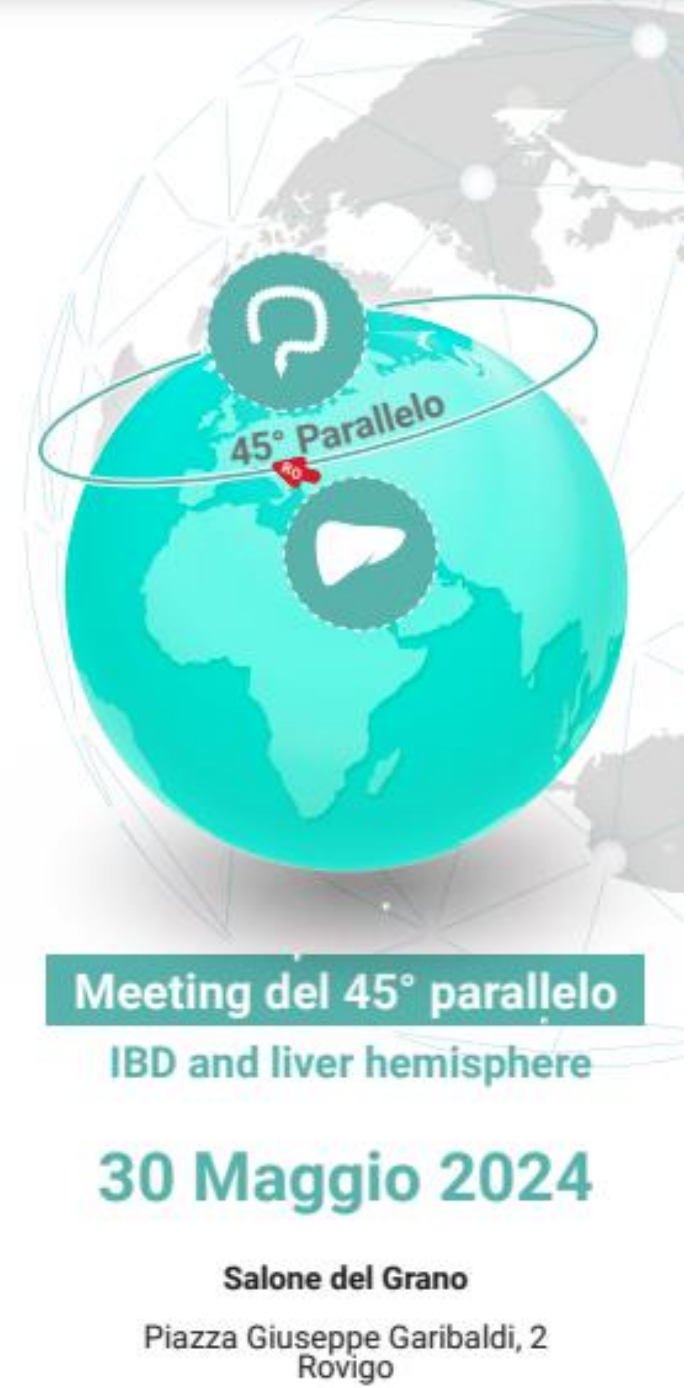


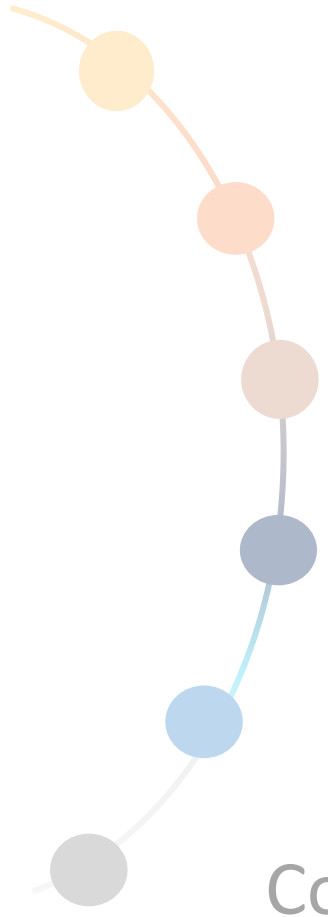
Long-term outcomes and real practice with anti IL12-23

Angela Variola

IBD Unit

IRCCS Sacro Cuore Don Calabria

Outline



Background

Long-term outcomes

Real practice: ideal positioning

Real practice: ideal patient

Weakness points?

Conclusions

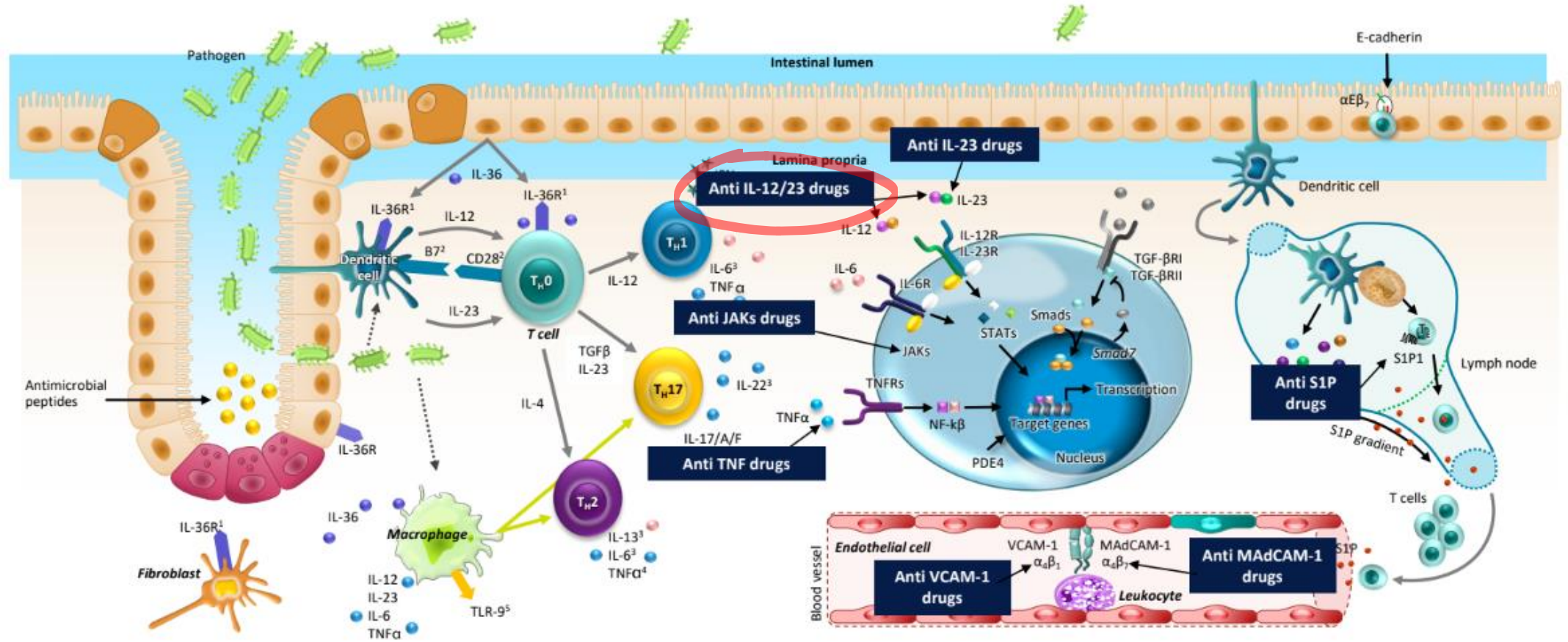
SACRO CUORE DON CALABRIA I R C C S

Background

- ✓ Therapeutic armamentarium is expanding both in UC and CD
- ✓ Therapeutic ceiling is still too low
- ✓ Steroid use is still too high, surgery rate is still too high, disability is still too high
- ✓ Need for a better choice and better positioning is mandatory
- ✓ For a better interaction with payer we need knowledge

SACRO CUORE DON CALABRIA I R C C S

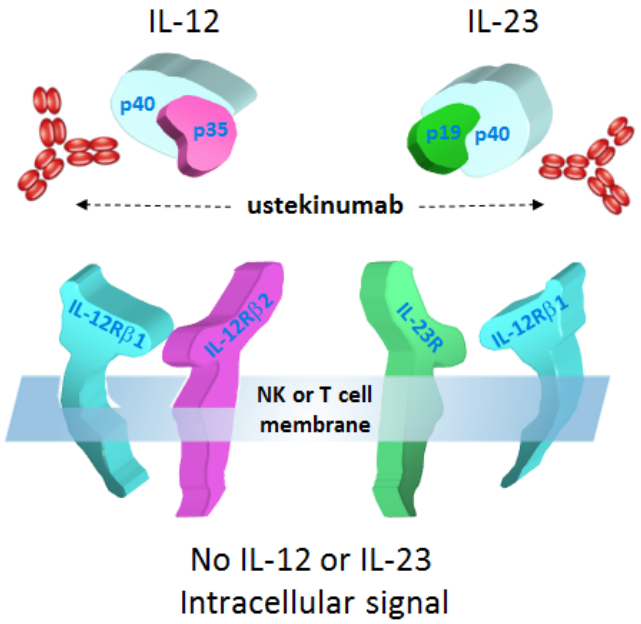
Background

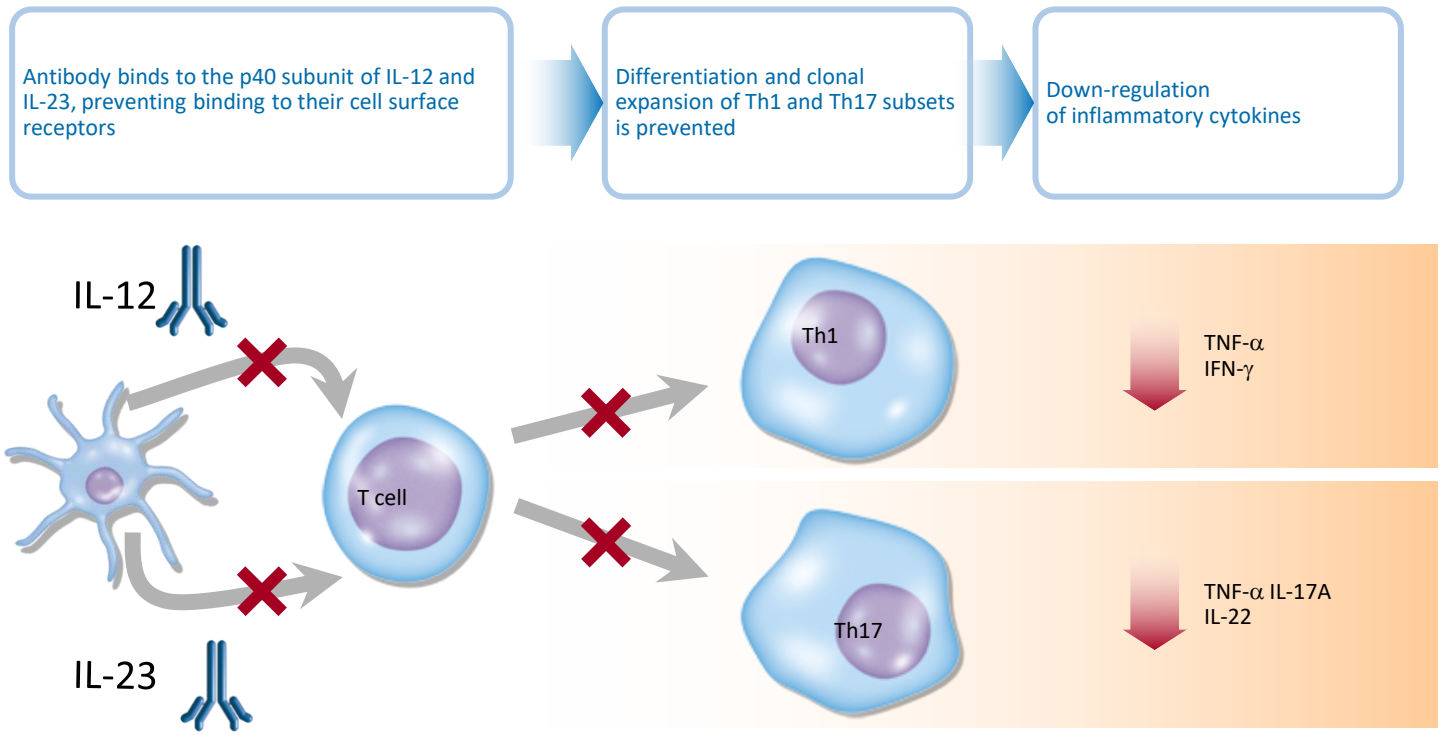


Adapted from Coskún M, et al. Trends Pharm Sci 2017;38:127–42 and Nielsen OH, et al. Expert Opin Investig Drugs 2016;25:709–18.

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: MoA

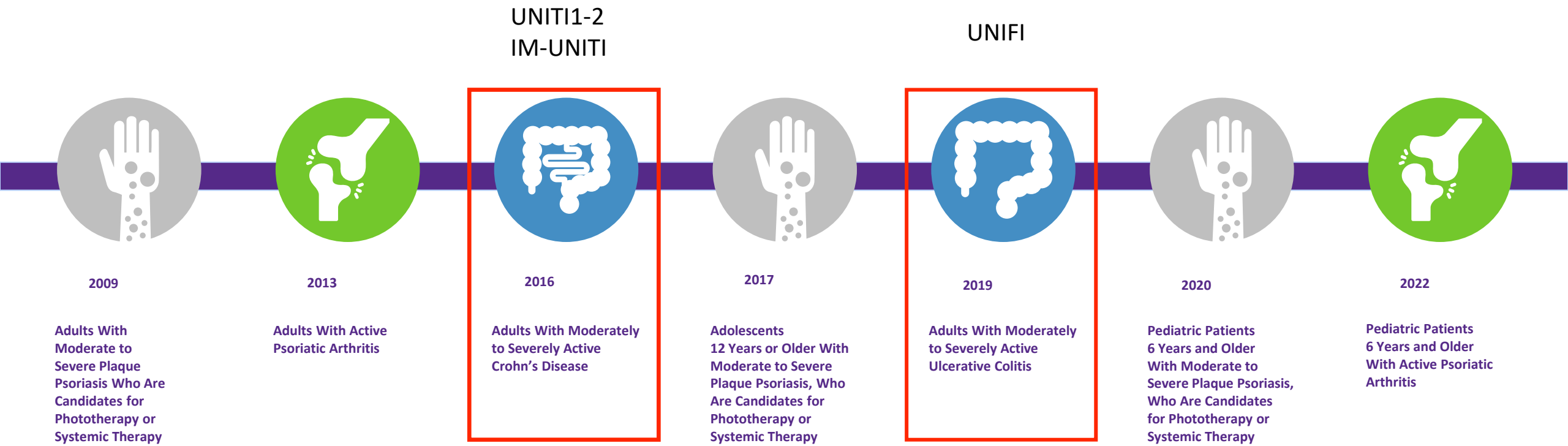




Wilson NJ,Nat Immunol 2007; Schmitt H, Immunology 2021

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: labels



Feagan NEJM 2016; BE Sands NEJM 2019

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: what we know from RCT?

