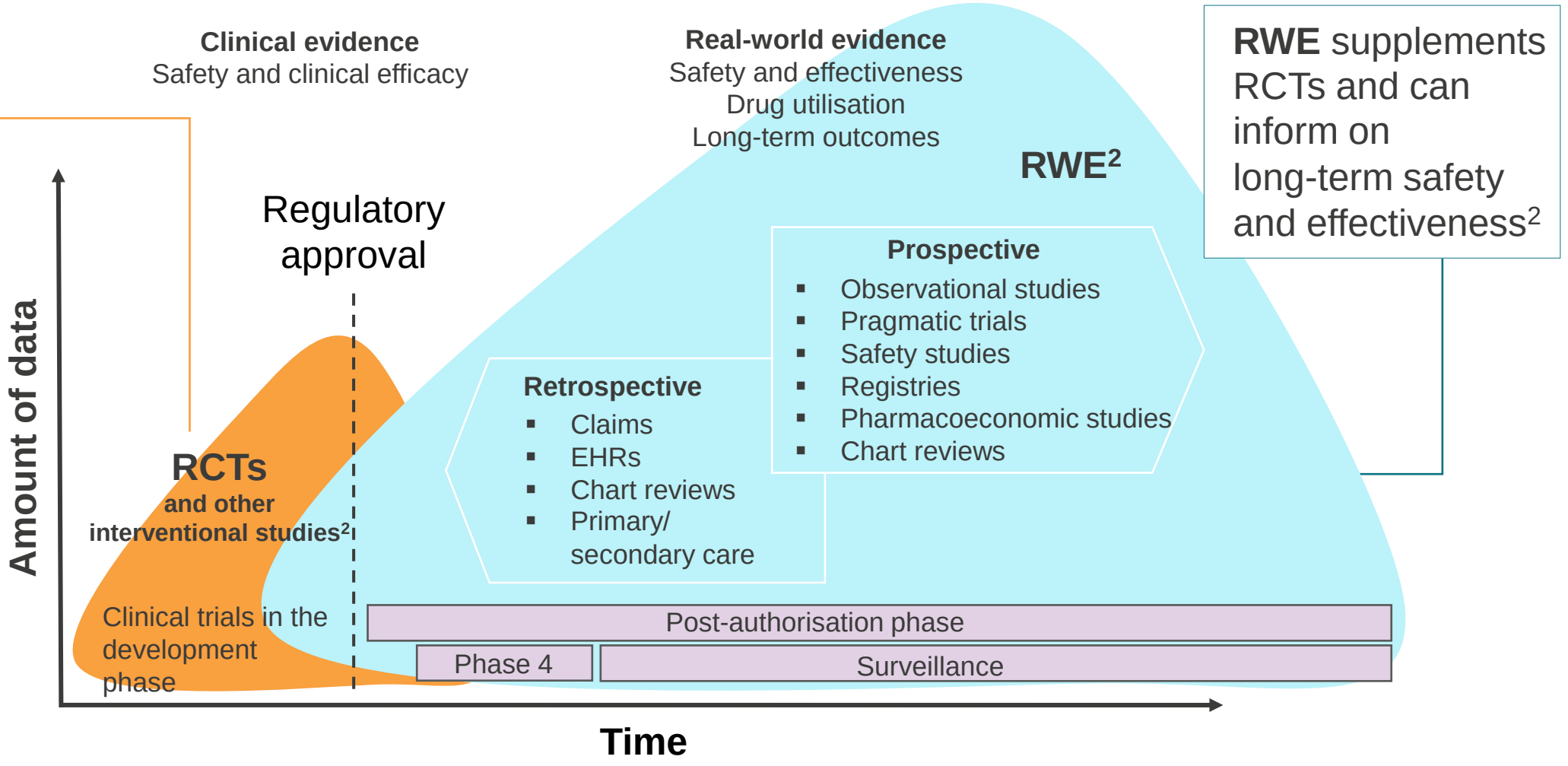
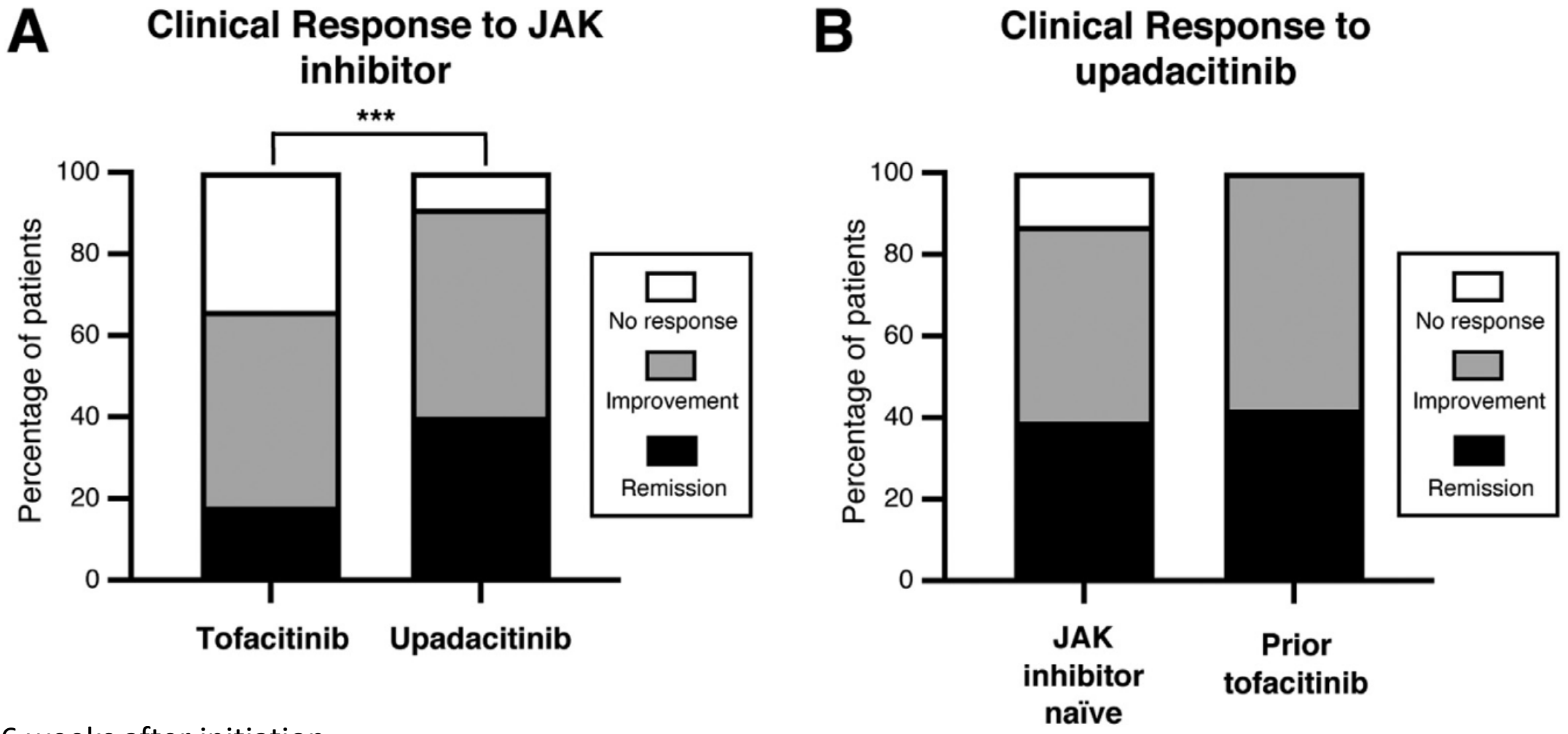