Ustekinumab showed **efficacy** in both CD and UC

Ustekinumab showed **safety** in both CD and UC

Rapid onset of action on symptoms?

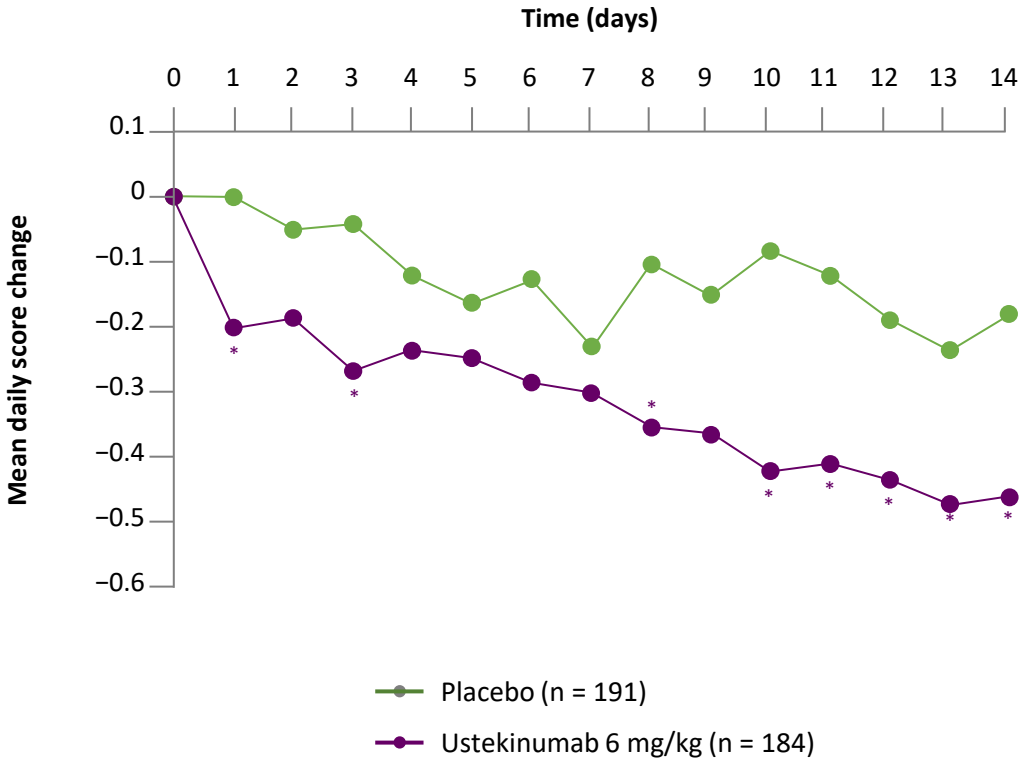
Feagan NEJM 2016; BE Sands NEJM 2019

SACRO CUORE DON CALABRIA IRCCS

Ustekinumab: what we know from RCT?

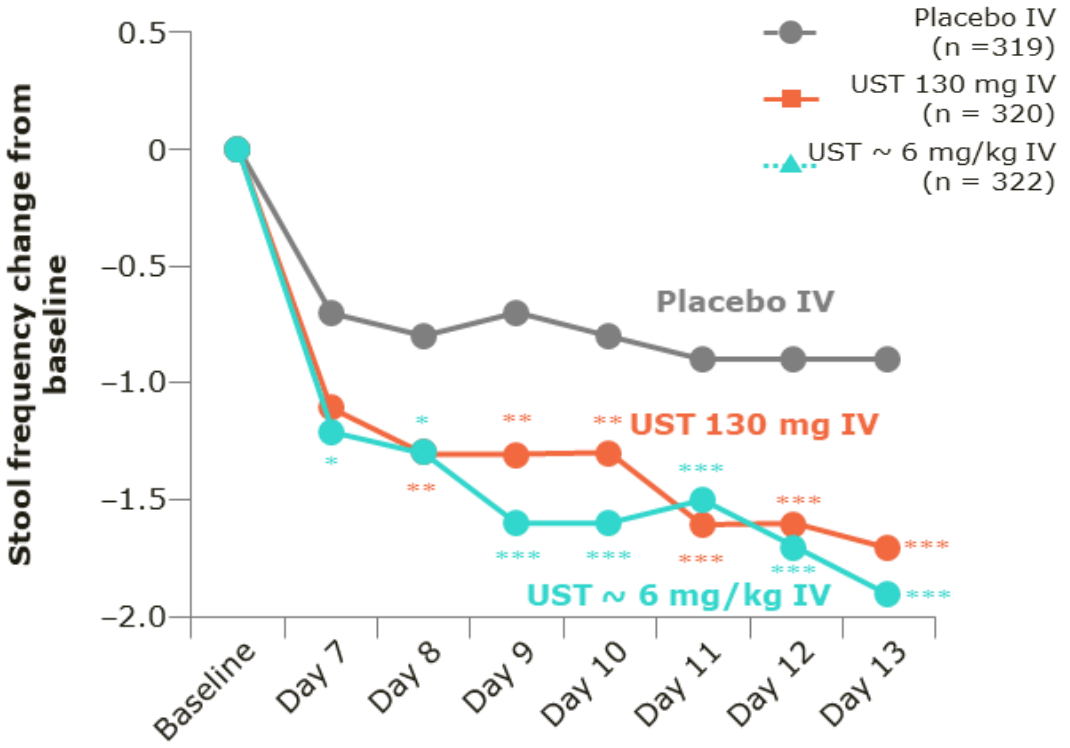
CD-UNITI

symptom relief by Day 1



UC-UNIFI

improved symptoms at Day 7 vs placebo



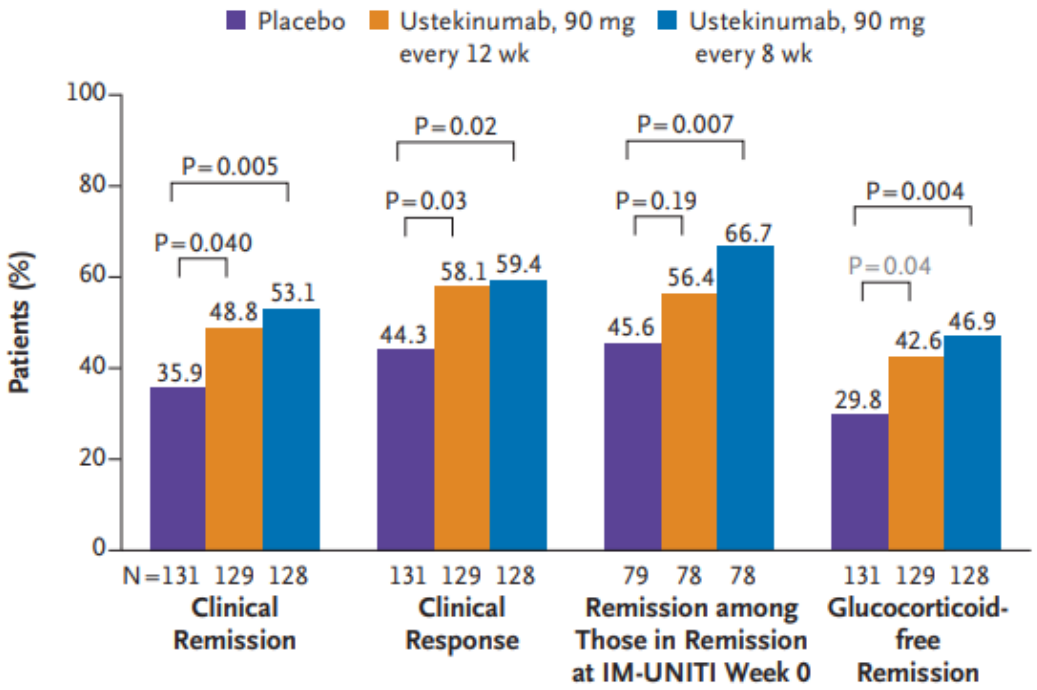
Colombel JF, et al, Clin Gastroenterol Hepatol. 2023; Danese S, et al. Clin Gastroenterol Hepatol.

SACRO CUORE DON CALABRIA I R C C S

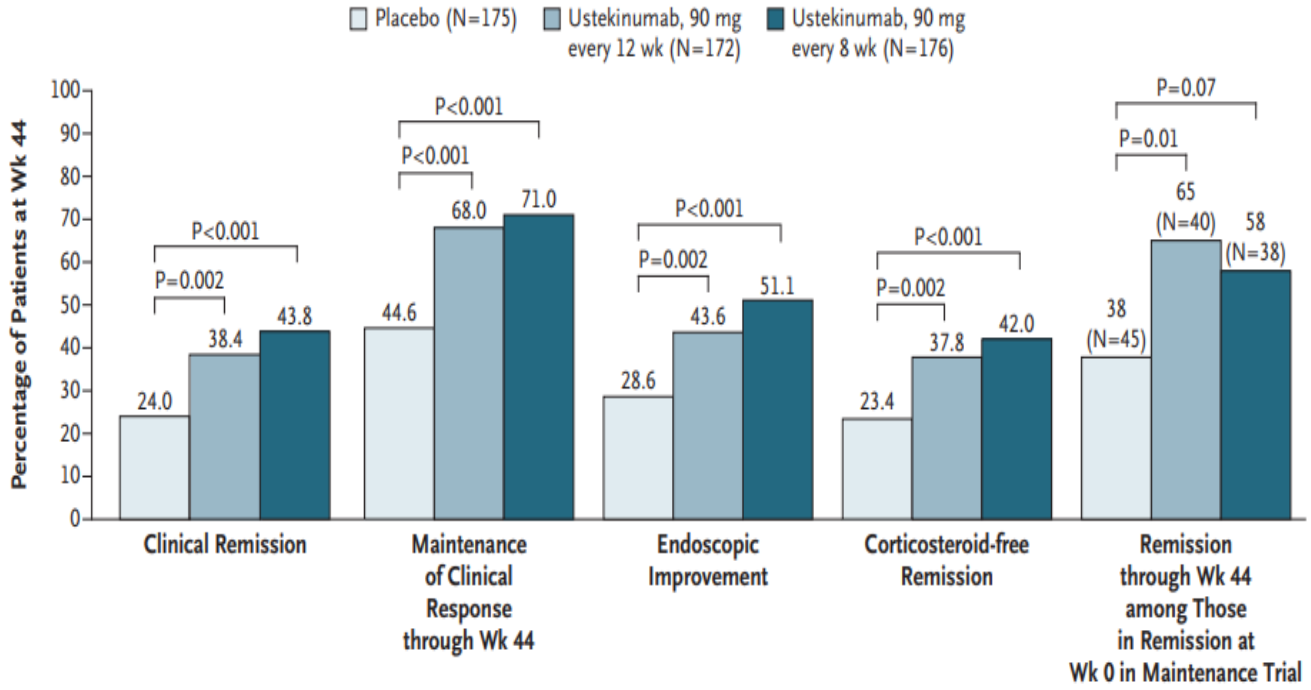
Ustekinumab: what we know from RCT?

Primary and major secondary endpoints

CD-UNITI



UC-UNIFI



Feagan B, et al. N Engl J Med. 2016, Sands BE, et al. N Engl J Med. 2019

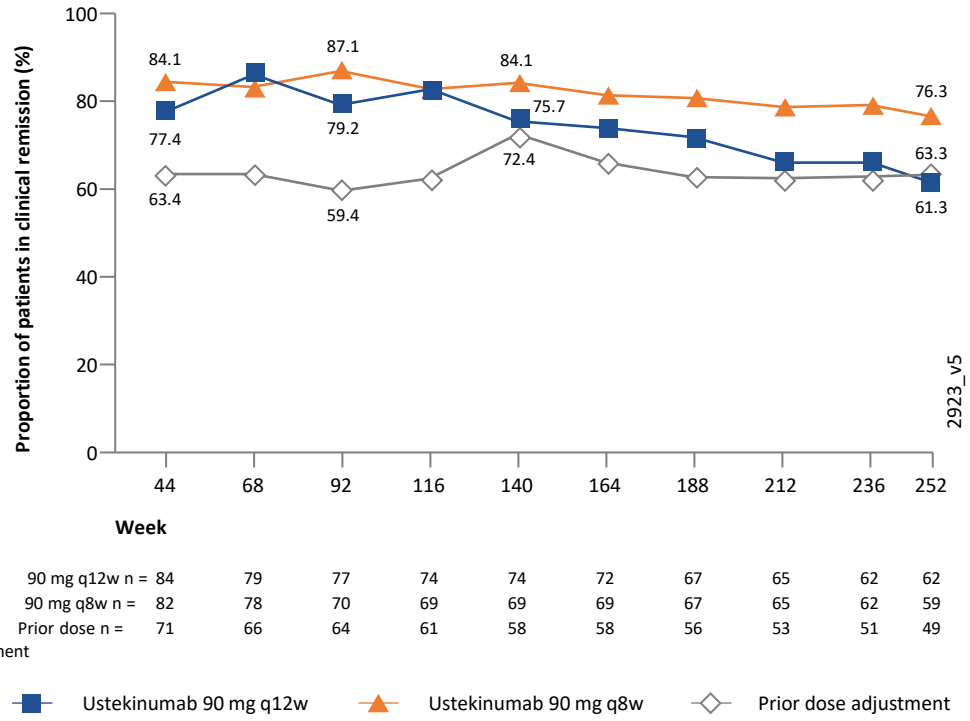
SACRO CUORE DON CALABRIA
IRCCS

Ustekinumab: what we know from RCT?

LONG TERM EXTENSION

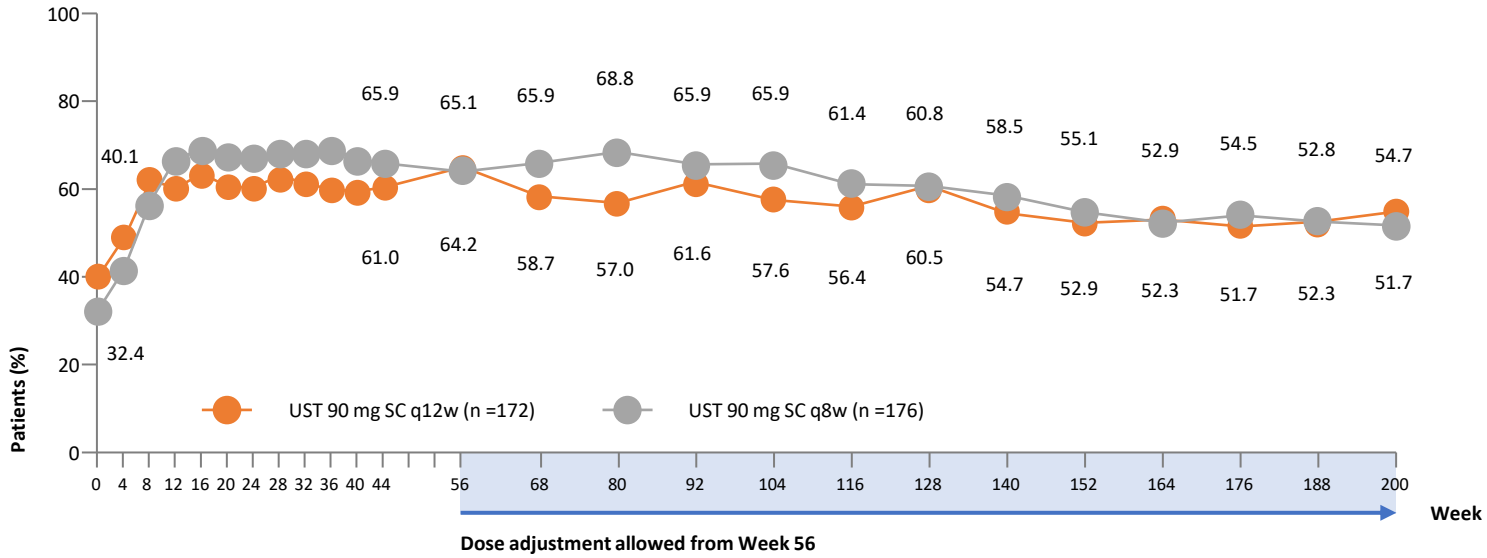
CD-UNITI

Clinical remission up to 5 years of treatment with ustekinumab



UC-UNIFI

Steroid- free symptomatic remission up to 4 years with ustekinumab



Sandborn WJ, et al. Clin Gastroenterol Hepatol. 2022, Afif W, et al. Am J Gastroenterol 2023

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: what we know from RCT?

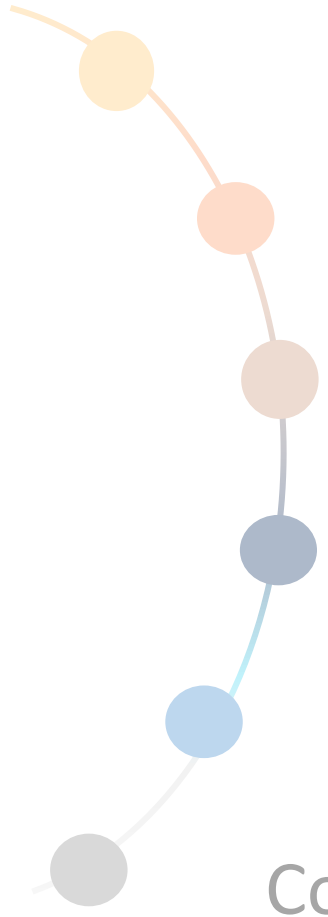
SAFETY

		Ustekinumab			
	Placebo SC[a] [N = 188]	90 mg SC q12w[b] [N = 141]	90 mg SC q8w[c] [N = 376]	Combined[d] [N = 457]	All ustekinumab[e] [N = 516]
Mean duration of follow-up [weeks]	84.1	124.0	124.5	140.7	126.4
Patient-years of follow-up	304.0	336.1	900.3	1236.4	1254.3
Number of events per 100 patient-years of follow-up [95% CI][f]					
Any AE	285.81[267.12, 305.46]	224.34 [208.61, 240.94]	251.90[241.64, 262.49]	244.41 [235.77, 253.28]	246.36[237.75, 255.20]
Infections[g]	85.51 [75.43, 96.56]	74.98 [66.01, 84.83]	76.53 [70.92, 82.46]	76.11 [71.32, 81.13]	76.62 [71.85, 81.62]
AEs leading to d/c of study agent	5.26 [3.01, 8.55]	2.08 [0.84, 4.29]	2.89 [1.89, 4.23]	2.67 [1.84, 3.75]	2.63 [1.81, 3.69]
Serious adverse events	10.52 [7.20, 14.86]	6.84 [4.34, 10.27]	8.44 [6.65, 10.57]	8.01 [6.51, 9.75]	7.89 [6.42, 9.61]
Serious infections[g]	3.29 [1.58, 6.05]	2.98 [1.43, 5.47]	2.22 [1.36, 3.43]	2.43 [1.64, 3.46]	2.39 [1.61, 3.41]
All malignancies	0.66 [0.08, 2.38]	0.89 [0.18, 2.61]	0.67 [0.24, 1.45]	0.73 [0.33, 1.38]	0.72 [0.33, 1.36]
Excluding nonmelanoma skin cancer	0.33 [0.01, 1.83]	0.00 [0.00, 0.89]	0.00 [0.00, 0.33]	0.00 [0.00, 0.24]	0.00 [0.00, 0.24]
Nonmelanoma skin cancer	0.33 [0.01, 1.83]	0.89 [0.18, 2.61]	0.67 [0.24, 1.45]	0.73 [0.33, 1.38]	0.72 [0.33, 1.36]
Death	0.00 [0.00, 0.99]	0.00 [0.00, 0.89]	0.11 [0.00, 0.62]	0.08 [0.00, 0.45]	0.08 [0.00, 0.44]

Abreu MT, JCC 2022

SACRO CUORE DON CALABRIA IRCCS

Outline



Background

Long-term outcomes

Real practice: ideal positioning

Real practice: ideal patient

Weakness points?

Conclusions

SACRO CUORE DON CALABRIA I R C C S

Original Article

Ustekinumab for Crohn's Disease: Two-Year Results of the Initiative on Crohn and Colitis (ICC) Registry, a Nationwide Prospective Observational Cohort Study

Tessa Straatmijer,[a,o] Vince B. C. Biemans,[a,o] Frank Hoentjen,[b] Nanne K. H. de Boer,[c] Alexander G. L. Bodelier,[d] Gerard Dijkstra,[e] Willemijn A. van Dop,[b] Jeoffrey J. L. Haans,[f] Jeroen M. Jansen,[g] P. W. Jeroen Maljaars,[h] Sander van der Marel,[i] Bas Oldenburg,[j] Cyriel Y. Ponsioen,[k] Marijn C. Visschedijk,[e] Annemarie C. de Vries,[l] Rachel L. West,[m] C. Janneke van der Woude,[l] Marieke Pierik,[f,o] Marjolijn Duijvestein,[k,*] Andrea E. van der Meulen-de Jong[h,*]

The Real-World Effectiveness and Safety of Ustekinumab in the Treatment of Crohn's Disease: Results from the SUCCESS Consortium

Amanda M Johnson, MD[1], Maria Barsky, MD[2], Waseem Ahmed, MD[3], Samantha Zullow, MD[4], Jonathan Galati, MD[5], Vipul Jairath, MD[6], Neeraj Narula, MD[7], Farhad Peerani, MD[8], Benjamin H. Click, MD[9], Elliot S Coburn, MD[10], ThucNhi Tran Dang, MD[8], Stephanie Gold, MD[11], Manasi Agrawal, MD, MS[11], Rajat Garg, MD, FACC, FSCAI[9], Manik Aggarwal, MD[9], Danah Mohammad, MD[7], Brendan Halloran, MD[8], Gursimran S Kochhar, MD[12], Hannah Todorowski, DO[12], Nabeeha Mohy Ud Din, MD[12], James Izanec, MD[13], Amanda Teeple, MPH[13], Chris Gasink, MD[13], Erik Muser, PharmD, MPH[13], Zhijie Ding, PhD, MS[13], Arun Swaminath, MD[14], Komal Lakhani, MD[14], Dan Hogan, DO[14], Samit Datta, MD[14], Ryan C Ungaro, MD[11], Brigid S. Boland, MD[2], Matthew Bohm, MD[3], Monika Fischer, MD[3], Sashidhar Sagi, MD[3], Anita Afzali, MD[15], Thomas Ullman, MD[16], Garrett Lawlor, MD[17], Daniel C Baumgart, PhD, MD, MBA[8], Shannon Chang, MD[4], David Hudesman, MD[4], Dana Lukin, MD[5], Ellen J Scherl, MD[5], Jean-Frederic Colombel, MD[11], Bruce E Sands, MD[11], Corey A Siegel, MD, MS[10], Miguel Regueiro, MD[9], William J Sandborn, MD[2], David Bruining, MD[1], Sunanda Kane, MD[1], Edward V. Loftus Jr., MD[1], Parambir S Dulai, MD[2,18]

Comparative Safety and Effectiveness of Biologic Therapy for Crohn's Disease: A CA-IBD Cohort Study

Siddharth Singh, Jihoon Kim, Jiyu Luo, Paulina Paul, Vivek Rudrapatna, Sunhee Park, Kai Zheng, Gaurav Syal, Christina Ha, Phillip Fleshner, Dermot McGovern, Jenny S. Sauk, Berkeley Limketkai, Parambir S. Dulai, Brigid S. Boland, Samuel Eisenstein, Sonia Ramamoorthy, Gil Melmed, Uma Mahadevan, William J. Sandborn, Lucila Ohno-Machado

Inflammatory Bowel Diseases, 2022, **28**, 1725–1736
https://doi.org/10.1093/ibd/izab357
Advance access publication 15 February 2022
Original Research Articles - Clinical

Long-Term Real-World Effectiveness and Safety of Ustekinumab in Crohn's Disease Patients: The SUSTAIN Study

María Chaparro, MD, PhD,[*] Iria Baston-Rey, MD,[†] Estela Fernández-Salgado, MD,[‡]

Original Article

Ustekinumab for Crohn's Disease: Results of the *ICC Registry*, a Nationwide Prospective Observational Cohort Study

Vince B. C. Biemans,[a,b,o] Andrea E. van der Meulen - de Jong,[c] Christine J. van der Woude,[d] Mark Löwenberg,[e] Gerard Dijkstra,[f] Bas Oldenburg,[g] Nanne K. H. de Boer,[h] Sander van der Marel,[i] Alexander G. L. Bodelier,[j] Jeroen M. Jansen,[k] Jeoffrey J. L. Haans,[b] Rosaline Theeuwen,[c] Dirk de Jong,[a] Marie J. Pierik,[b,*] Frank Hoentjen[a,*]; on behalf of the Dutch Initiative on Crohn and Colitis (ICC)

Open

An Objective Comparison of Vedolizumab and Ustekinumab Effectiveness in Crohn's Disease Patients' Failure to TNF-Alpha Inhibitors

Sara Onali, MD, PhD[1-2], Daniela Pugliese, MD, PhD[3], Flavio Andrea Caprioli, MD, PhD[4-5], Ambrogio Orlando, MD[6], Livia Biancone, MD, PhD[7], Olga Maria Nardone, MD[8], Nicola Imperatore, MD[9], Gionata Fiorino, MD, PhD[10], Maria Cappello, MD[11], Anna Viola, MD[12], Maria Beatrice Principi, MD, PhD[13], Cristina Bezzio, MD[14], Annalisa Aratari, MD[15], Sonia Carparelli, MD[16], Silvia Mazzuoli, MD[17], Francesco Manguso, MD, PhD[9], Laurino Grossi, MD, PhD[18], Giorgia Bodini, MD, PhD[19], Davide Ribaldone, MD[20], Giammarco Mocci, MD[21], Agnese Miranda, MD[22], Luigi Minerba, MD, PhD[1-2], Agnese Favale, MD[1-2], Mauro Grova, MD[6], Ludovica Scucchi, MD[7], Simone Segato, MD[23-24], Walter Fries, MD, PhD[12], Fabiana Castiglione, MD, PhD[8], Alessandro Armuzzi, MD, PhD[25-26] and Massimo C. Fantini, MD, PhD[1-2], on behalf of the IG-IBD