Figure adapted from Katkade VB, et al. J Multidiscip Healthc. 2018;11:295–304.
EHR, electronic health record; RCT, randomised controlled trial, RWE, real-world evidence.
1. Nallamothu BK, et al. Circulation. 2008;118(12):1294–1303; 2. Katkade VB, et al. J Multidiscip Healthc. 2018;11:295–304.

Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in UC: Real-World Data

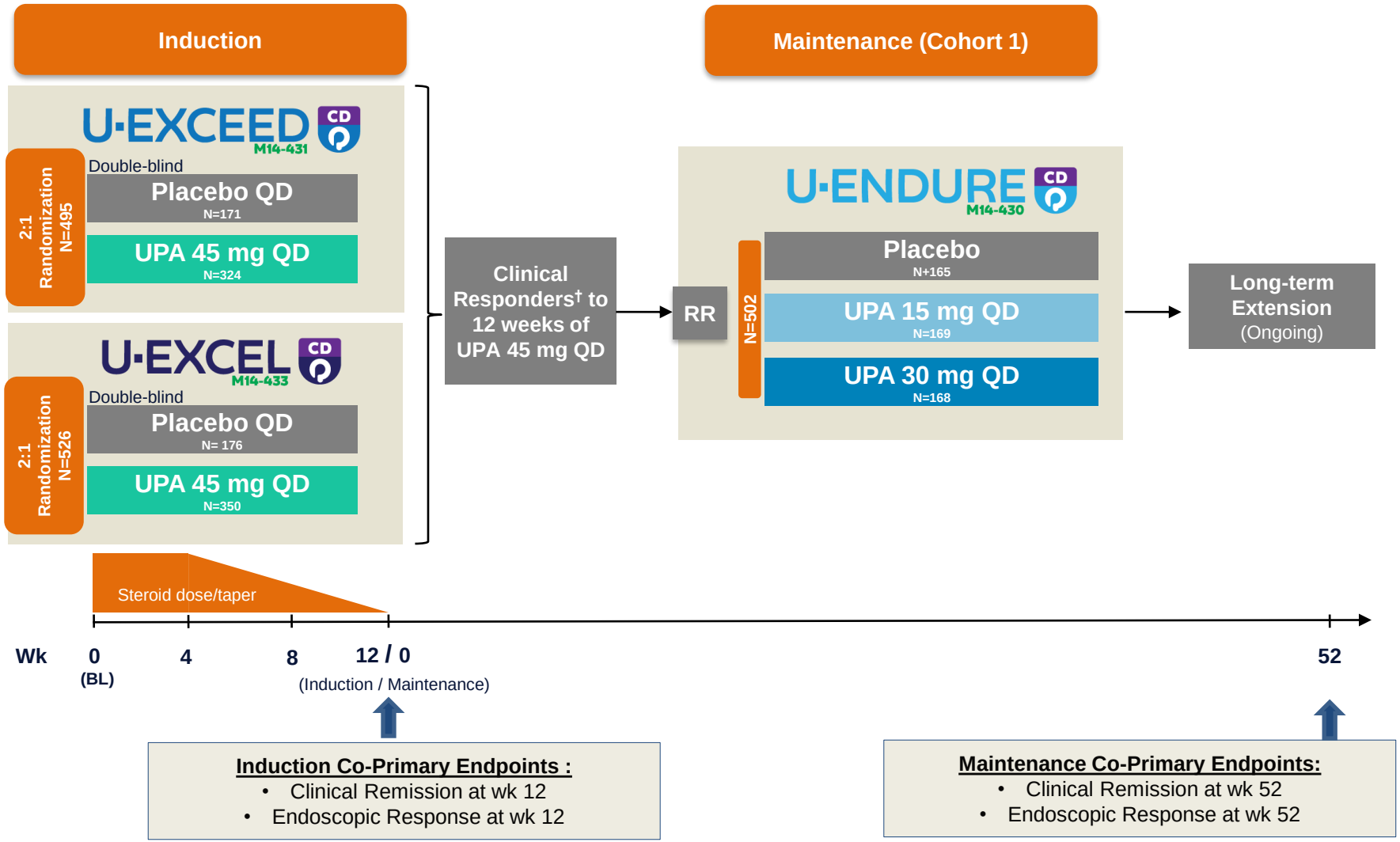


8 to 16 weeks after initiation

Boneschansker L et al. Clin Gastroenterol Hepatol 2023 Aug;21(9):2427-2429.e1

Upadacitinib Phase 3 CD Clinical Program Study Design

mandatory steroid tapering already during induction



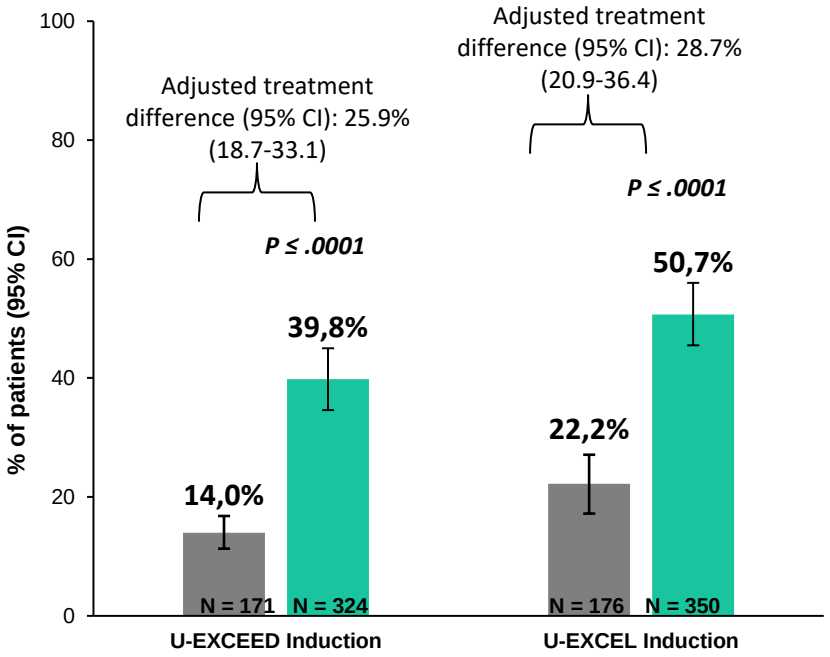
*Induction non-responders at week 12 (UPA 45 mg or PBO) were eligible to move to the 12-week extended treatment period, patients who received placebo (induction)/45mg (extended treatment) and achieved clinical response at Week 24 were randomized to U-ENDURE Maintenance.[3] †**Clinical Response per SF/APS:** ≥ 30% decrease in average daily SF and/or in average daily APS and both not greater than baseline. APS, abdominal pain score; BL, baseline; CD, Crohn's disease; QD, once daily; R, randomization; RR, rerandomization; SF, stool frequency; UPA, upadacitinib; Wk, week.