Adv Ther (2023) 40:4421–4439
https://doi.org/10.1007/s12325-023-02611-0

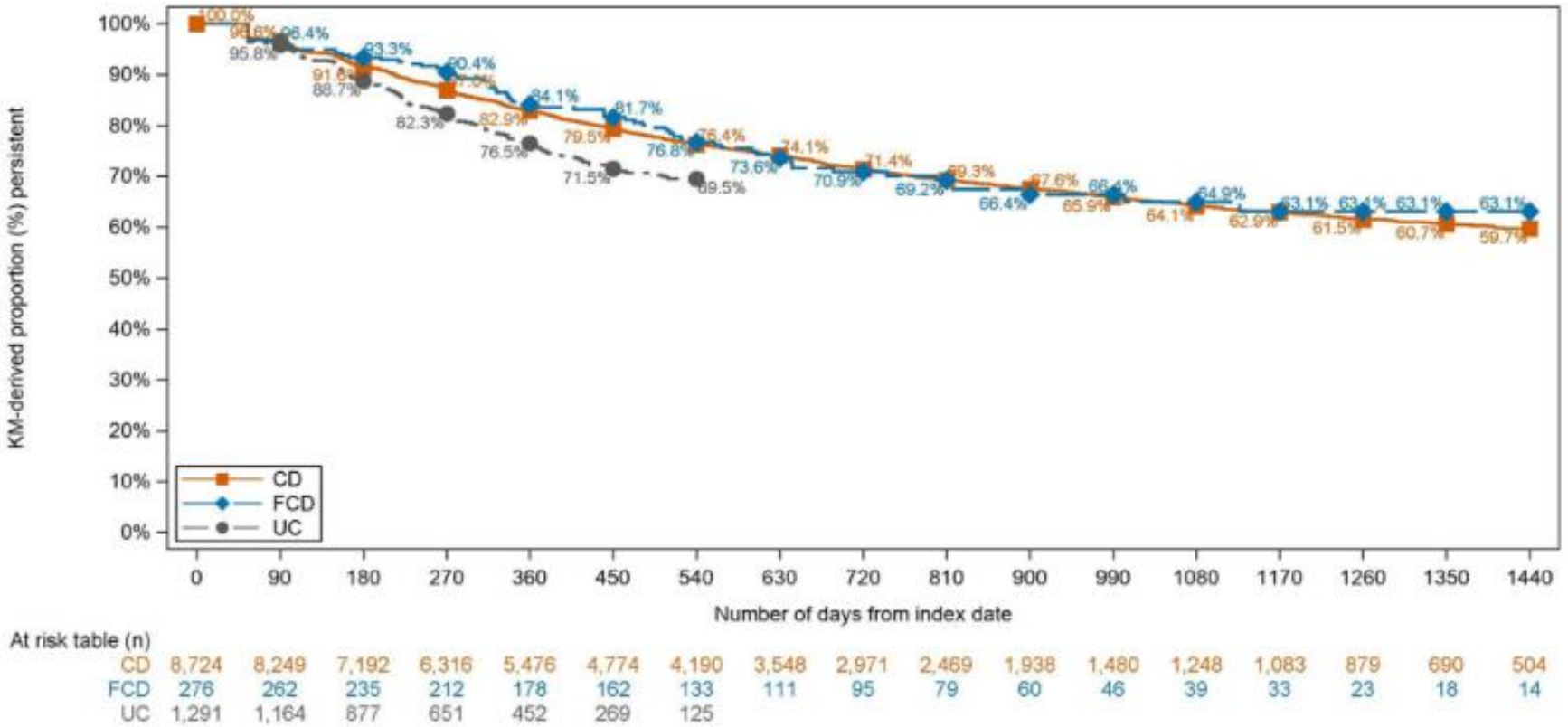
ORIGINAL RESEARCH

Real-World Persistence of Ustekinumab in the Treatment of Inflammatory Bowel Disease

Brian Bressler · Jennifer Jones · Tracy S. H. In · Tommy Lan · Cristian Iconaru · John K. Marshall

Persistence rates for 8724 patients with **CD** were 82.9%, 71.4%, 64.1%, and 59.7% at 1 2, 3, and 4 years, respectively. Similarly, persistence rates for 276 patients with **FCD** were 84.1%, 70.9%, 64.9%, and 63.1% at 1, 2, 3, and 4 years, respectively.
Persistence rates for 1291 patients with **UC** were 76.5% at 1 year and 69.5% at 1.5 years.

When stratified by prior IBD-indicated biologic experience, persistence wasnumerically higher in biologic-naive



EXPERT OPINION ON BIOLOGICAL THERAPY

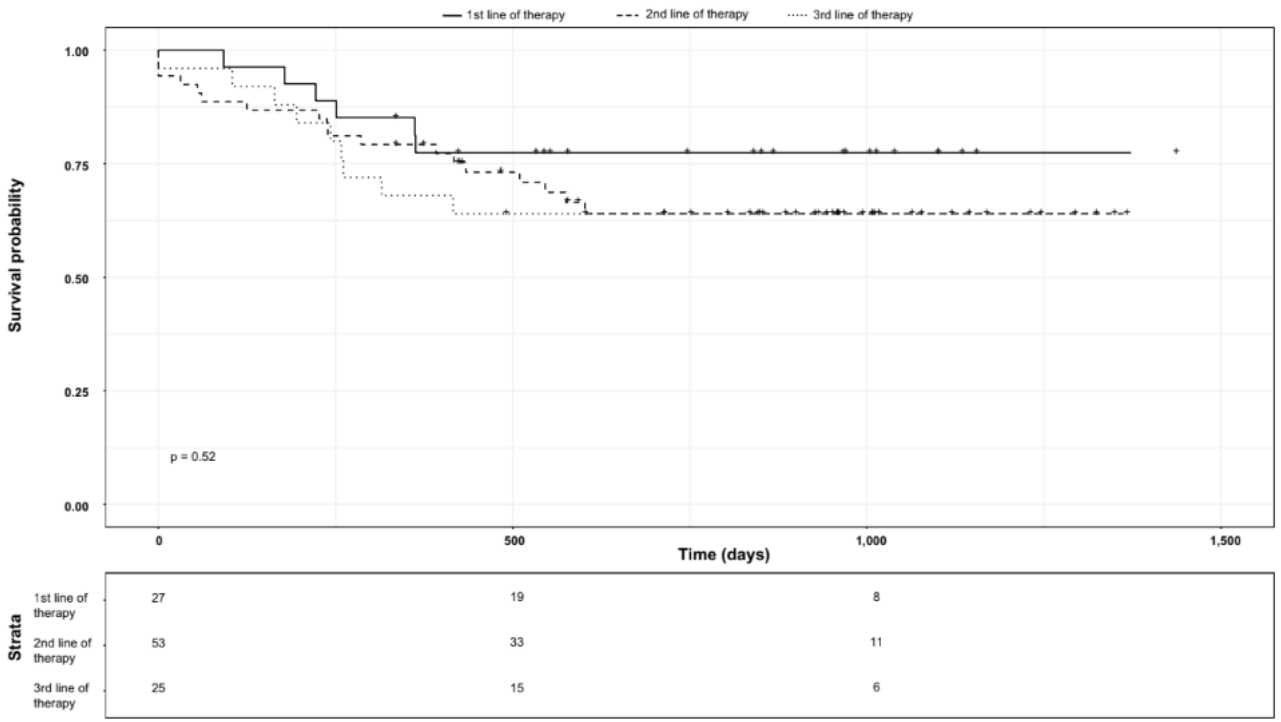
Taylor & Francis
Taylor & Francis Group

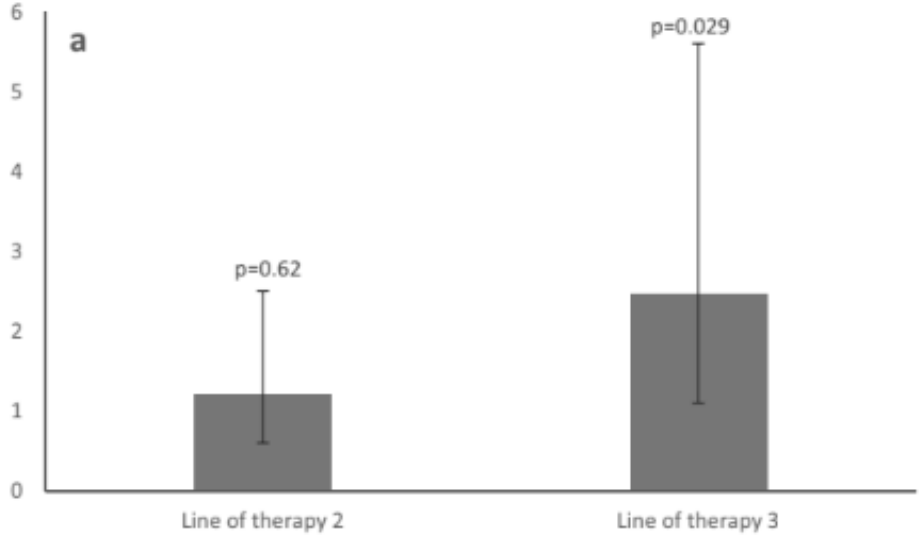
Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iebt20

Use of real-world data to assess the effectiveness of ustekinumab in treating IBD patients: a retrospective linked database study in northwest London

Nik Kamperidis, Moulesh Shah, Sophie Young, Evgeniy Galimov, Shruti Sweeney & Naila Arebi



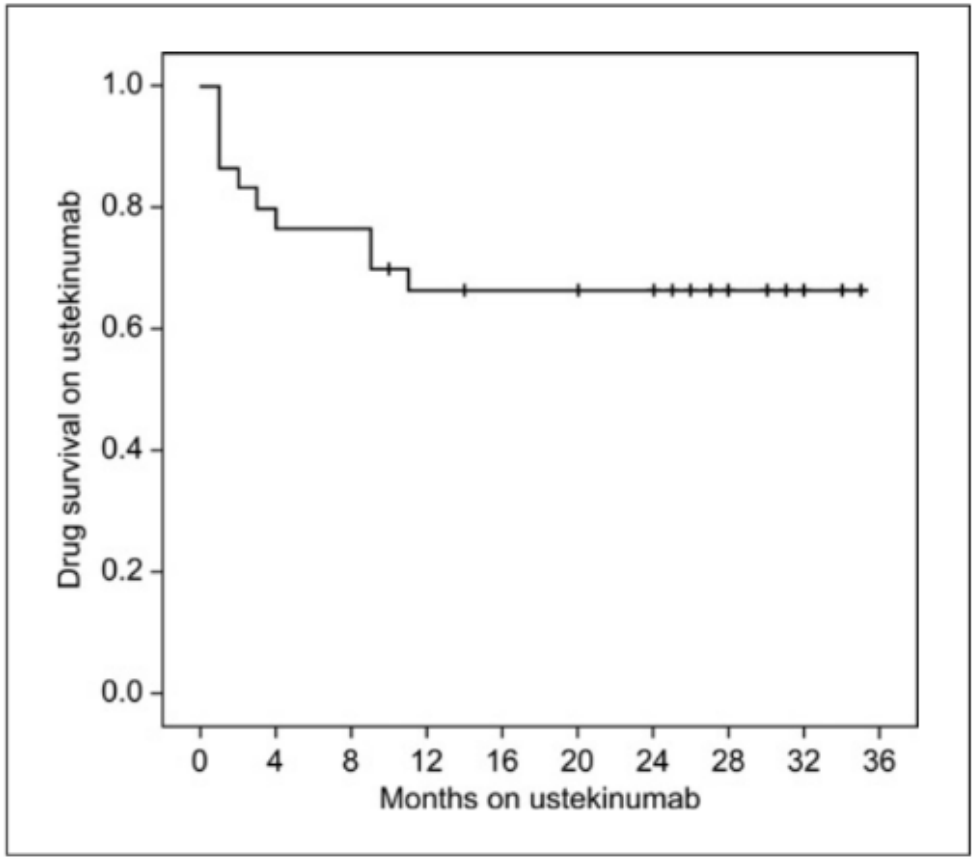


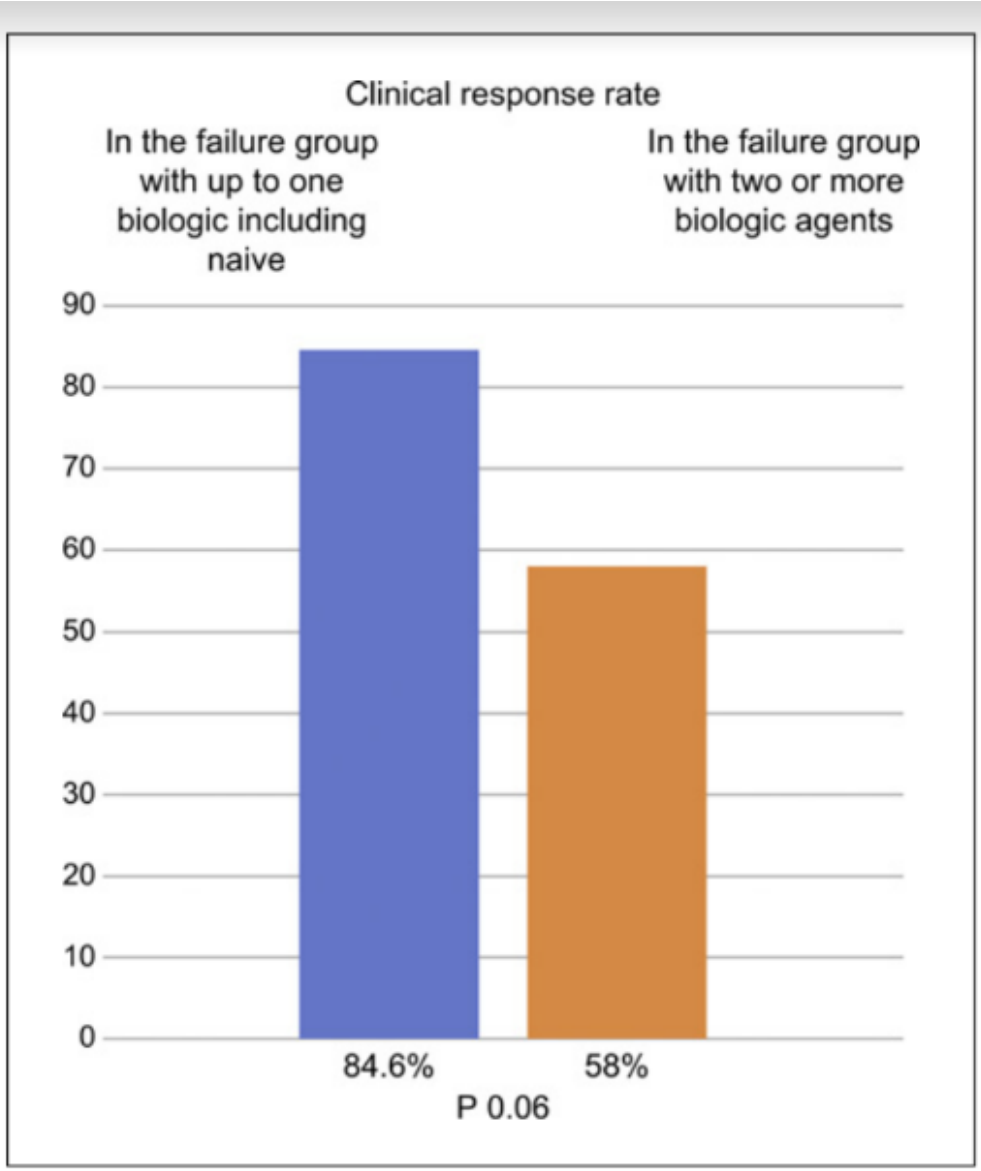
Effects of line of therapy on IBD-associated hospitalization