Loftus EV et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023;388(21):1966-1980.

Clinical remission at week 12[1]

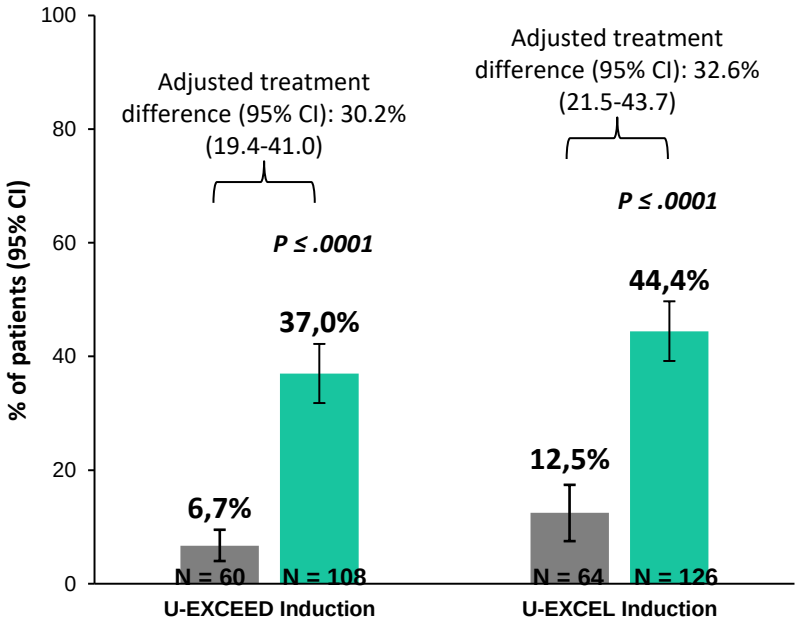
Clinical Remission per SF/APS (NRI-C)[1]

Co-Primary Endpoint



Steroid-Free Clinical Remission (SF/APS) at Week 12 in Patients Taking CS at BL (NRI-C)

Ranked Secondary Endpoint



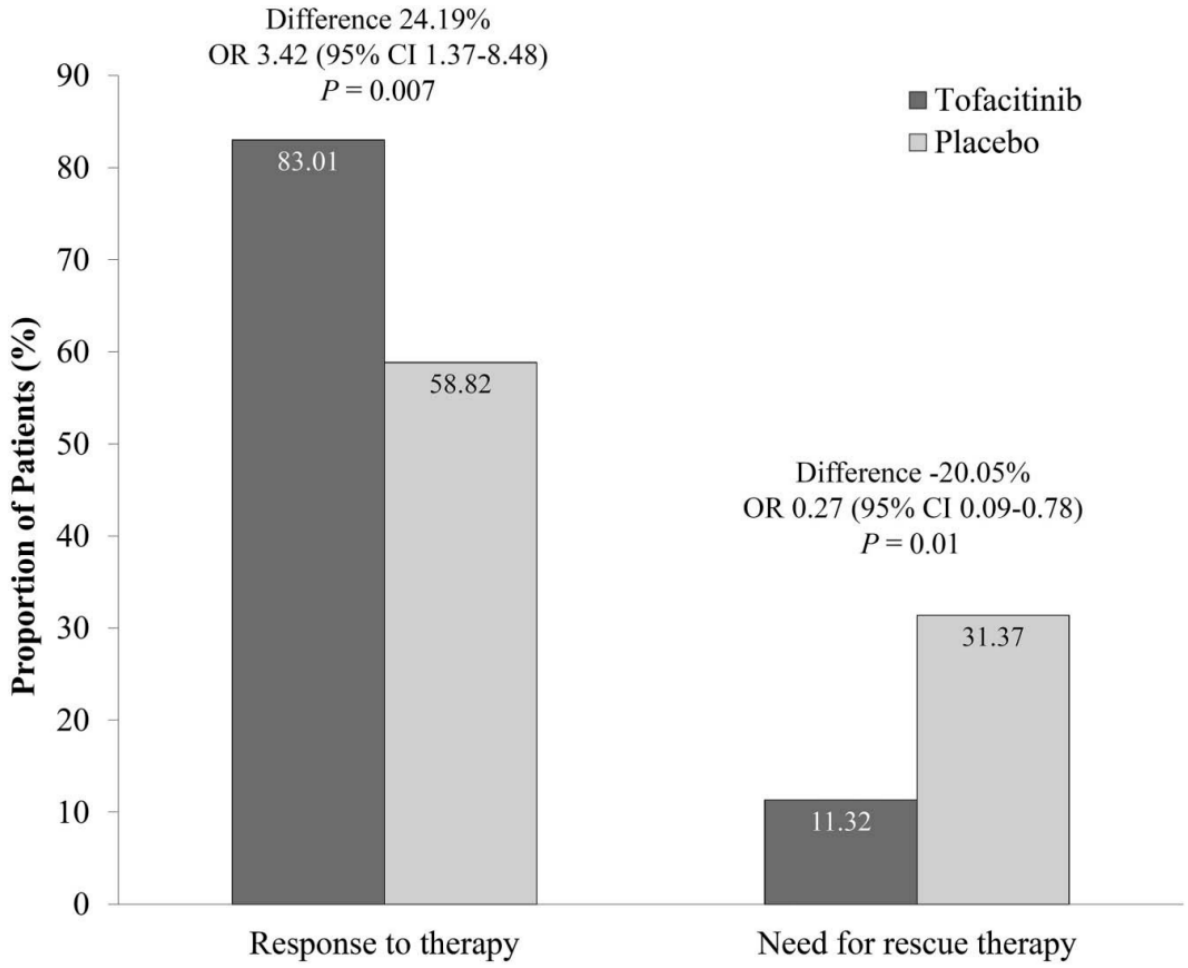
Placebo UPA 45 mg

- **Clinical remission (SF/APS):** average daily SF ≤ 2.8 and not worse than BL AND average daily APS ≤ 1 and not worse than BL (co-primary Endpoint)
  Steroid-free clinical remission (SF/APS): discontinuation of corticosteroid use and achievement of clinical remission per SF/APS among patients on corticosteroids (CS) at BL (ranked sec. Endpoint)
- APS, abdominal pain score; BL, baseline; CDAI, Crohn's Disease Activity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; NRI-C, nonresponder imputation–COVID-19; SF, Stool frequeny; UPA, upadacitinib; wk, week
- 1. Loftus et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. NEJM. 2023;388:1966 1980. Incl. Suppl.

ASUC?

Table 1. Baseline characteristics of the enrolled population

	Tofacitinib (n = 53)	Placebo (n = 51)
Age, yr, median (IQR)	37 (26–47)	38 (30–47)
Male, n (%)	29 (54.71)	30 (58.82)
Disease duration, yr, median (IQR)	3 (2–5)	2 (1–4)
Body mass index, kg/m^2, median (IQR)	21.64 (18.43–23.91)	21.27 (18.57–23.32)
Previous treatment exposures, n (%)		
5-ASA	52 (98.11)	51 (100)
Azathioprine	8 (15.09)	6 (11.76)
Corticosteroids	39 (73.58)	25 (49.01)
Anti-TNF agents	3 (5.66)	2 (3.92)
Oral corticosteroids on admission,[a] n (%)	26 (49.05)	23 (45.09)

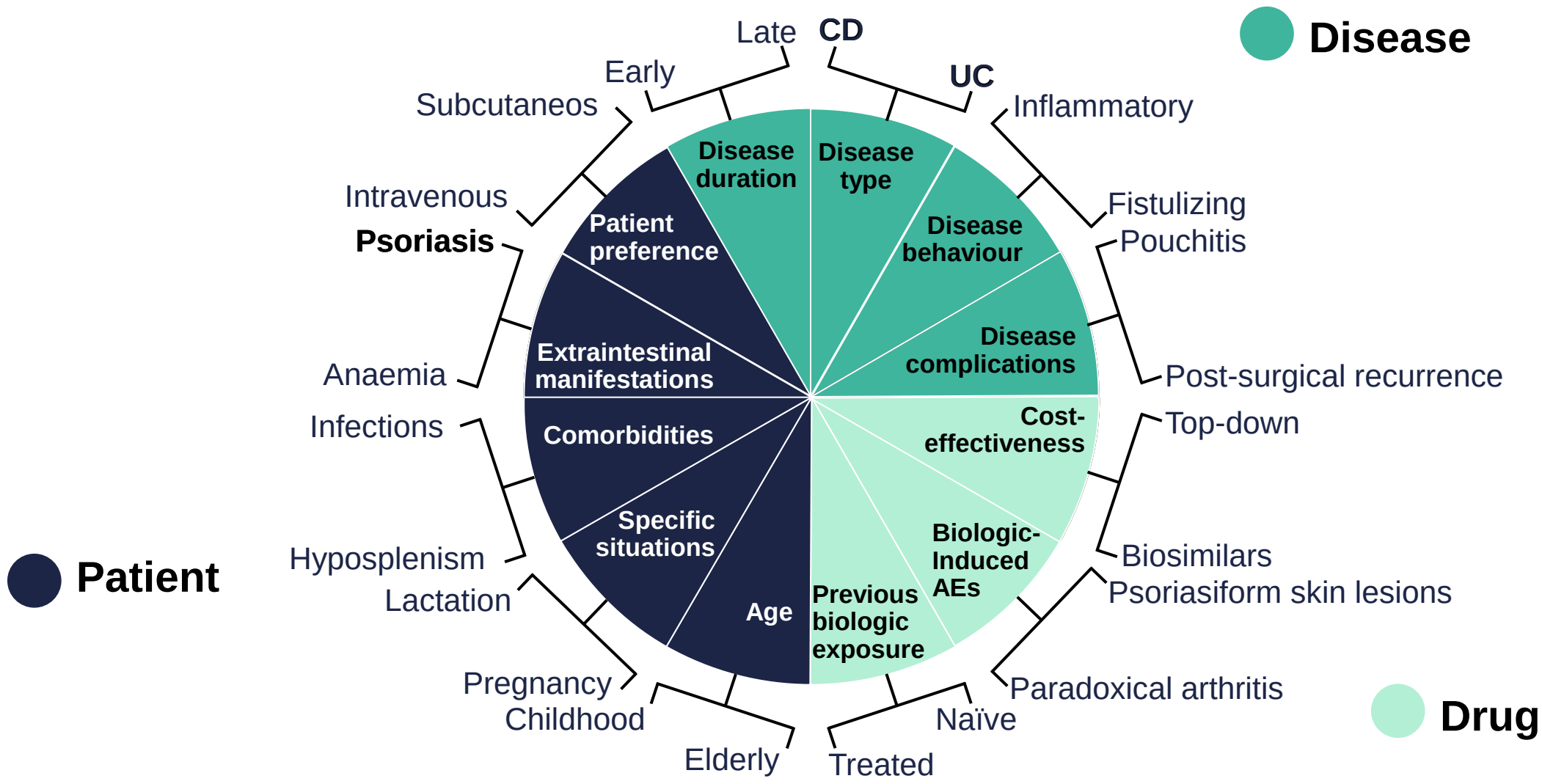


Tofacitinib 10 mg x 3/day

4.8% Mortality

Singh et al. AJG 2024

Factors affecting therapeutic decision-making in IBD



Factors affecting therapeutic decision-making in IBD

- Disease: high heterogeneity
- Patient: comorbidities, frailty, adherence, preference (making active part of decision!)
- Drug: efficacy, **safety**, cost-effectiveness

JAK preferential inhibition and changes in laboratory parameters

	Tofacitinib	Upadacitinib	Filgotinib
Selectivity	**JAK1 > JAK3 > JAK2**	**JAK1**	**JAK1**
Haemoglobin level	↑	↓	↑
Lymphocyte number	↓	↓	**No change**
Neutrophil number	↓	↓	↓
Platelet count	↓	**No data**	↓
NK cell number	↓	↓	**No change**
HDL level	↑	↑	↑
LDL level	↑	↑	**No change**
Liver transaminase level	↑	↑	**No change**
Creatine level	↑	↑	↑
Creatine phosphokinase level	↑	↑	**No change**

No JAK2 inhibition

No JAK3 inhibition

Reduced VTE?