SACRO CUORE DON CALABRIA
I R C C S

Real-World Data on Short-Term and Long-Term Treatment Results of Ustekinumab in Patients with Steroid-Resistant/Dependent Ulcerative Colitis

Yoriaki Komeda[a] George Tribonias[b] Masashi Kono[a] Kohei Handa[a] Shunsuke Omoto[a] Mamoru Takenaka[a] Satoru Hagiwara[a] Naoko Tsuji[a] Naoshi Nishida[a] Hiroshi Kashida[a] Masatoshi Kudo[a]





SUCCESS CONSORTIUM

- Retrospective multicentric study, 1113 pts, median follow up 386 days (204-562)
- 88.7% prior anti-TNF exposure
- 65% 2 or more biologics
- 37% history of perianal disease
- 59% previous intestinal surgery

	6 months	12 months
Clinical remission	21%	40%
Steroid-free remission	15%	32%
Endoscopic remission	17%	39%
Radiographic remission	19%	30%

Johnson 2022, American Journal of Gastroenterology

SUCCESS CONSORTIUM

- Retrospective multicentric study, 1113 pts, median follow up 386 days (204-562)
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- 37% history of perianal disease
- 59% previous intestinal surgery

	6 months	12 months
Clinical remission	21%	40%
Steroid-free remission	15%	32%
Endoscopic remission	17%	39%
Radiographic remission	19%	30%
Clinical remission (naive)		63
Endoscopic remission (naive)		55

Johnson 2022, American Journal of Gastroenterology

SUCCESS CONSORTIUM

Clinical predictors of treatment response:

- Number of prior biologics (cumulative rates of clinical and endoscopic remission lower with each additional prior biologic exposure)

- Prior anti-TNF (lower probability)

- Prior vedolizumab (lower probability of endoscopic remission, not clinical remission)

Johnson 2022, American Journal of Gastroenterology

SUCCESS CONSORTIUM

Clinical predictors of treatment response:

- Number of prior biologics (cumulative rates of clinical and endoscopic remission lower with each additional prior biologic exposure)
- Prior anti-TNF (lower probability)
- Prior vedolizumab (lower probability of endoscopic remission, not clinical remission)

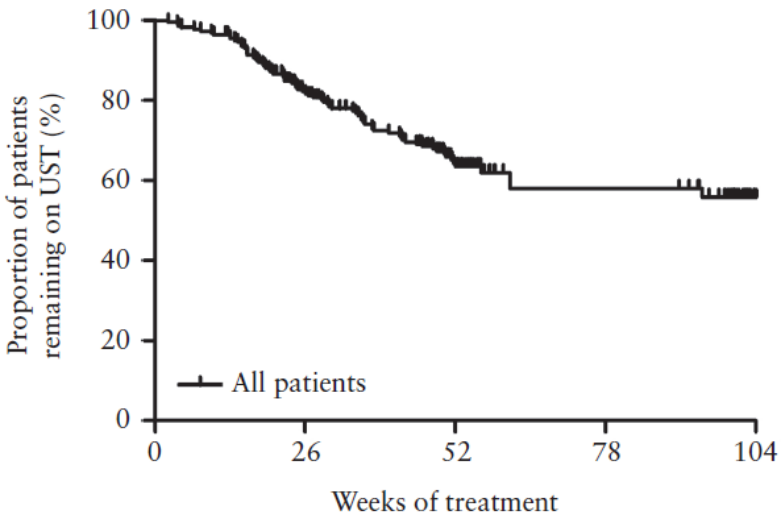
From UNITI trials:
- Baseline albumin
- Absence of prior intestinal surgery
- No prior anti-TNF
- Lack of draining fistula
- No prior smoking history

Dulai P, American College of Gastroenterology 2019

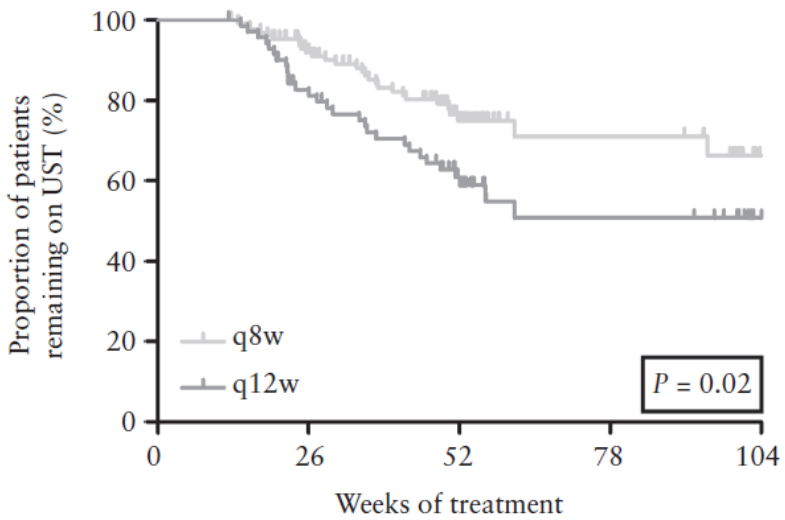
Johnson 2022, American Journal of Gastroenterology

ICC REGISTRY

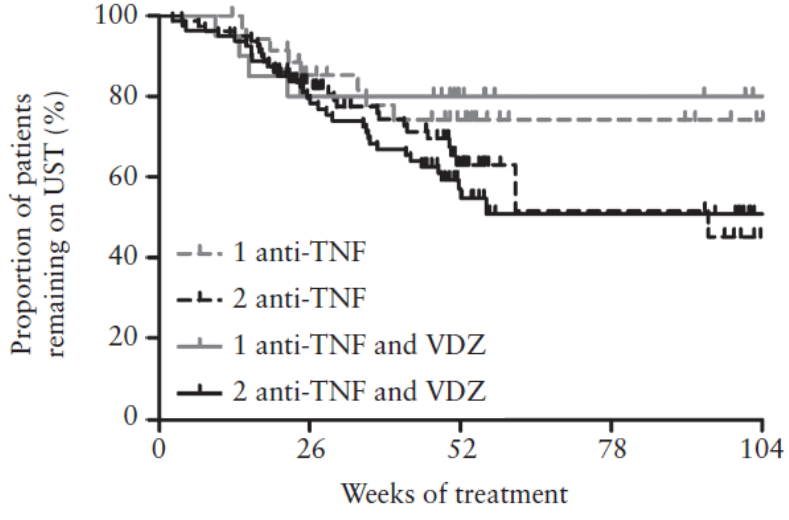
Among All Patients



Among Patients on q12w or q8w Maintenance Interval



Among Patients With Prior One Or Two Anti-TNF With Or Without VDZ Therapy



A prospective, observational registry study evaluated the long-term effectiveness and safety of UST in a real-world setting with a follow-up of 2 years (**N=252 CD patients**).

Biemans et al. J Crohns Colitis 2020;14:33-45.

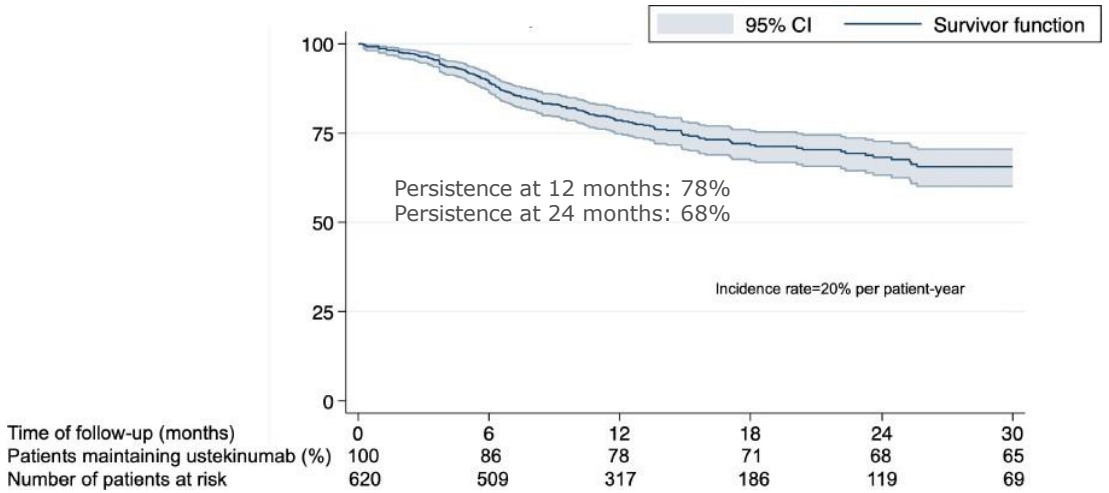
ICC REGISTRY

EXTRAINTESTINAL MANIFESTATIONS:

- At baseline 67 EIMs were reported in 59 patients.
- During follow-up, 32.8% of patients (22/67) with arthralgia achieved EIM remission.
  - All patients with uveitis, apthous stomatitis, and pyoderma gangrenosum achieved EIM remission and one of the two patients with erythema nodosum achieved EIM remission during follow-up.
- Thirty-nine patients developed new arthralgias during follow-up, of whom 66.7% (26/39) achieved EIM remission before Week 104.
- Three patients developed transient aphthous stomatitis during follow-up, two patient's uveitis, two patients' erythema nodosum and one patient pyoderma gangrenosum.

Straatmijer et al. J Crohns Colitis 2021

ULISES study in UC



Reasons for discontinuation	%
Primary non-response	39
Loss of response	35
Medical decision	13
Partial response	5.8
Adverse event	7

Treatment after discontinuation	%
Tofacitinib	25
Anti-TNF	19
Vedolizumab	12
Upadacitinib	10
Filgotinib	4.5
Other options	22
Surgery	18

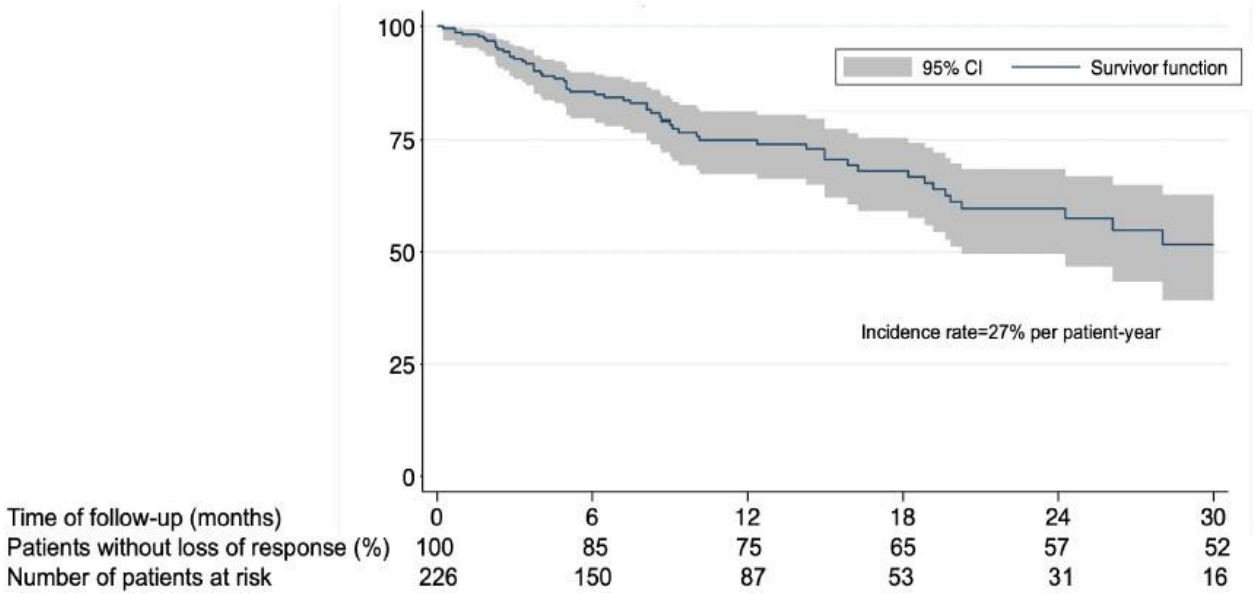
Multivariant analysis of associating factors of drug discontinuation

Variables	Hazard ratio	95% confidence interval
Anaemia	1.5	1.1 - 2.1
Severe activity	1.5	1.09 - 2.06
Systemic steroids	1.48	1.06 - 2.08

Chaparro M, et al. Presented at ECCO, Stockholm, Sweden, 21st–24th February 2024. DOP74.

ULISES study in UC

Survival curve of the response of patients who had steroid-free clinical remission at Week 16



57/226 patients (25%) lost response, median follow-up was 12 months

Dose escalation (72%)

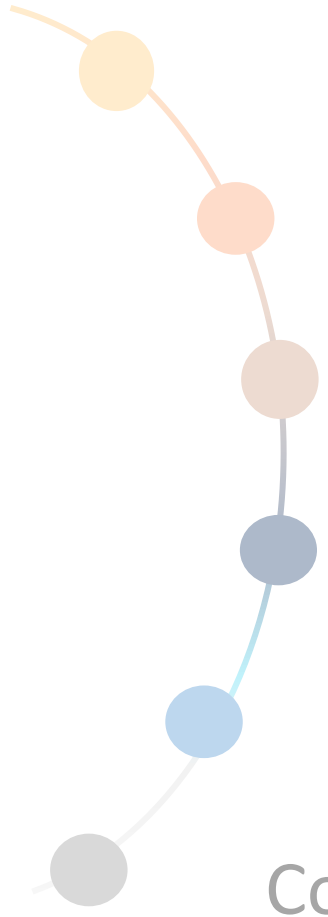
66% remission
15% response

Re-induction (5%)

No patient responded

Chaparro M, et al. Presented at ECCO, Stockholm, Sweden, 21st–24th February 2024. DOP74.

Outline



Background

Long-term outcomes

Real practice: ideal positioning

Real practice: ideal patient

Weakness points?