Danese S, *et al. Gut* 2019. 0: 1–7. Han P, *et al.* EULAR 2019 (Abstract 017; poster)

JAK inhibitor safety

EMA recommendations to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

EMA's safety committee (PRAC) conclusions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
News 28/10/2022

The review confirmed Tofacitinib increases the risk of major CV problems, cancer, VTE, serious infections and death due to any cause when compared with TNF-alpha inhibitors

These safety findings apply to **all approved uses of JAK inhibitors** in chronic inflammatory disorders (RA, PsA, JIA, axSpA, UC, AD and alopecia areata)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
News 11/11/2022

EMA recommendations to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic

In patients with:

- **> 65 years or above**
- **increased risk of major CV problems** (such as heart attack, stroke)
- **history of current or past smoking**
- **increased risk of cancer**

JAK-is should be used **only if no suitable treatment alternatives are available**

In patients with:

- **risk factors for blood clots in the lungs and in deep veins (VTE)**

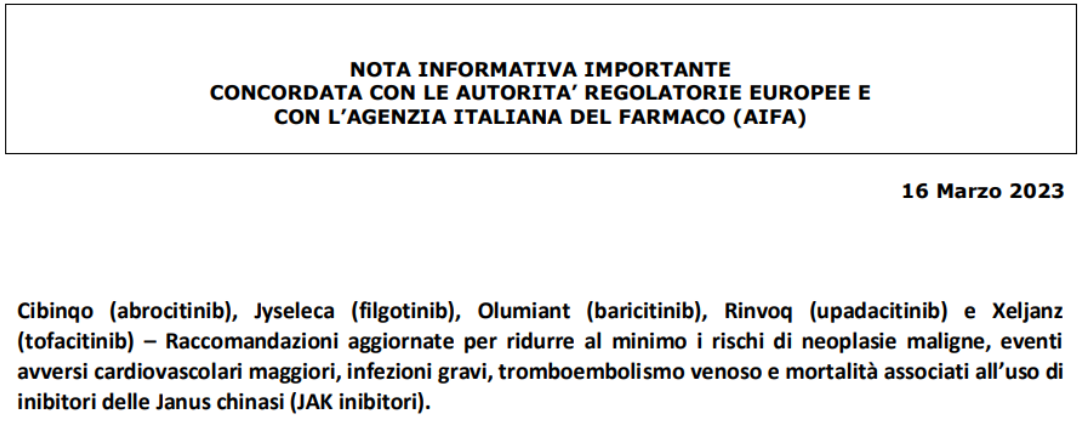
The doses should be reduced in some patient groups who may be at risk of VTE, cancer or major CV problems

Use JAK inhibitors with caution

JAK Inhibitors Safety: EMA (PRAC) Restrictions

Doctors need caution to prescribe JAKs in patients without therapeutic alternatives in the following seetings:

- with heart failure
- with inherited coagulation disorders
- who have had venous thromboembolism, either deep venous thrombosis or pulmonary embolism
- who use combined hormonal contraceptives or hormone replacement therapy
- with malignancy
- who are undergoing major surgery
- Age >65 years
- Obesity (BMI>30)
- smoking
- immobilisation.



NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E
CON L'AGENZIA ITALIANA DEL FARMACO (AIFA)

16 Marzo 2023

Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) e Xeljanz (tofacitinib) – Raccomandazioni aggiornate per ridurre al minimo i rischi di neoplasie maligne, eventi avversi cardiovascolari maggiori, infezioni gravi, tromboembolismo venoso e mortalità associati all'uso di inibitori delle Janus chinasi (JAK inibitori).

Journal of Crohn's and Colitis, 2022, **XX**, 1–27
https://doi.org/10.1093/ecco-jcc/jjac115
Advance access publication 25 August 2022
ECCO Guideline/Consensus Paper

AQ1-AQ4

European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation

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Drug	During pregnancy	During lactation
Mesalazine	Low risk	Low risk
Sulphasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk
Metronidazole	Low risk*	Avoid
Ciprofloxacin	Avoid in T1*	Low risk[a]
Thiopurines	Low risk	Low risk
Thiopurines + allopurinol	Limited data	Limited data
Ciclosporin Tacrolimus	Low risk, limited data	Limited data
Anti-TNF	Low risk	Low risk
Vedolizumab	Low risk, limited data	Low risk, limited data
Ustekinumab	Low risk, limited data	Low risk, limited data
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated
Tofacitinib	Contraindicated	No data; avoid
Filgotinib	Contraindicated	No data; avoid
Ozanimod	Contraindicated	No data; avoid

Tofacitinib Safety in Ulcerative Colitis

Table 4. Safety Outcomes at 8 Weeks in the OCTAVE Induction 1 and 2 Trials and at 52 Weeks in the OCTAVE Sustain Trial.*

End Point	OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Placebo (N=198)	Tofacitinib, 5 mg (N=198)	Tofacitinib, 10 mg (N=196)
Adverse events — no. (%)	73 (59.8)	269 (56.5)	59 (52.7)	232 (54.1)	149 (75.3)	143 (72.2)	156 (79.6)
Serious adverse events — no. (%)	5 (4.1)	16 (3.4)	9 (8.0)	18 (4.2)	13 (6.6)	10 (5.1)	11 (5.6)
Most frequent adverse events — no. (%)†							
Worsening ulcerative colitis	5 (4.1)	11 (2.3)	6 (5.4)	13 (3.0)	71 (35.9)	36 (18.2)	29 (14.8)
Nasopharyngitis	9 (7.4)	34 (7.1)	4 (3.6)	21 (4.9)	11 (5.6)	19 (9.6)	27 (13.8)
Arthralgia	6 (4.9)	14 (2.9)	6 (5.4)	11 (2.6)	19 (9.6)	17 (8.6)	17 (8.7)
Headache	8 (6.6)	37 (7.8)	9 (8.0)	33 (7.7)	12 (6.1)	17 (8.6)	6 (3.1)
Infections — no. (%)							
Any infection	19 (15.6)	111 (23.3)	17 (15.2)	78 (18.2)	48 (24.2)	71 (35.9)	78 (39.8)
Serious infection‡	0	6 (1.3)	0	1 (0.2)	2 (1.0)	2 (1.0)	1 (0.5)
Herpes zoster	1 (0.8)	3 (0.6)	0	2 (0.5)	1 (0.5)	3 (1.5)	10 (5.1)
Adverse events of special interest — no.							
Intestinal perforation§	0	1	1	0	0	0	0
Cancer other than nonmelanoma skin cancer¶	0	0	0	0	1‖	0	0
Nonmelanoma skin cancer¶	0	1	0	1	1	0	3
Cardiovascular events¶	0	2	0	2	0	1	1
Adverse events leading to discontinuation — no. (%)**	2 (1.6)	18 (3.8)	8 (7.1)	17 (4.0)	37 (18.7)	18 (9.1)	19 (9.7)
Abnormal laboratory test results — no./total no. (%)††							
Total cholesterol >1.3× ULN	11/122 (9.0)	80/471 (17.0)	6/111 (5.4)	73/424 (17.2)	16/198 (8.1)	54/198 (27.3)	44/195 (22.6)
Low-density lipoprotein >1.2× ULN	11/122 (9.0)	91/471 (19.3)	12/111 (10.8)	92/424 (21.7)	37/198 (18.7)	62/198 (31.3)	55/195 (28.2)
High-density lipoprotein <0.8× LLN	2/122 (1.6)	6/471 (1.3)	1/111 (0.9)	7/424 (1.7)	12/198 (6.1)	9/198 (4.5)	3/195 (1.5)
Triglycerides >1.3× ULN	1/122 (0.8)	15/471 (3.2)	2/111 (1.8)	12/424 (2.8)	7/198 (3.5)	9/198 (4.5)	15/195 (7.7)
Creatine kinase >2× ULN	2/122 (1.6)	45/474 (9.5)	10/112 (8.9)	40/425 (9.4)	14/198 (7.1)	37/198 (18.7)	54/195 (27.7)
Addition or increase in dose of lipid-lowering agent — no. (%)	0	4 (0.8)	1 (0.9)	2 (0.5)	3 (1.5)	2 (1.0)	8 (4.1)

Sandborn WJ et al. N Engl J Med 2017

SACRO CUORE DON CALABRIA I R C C S

Filgotinib Safety Profile

	Placebo* (n=93)	Placebo‡ (n=99)	Filgotinib 200 mg (n=202)
Total duration of study drug exposure, weeks	38·1 (15·2)	28·8 (17·7)	39·4 (14·3)
Treatment-emergent adverse events			
Adverse events	57 (61·3%)	59 (59·6%)	135 (66·8%)
Serious adverse events	4 (4·3%)	0	9 (4·5%)
Adverse events leading to study drug discontinuation	3 (3·2%)	2 (2·0%)	7 (3·5%)
Deaths	0	0	2 (1·0%)
Adverse events of interest			
Infections	21 (22·6%)	25 (25·3%)	71 (35·1%)
Serious infections	1 (1·1%)	0	2 (1·0%)
Herpes zoster	0	0	1 (0·5%)
Opportunistic infections	0	0	0
Malignancies§	0	0	1 (0·5%)
Non-melanoma skin cancer	0	0	0
Gastrointestinal perforation	0	0	0
Venous thrombosis excluding pulmonary embolism	2 (2·2%)	0	0
Pulmonary embolism	0	0	0
Arterial thrombosis¶	0	0	0
Cerebrovascular events¶	0	0	0

Feagan et al. Lancet . 2021

SACRO CUORE DON CALABRIA IRCCS

Upadacitinib Safety Profile in UC

- No active tuberculosis or lymphoma were reported in the study.

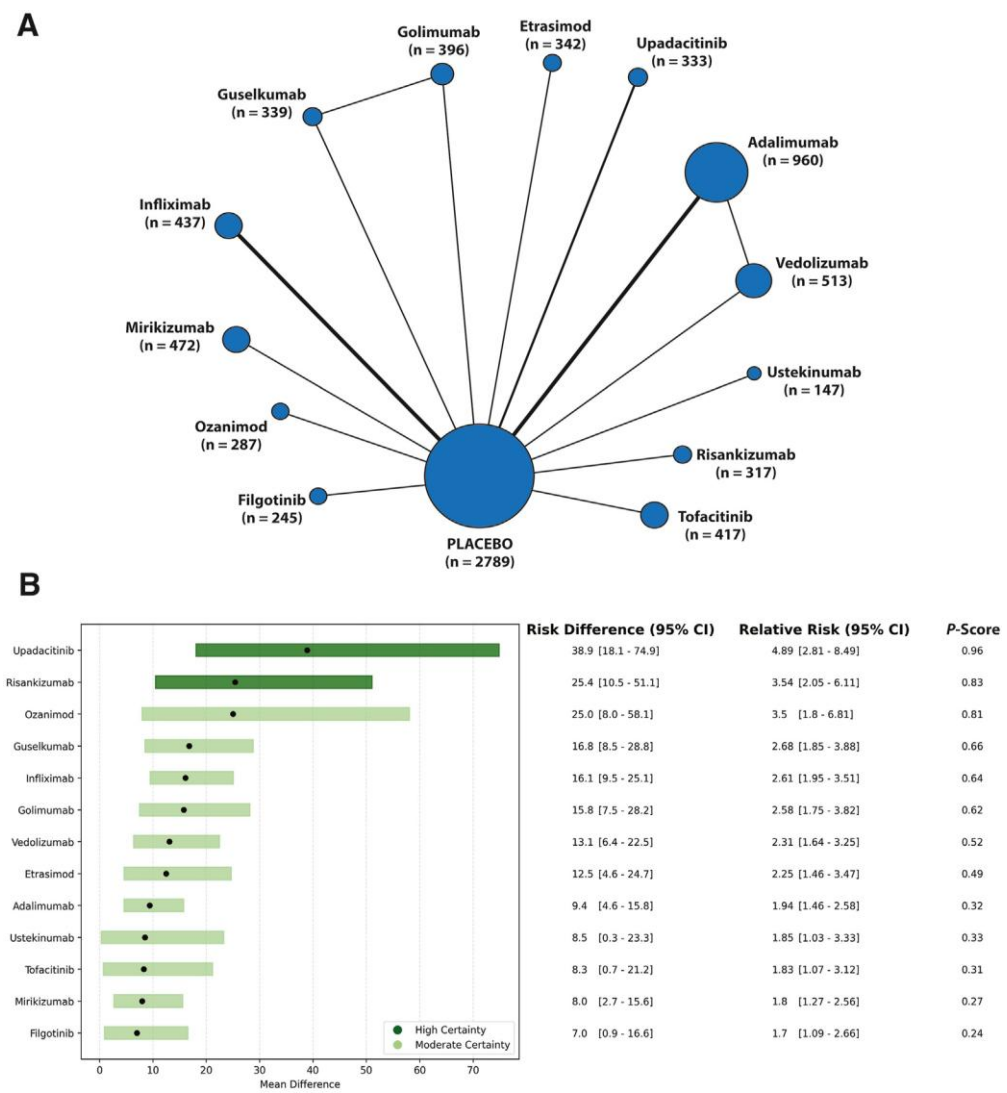
Adverse Event	PBO N=149, (PYS =87.4)		UPA 15 mg QD N=148, (PYS= 119.3)		UPA 30 mg QD N=154, (PYS=135.1)	
	%	E/100 PY†	%	E/100 PY†	%	E/100 PY†
Serious infection	4.0	6.9	3.4	4.2	2.6	3.0
Opportunistic infection excluding TB or herpes zoster	0	0	0.7	0.8	0	0
Herpes zoster	0	0	4.1	5.0	3.9	4.4
Any malignancy excluding NMSC	0.7	1.1	0.7	0.8	1.3	1.5
Any NMSC	0	0	0	0	1.3	1.5
Adjudicated VTE§	0	0	0	0	1.3	1.5
Adjudicated MACE‡	0.7	1.1	0	0	0	0
Adjudicated gastrointestinal perforation	0.7	2.3	0	0	0	0