Conclusions

SACRO CUORE DON CALABRIA IRCCS

CD guidelines and AIFA

1A: Biologics vs. no treatment in biologic-naïve patients

Statement 1: For adults with moderate-to-severe CD refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, vedolizumab or ustekinumab to induce remission. (*Strong recommendation. Moderate-quality evidence for infliximab, adalimumab and vedolizumab; very low-quality evidence for ustekinumab. Agreement rate: 100%*)

TNFi first

Statement 4: For adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD recommends using adalimumab, vedolizumab or ustekinumab to induce remission. (*Strong recommendation. Moderate-quality evidence for adalimumab and vedolizumab, very low-quality evidence for ustekinumab. Agreement rate: 80%*)

UC guidelines and AIFA


Digestive and Liver Disease 54 (2022) 440–451

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Guidelines

Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology ☆

Fabio Salvatore Macaluso[a,c], Ambrogio Orlando[a], Claudio Papi[b], Stefano Festa[b], Daniela Pugliese[c], Stefanos Bonovas[d,e], Claudia Pansieri[d,e], Daniele Piovani[d,e], Gionata Fiorino[f], Massimo Claudio Fantini[g,h], Flavio Caprioli[i,j], Marco Daperno[k], Alessandro Armuzzi[l,j], Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

Statement 1: For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib over no treatment to induce remission. (*Strong recommendation; high-quality evidence for infliximab and adalimumab; moderate-quality evidence for vedolizumab and tofacitinib; low-quality evidence for golimumab and ustekinumab – Agreement rate: 100%*)

Statement 7: For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission. (*Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%*)

Free choice for first line therapy except for JAK-inhibitors (refundability)

Positioning Ustekinumab

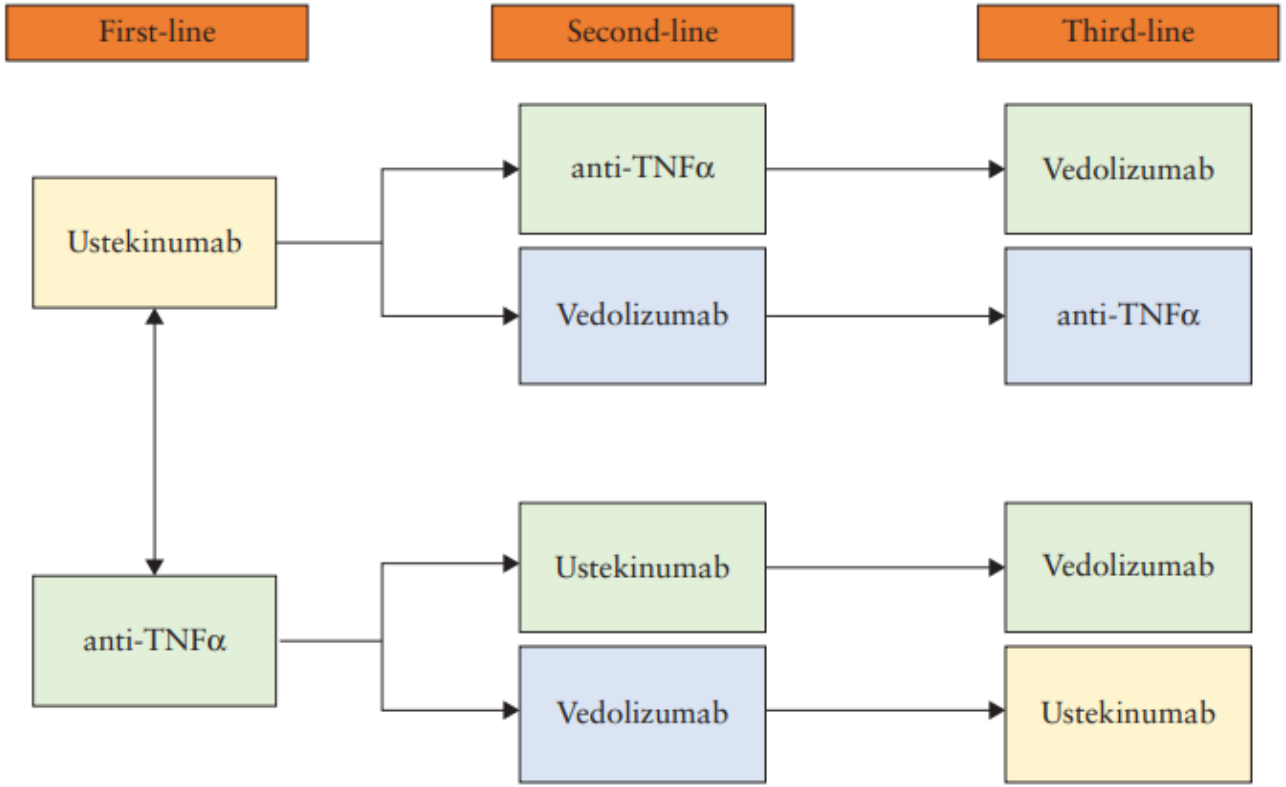
Journal of Crohn's and Colitis, 2022, **16**, ii30–ii41
https://doi.org/10.1093/ecco-jcc/jjac011
Supplement Article

Ustekinumab in Crohn's Disease: New Data for Positioning in Treatment Algorithm

Ferdinando D'Amico,[a,b] **Laurent Peyrin-Biroulet,**[c] **Silvio Danese**[b]

[a]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[b]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and Vita-Salute San Raffaele University, Milan, Italy
[c]Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France

Corresponding author: Prof. Silvio Danese, MD, PhD, Gastroenterology and Endoscopy IRCCS Ospedale San Raffaele and Vita-Salute San Raffaele University, Via Olgettina 60, Milan, Italy, Tel.: [+39] 0282244771; fax: [+39] 0282242591; email: sdanese@hotmail.com



Positioning Ustekinumab

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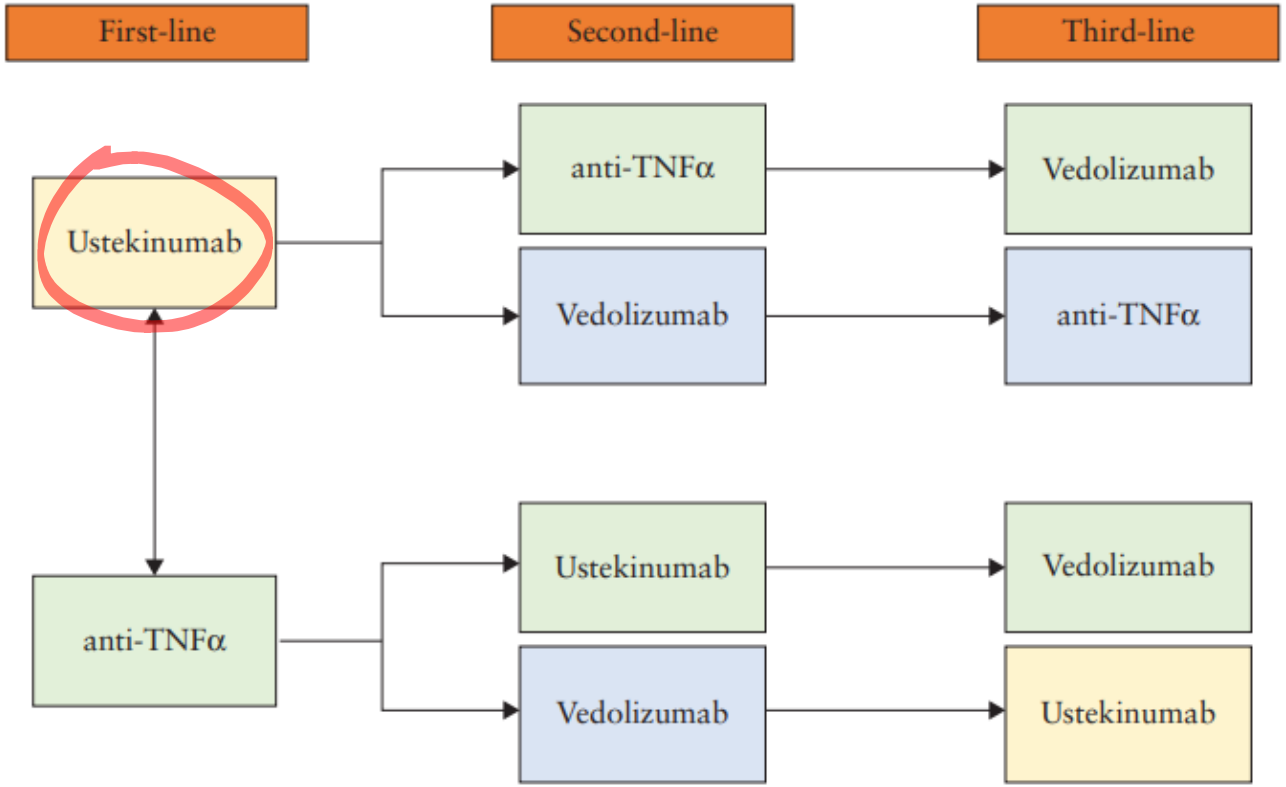
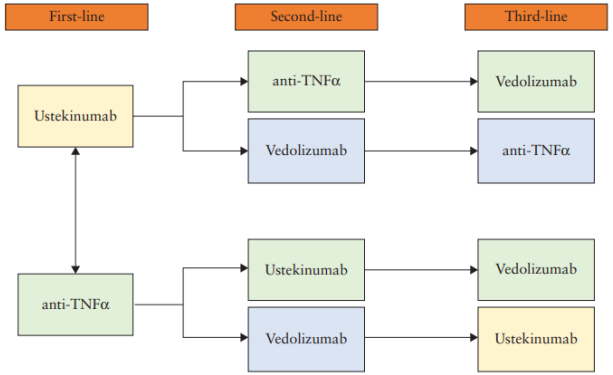


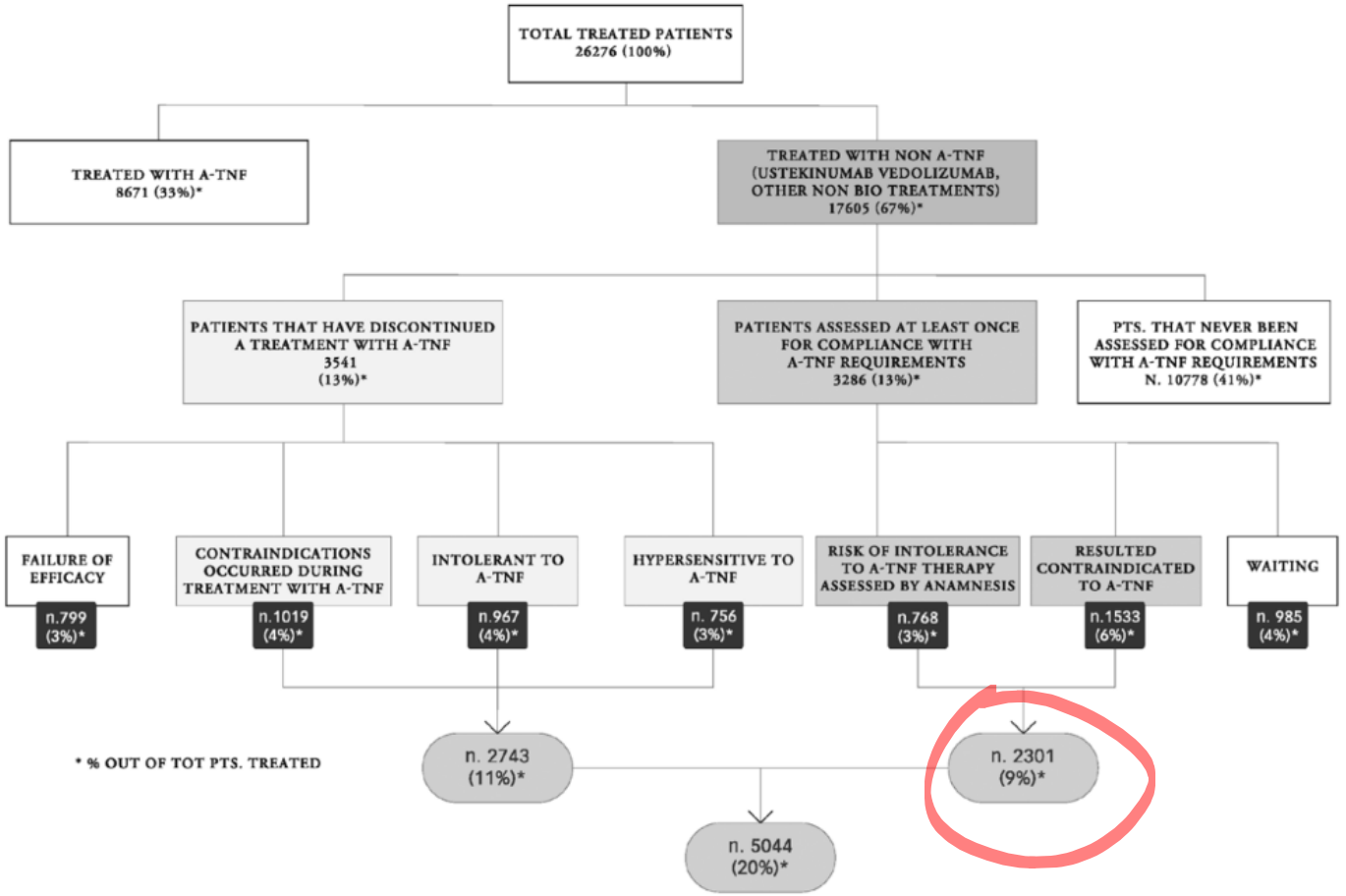
Positioning Ustekinumab



D'Amico et al, JCC 2022

Who are the patients with Crohn's disease unsuitable to receive an anti-TNFα therapy? Results from a survey of Italian physicians and literature review

Flavio Caprioli[a], Marco Daperno[b], Ivana Bravatà[c], Alessia Brigido[c], Daniela Frigerio[c], Ottavio Secchi[c] and Antonio Rispo[d]



Look at the patient contraindicated to anti-TNF!

Sequencing

Is there an optimal sequence of biologic therapies for inflammatory bowel disease?

Brian Bressler

Table 1. Clinical remission in UC with and without prior use of anti-TNF therapy.*

	Overall			TNF naive			TNF exposed		
	Drug	Placebo	Difference	Drug	Placebo	Difference	Drug	Placebo	Difference
Drugs that show lower clinical remission rates after anti-TNF therapy									
Adalimumab (ULTRA 2)	16.5%	9.3%	7.2	21.3%	11.0%	10.3	9.2%	6.9%	2.3
Vedolizumab (GEMINI 1)	16.9%	5.4%	11.5	23.1%	6.6%	16.5	9.8%	3.2%	6.5
Ozanimod (True North)	18.4%	6.0%	12.0	22.1%	6.6%	15.5	10%	4.6%	5.4
Drugs that show similar clinical remission rates before and after anti-TNF therapy									
Ustekinumab (UNIFI)	15.5%	5.3%	10.2	18.4%	9.9%	8.5	12.7%	1.2%	11.5
Tofacitinib (OCTAVE 1, OCTAVE 2)	18.5%, 16.6%	8.2%, 3.6%	10.3, 13.0	23.7%, 22.1%	12.5%, 8.5%	11.2, 13.5	12.3%, 12.0%	0.8%, 0.0%	11.5, 12.0
Upadacitinib (U-ACHIEVE, U-ACCOMPLISH)	16.0%, 33.0%	5.0%, 4.0%	21.0, 29.0	35.2%, 37.5%	9.2%, 5.9%	26.0, 31.6	29.6%, 17.9%	2.4%, 0.4%	27.2, 17.5

*Data shown are from independent trials with different trial designs. It is not possible to compare across trials. Difference represents absolute change in percentage points between drug and placebo.
TNF, tumor necrosis factor; UC, ulcerative colitis.

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Sequencing

Is there an optimal sequence of biologic therapies for inflammatory bowel disease?

Brian Bressler

Table 4. Potential sequence of biologic agents.

	UC (considering magnitude of benefit for clinical remission)		CD (considering magnitude of benefit for endoscopic remission/mucosal healing)	
	Anti-TNF naïve	**Anti-TNF exposed**	**Anti-TNF naïve**	**Anti-TNF exposed**
First line*	Vedolizumab, ozanimod, or ustekinumab	Ustekinumab, tofacitinib, or upadacitinib	Risankizumab, ustekinumab, vedolizumab	Risankizumab or ustekinumab
Second line*	Tofacitinib or upadacitinib			
Third line	Anti-TNF			

*No sequence is recommended within each category.
CD, Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

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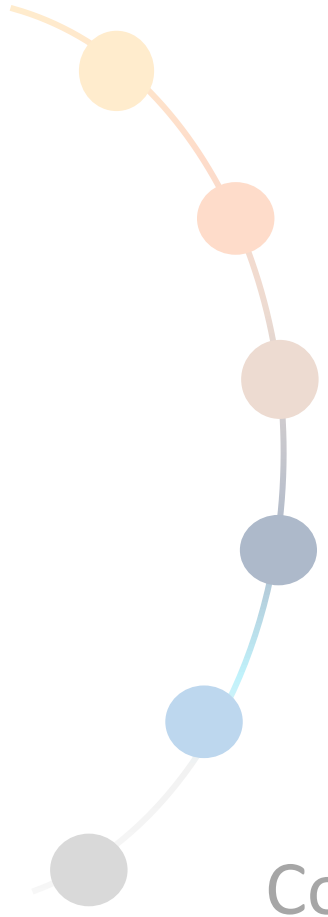
Outline



Background

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Real practice: ideal positioning

Real practice: ideal patient

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Ustekinumab: main features

	Anti-TNF	Anti-integrin	Ustekinumab	Risankizumab
Luminal CD	✓	✓	✓	
Patient profile	▪ EIM ▪ ≥ 2 IMIDs ▪ Children	▪ Serious infection ▪ Elderly	▪ EIM ▪ ≥ 2 IMIDs ▪ Anti-TNF-induced psoriaform lesions ▪ Children †	
Perianal fistulizing CD	Infliximab			
Postoperative prophylaxis ‡	✓			

Paediatric CD patients; only case series of ustekinumab use are available

Danese, JCC 2019

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Ustekinumab: EIMs

	Anti-TNF				Anti-integrins		JAK	IL-12/23
	IFX	ADA	CZP	Goli	VDZ	Natalizumab	Tofa	Ustekinumab
Arthritis								
SpA								
EN								
PG								
Uveitis								

Greuter et al. Gut 2021

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Ustekinumab: EIMs

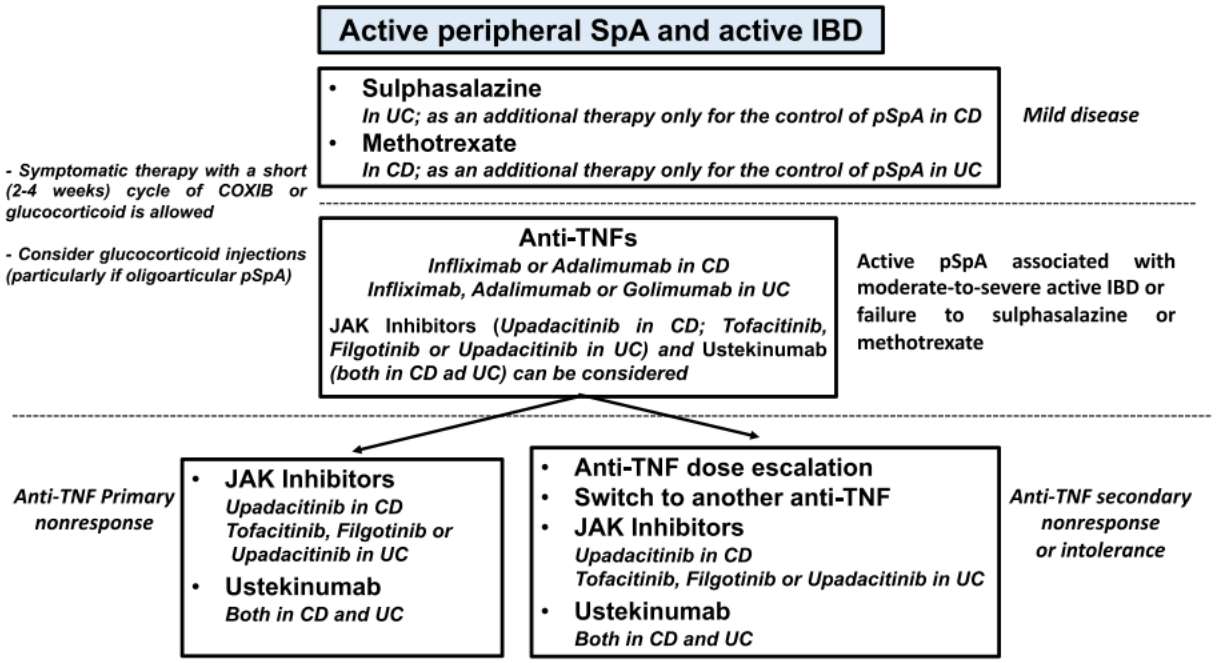

Fig. 3. Active peripheral SpA and active IBD: therapeutic algorithm.

Autoimmunity Reviews 23 (2024) 103533

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Review

The management of patients with inflammatory bowel disease-associated spondyloarthritis: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and Italian Society of Rheumatology (SIR) recommendations based on a pseudo-Delphi consensus

Fabio Salvatore Macaluso [a,*], Flavio Caprioli [b,c,*], Laura Benedan [d], Cristina Bezzio [e,f],

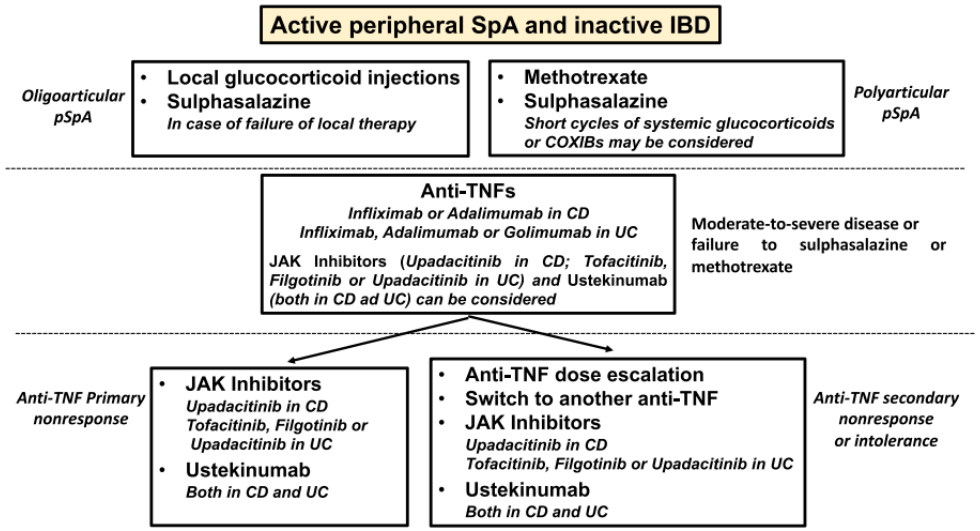

Fig. 4. Active peripheral SpA and IBD in remission: therapeutic algorithm.

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: EIMs

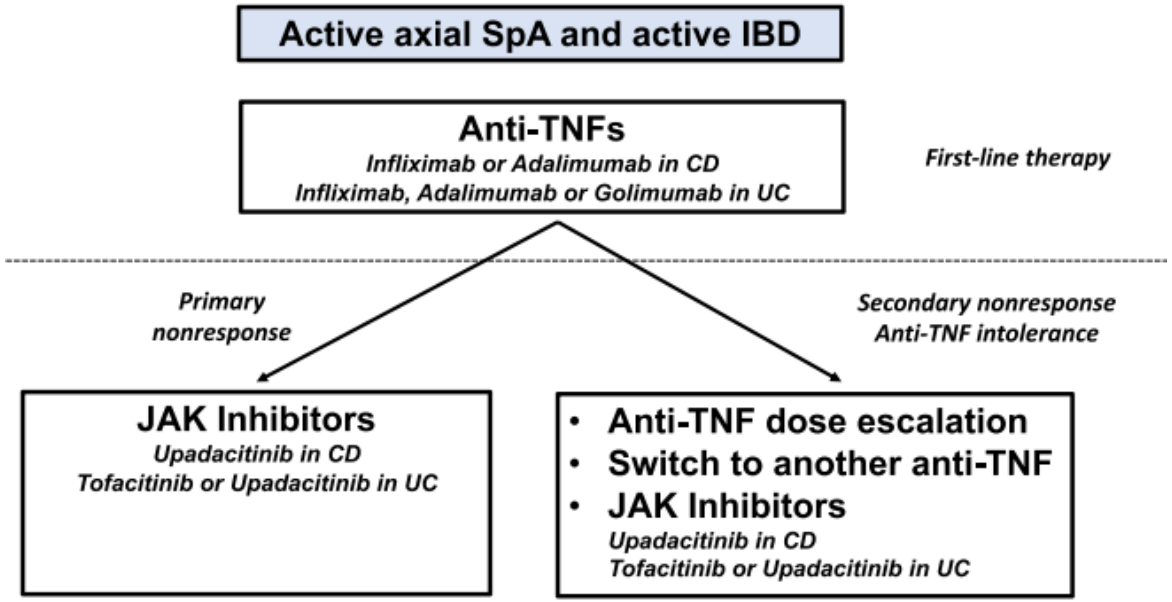

Fig. 1. Active axial SpA and active IBD: therapeutic algorithm.

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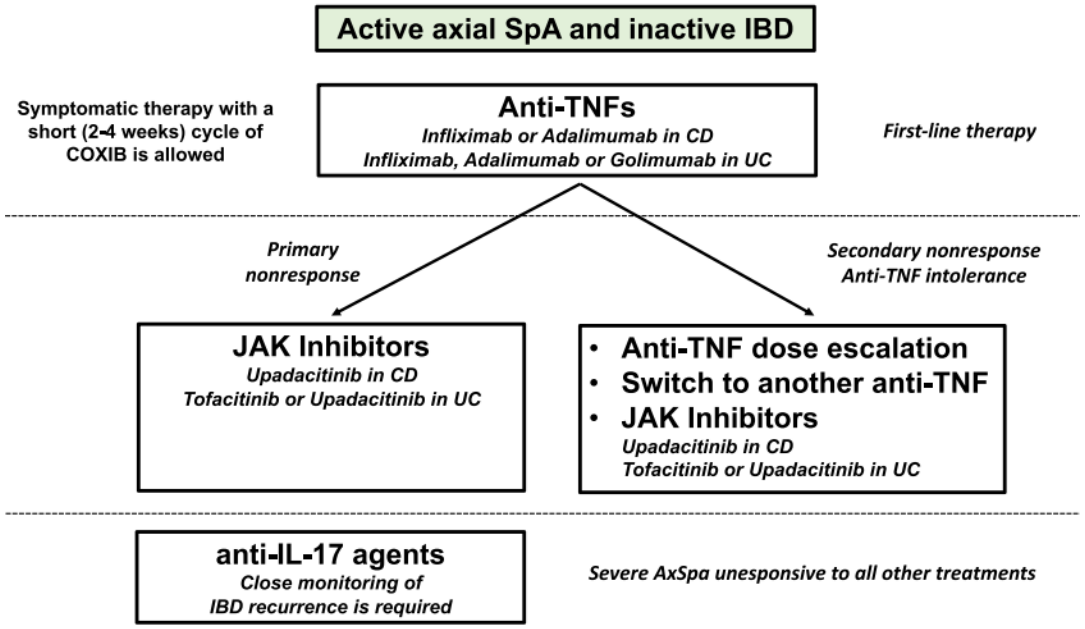

Fig. 2. Active axial SpA and IBD in remission: therapeutic algorithm.