Panaccione et al. UEGW 2021

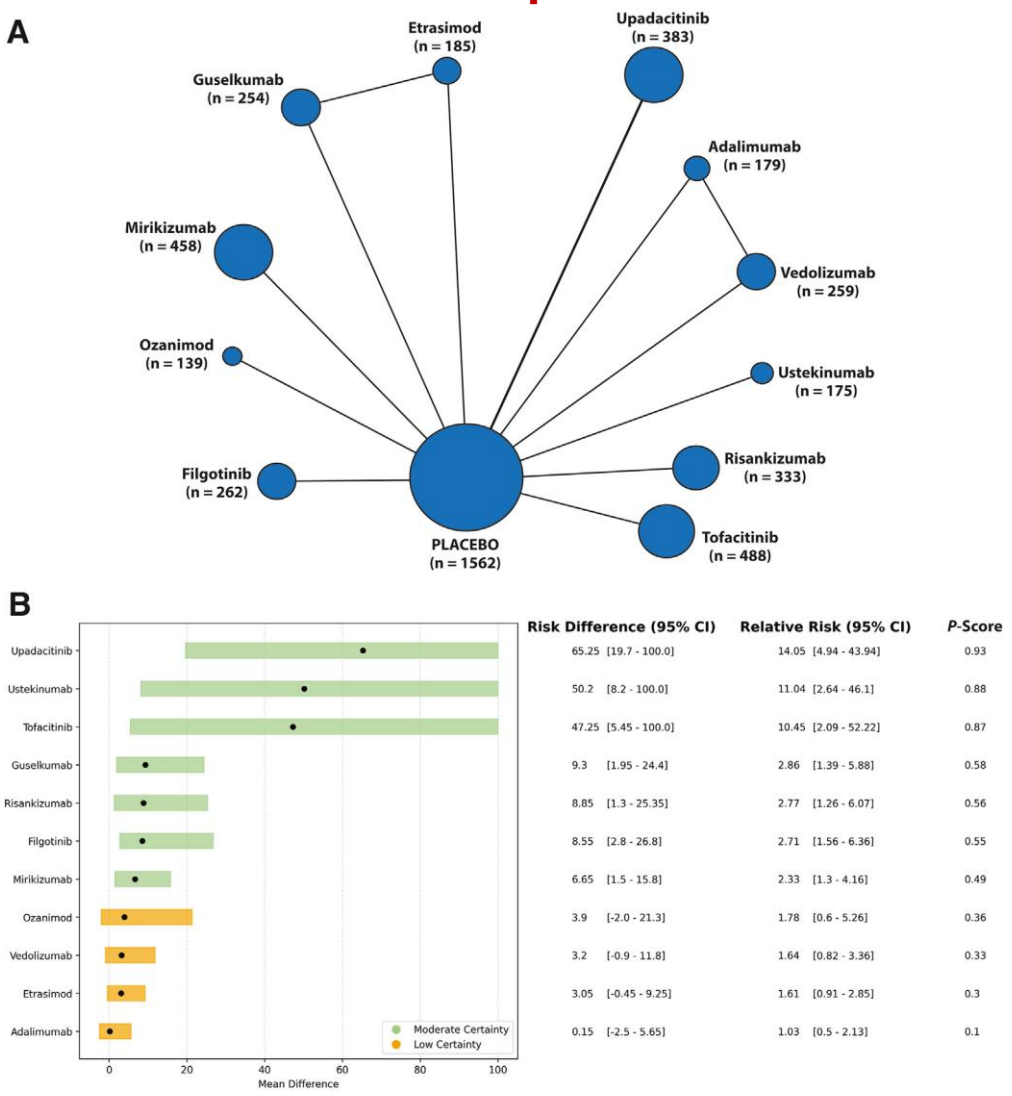
SACRO CUORE DON CALABRIA I R C C S

Comparative Efficacy of Advanced Therapies for Management of Moderate-to-Severe Ulcerative Colitis: 2024 AGA Evidence Synthesis

Bio-naïve



Bio-exposed



Ananthakrishnan AN, et al. Gastroenterology 2024; DOI: 10.1053/j.gastro.2024.07.046

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

	Induction i	Maintenance i	Perianal disease ii	Peripheral Spondylo-arthropathy	Axial Spondylo-arthropathy	Pregnancy	Over 65 years
Systemic corticosteroids	iv			iv	iv	iv	iv
Enteral release corticosteroids						v	v
Enteral Nutrition							
Thiopurines monotherapy						vi	vii
Methotrexate							
Infliximab							
Adalimumab							
Certolizumab							
Vedolizumab							
Ustekinumab							
Risankizumab				viii	ix		
Upadacitinib			x	xi	xii		xiii

Recommended

Can be considered

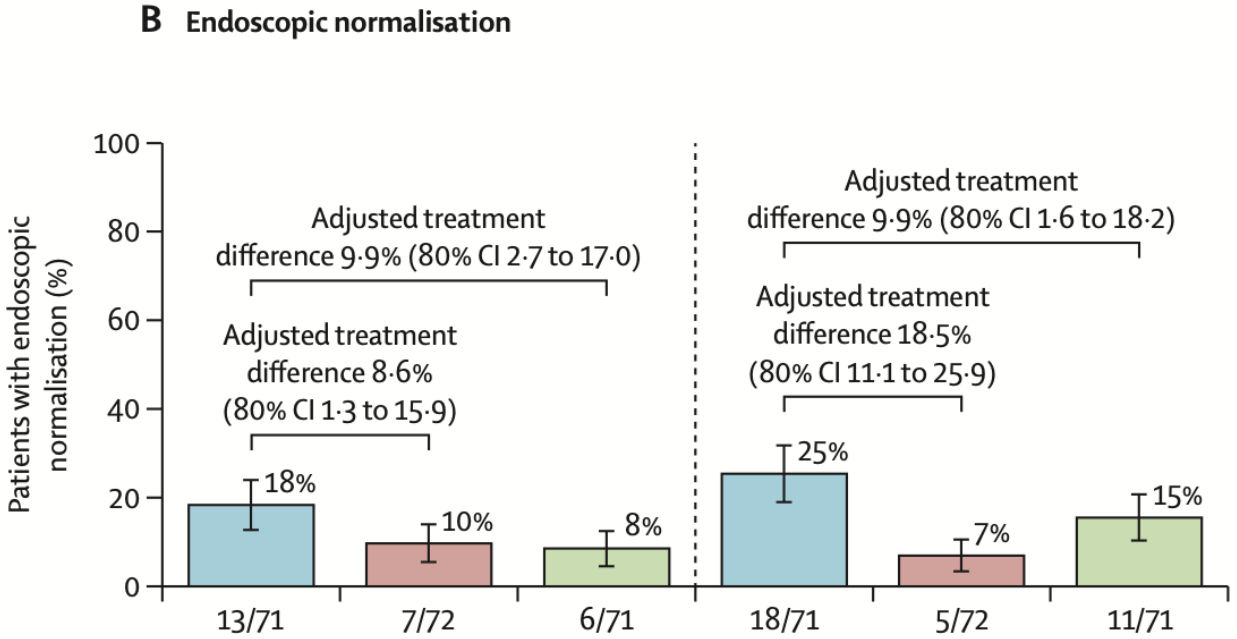
Not recommended

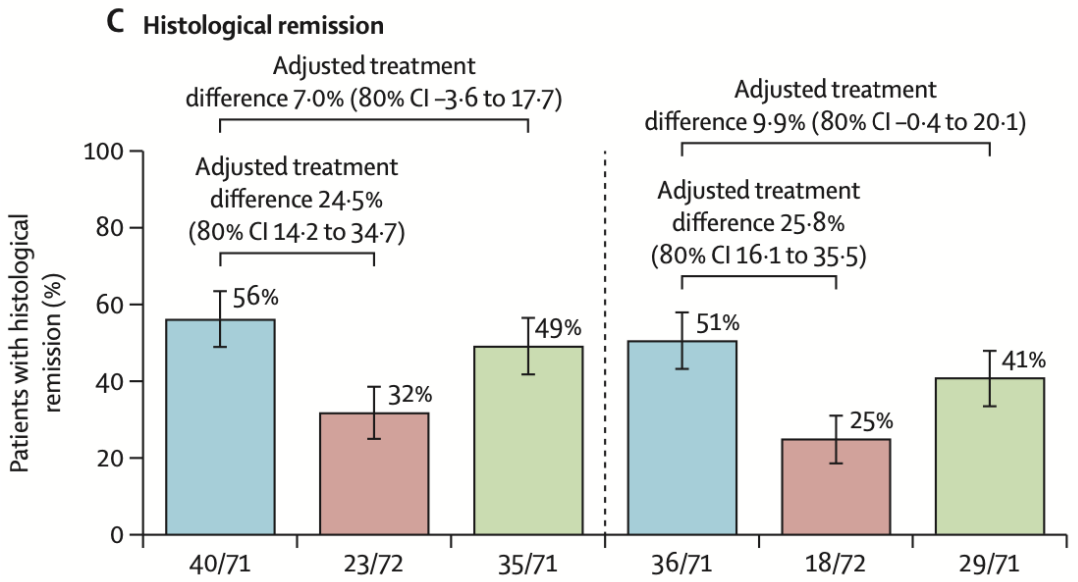
Insufficient evidence

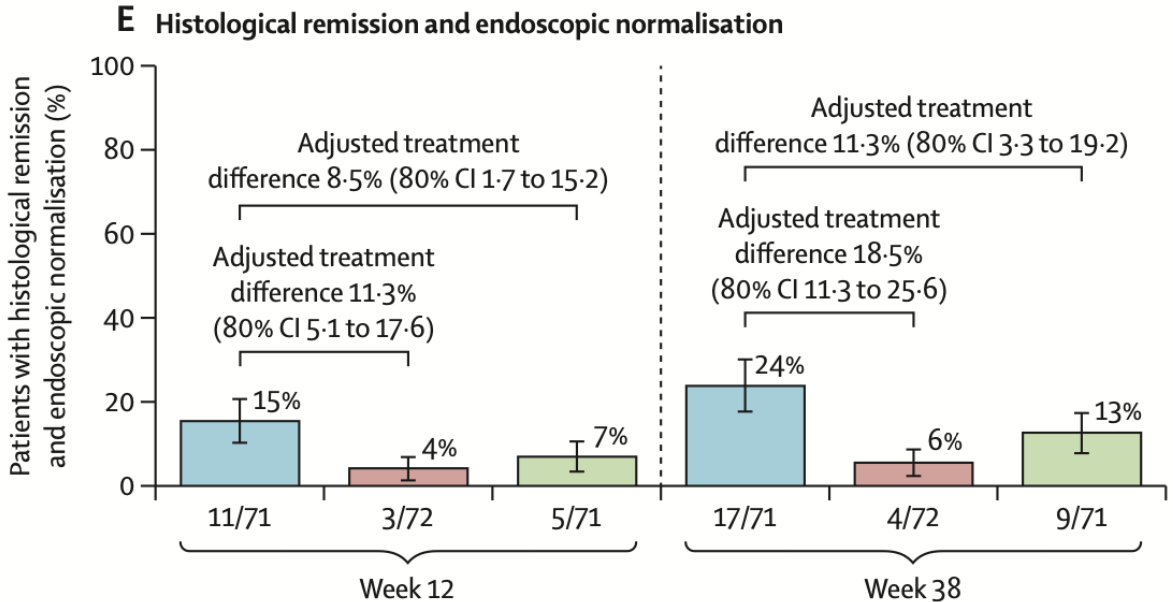
x. Upadacitinib may represent a therapeutic alternative in patients with prior anti-tumour necrosis factor [TNF] failure, intolerance, or contraindications. This is based upon post-hoc analysis of randomised controlled trial [RCT] data showing a signifcant beneft over placebo across a range of relevant fistula endpoints.

Gordon H, et al. *ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment* Journal of Crohn's and Colitis, 2024, 18, 1531–1555

Guselkumab plus Golimumab – VEGA trial (38 wks)







Combination therapy
Golimumab monotherapy
Guselkumab monotherapy

Endoscopy normalization = MES 0
Histologic remission = RHI < 6

Feagan BG et al. Lancet Gastroenterol Hepatol 2023; 8: 307–20

Current yearly costs of therapies

- Adalimumab biosimilars 1.000 E
- Infliximab biosimilars 2.000 E
- Jack-inhibitors (tofa, upa, filgo) 6.000 E
- Ustekinumab biosimilars 6.000 E
- Anti-IL23 (Risa, Miri, Gus) 12.000 E
- Vedolizumab 14.000 E

Conclusions

- Be pragmatic
- Perhaps **more important than sequencing** of drugs is the need for
  - **prompt diagnosis**
  - treating **“early”**
  - **personalized approach and tight monitoring**
- **Don’t forget surgery**
- **Don’t forget that patient’s disease burden is complex**

Thank you for your attention!