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CA-IBD cohort study

Multi-center California-IBD cohort study

Ustekinumab vs. TNFα antagonists (1,030 patients)	Ustekinumab vs. Vedolizumab (442 patients)	Vedolizumab vs. TNFα antagonists (663 patients)
• **64% lower risk of serious infections** • No difference in risk of hospitalization or surgery	• **80% lower risk of serious infections** • No difference in risk of hospitalization or surgery	• No difference in risk of serious infections, hospitalization or surgery

Clinical Gastroenterology and Hepatology

Effectiveness: rate of hospitalization or surgery
Safety: risk of serious infections

Singh 2022, Clinical Gastroenterology and Hepatology

SACRO CUORE DON CALABRIA I R C C S

Ustekinumab: safety

Clinical Gastroenterology and Hepatology 2023;21:907–921

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Comparative Risk of Serious Infections With Biologic Agents and Oral Small Molecules in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

Virginia Solitano,[1,*] Antonio Facciorusso,[2,*] Tine Jess,[3,4] Christopher Ma,[5,6,7] Cesare Hassan,[1,8] Alessandro Repici,[1,8] Vipul Jairath,[7,9,10] Alessandro Armuzzi,[1,8] and Siddharth Singh[11,12]

Risk of serious infections with advanced therapies for IBD

Meta-analysis of 20 head-to-head studies

Ustekinumab vs. TNFα antagonists (5 cohorts; 23,232 patients)	**Vedolizumab vs. TNFα antagonists** (17 cohorts; 51,596 patients)	**Ustekinumab vs. vedolizumab** (5 cohorts; 1,420 patients)
• **CD**: **51% lower risk** of serious infections with ustekinumab • **UC**: Knowledge gap	• **CD**: **No difference** in risk of serious infections (OR, 1.03) • **UC**: **32% lower risk** of serious infections with vedolizumab	• **CD**: **60% lower risk** of serious infections with ustekinumab • **UC**: Knowledge gap

Safety profile of advanced therapies for IBD varies, and is influenced by treatment effectiveness and intrinsic immune suppression Clinical Gastroenterology and Hepatology

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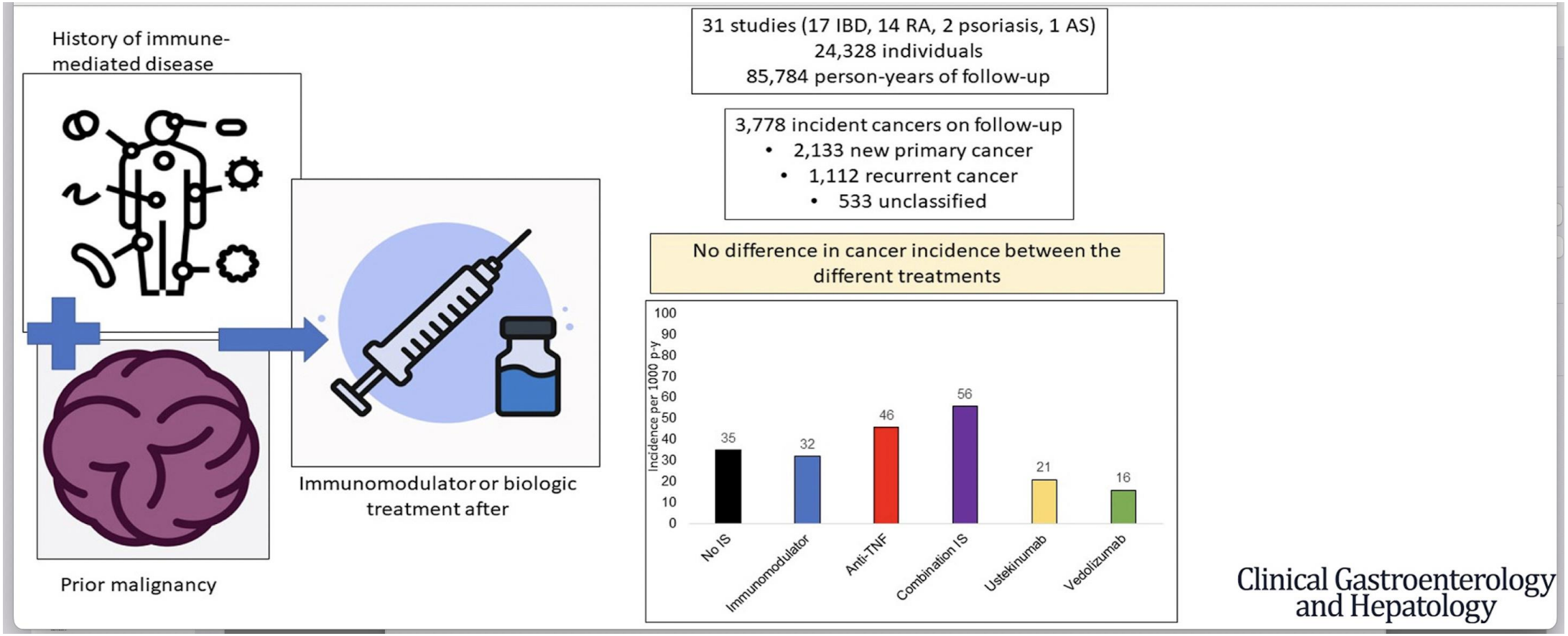
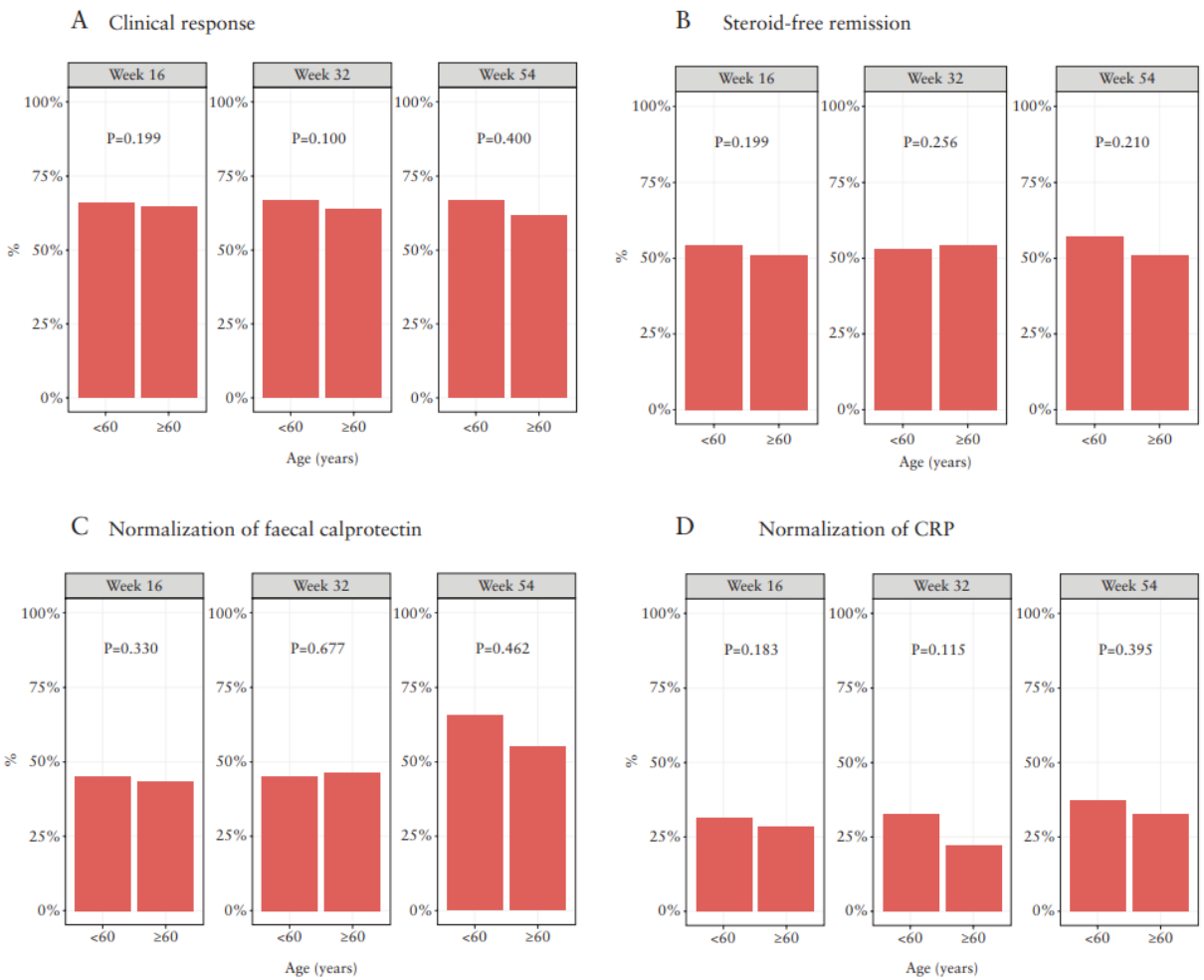
Ustekinumab: safety

RISK OF CANCER RECURRENCE IN PATIENTS WITH IMMUNE-MEDIATED DISEASES WITH USE OF IMMUNOSUPPRESSIVE THERAPIES: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS



Gupta A Clin Gastroenterol Hepatol, 2023

Ustekinumab: elderly



Variable	Non-elderly patients	Elderly patients	*p* value
Adverse events	49 [11.2%]	30 [14.2%]	0.35
Worsening extraintestinal manifestations	23 [5.28%]	10 [4.74%]	0.92
Worsening perianal disease	15 [3.44%]	2 [0.94%]	0.11
Severe infection	32 [7.34%]	15 [7.08%]	1.00
Development of neo-plasms	3 [0.69%]	9 [4.25%]	0.003

648 patients were included

Casas-Deza D, JCC 2023

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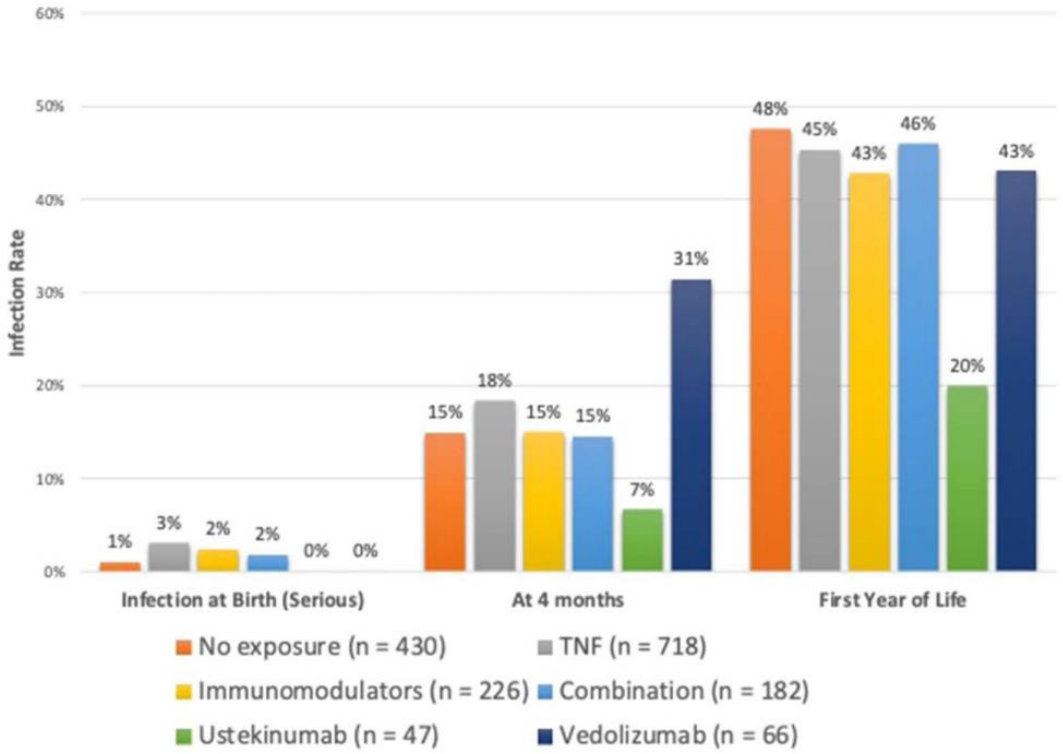
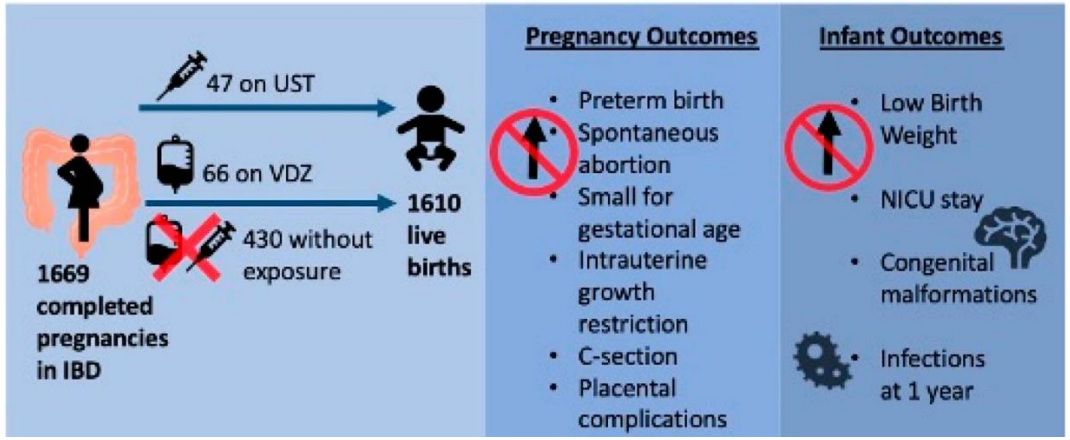
Ustekinumab: pregnancy

PIANO Study
Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes
Prospective, observational, multicenter USA study





"Continuation of UST and VDZ throughout pregnancy is recommended"

Abreu MT, JCC 2023

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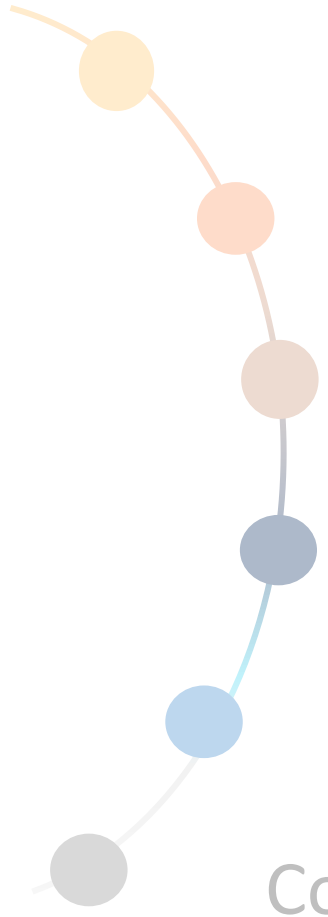
Outline



Background

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Real practice: ideal positioning

Real practice: ideal patient

Weakness points?

Conclusions

SACRO CUORE DON CALABRIA IRCCS

Ustekinumab: any weakness points?

Challenges

- Pediatric patients
- ~~Pregnancy and breastfeeding~~
- Strictures
- Perianal disease
- Operated patients
- Malignancies
- Cost-efficacy

D'Amico et al, JCC 2022

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Ustekinumab: any weakness points?

Challenges

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- ~~Pregnancy and breastfeeding~~
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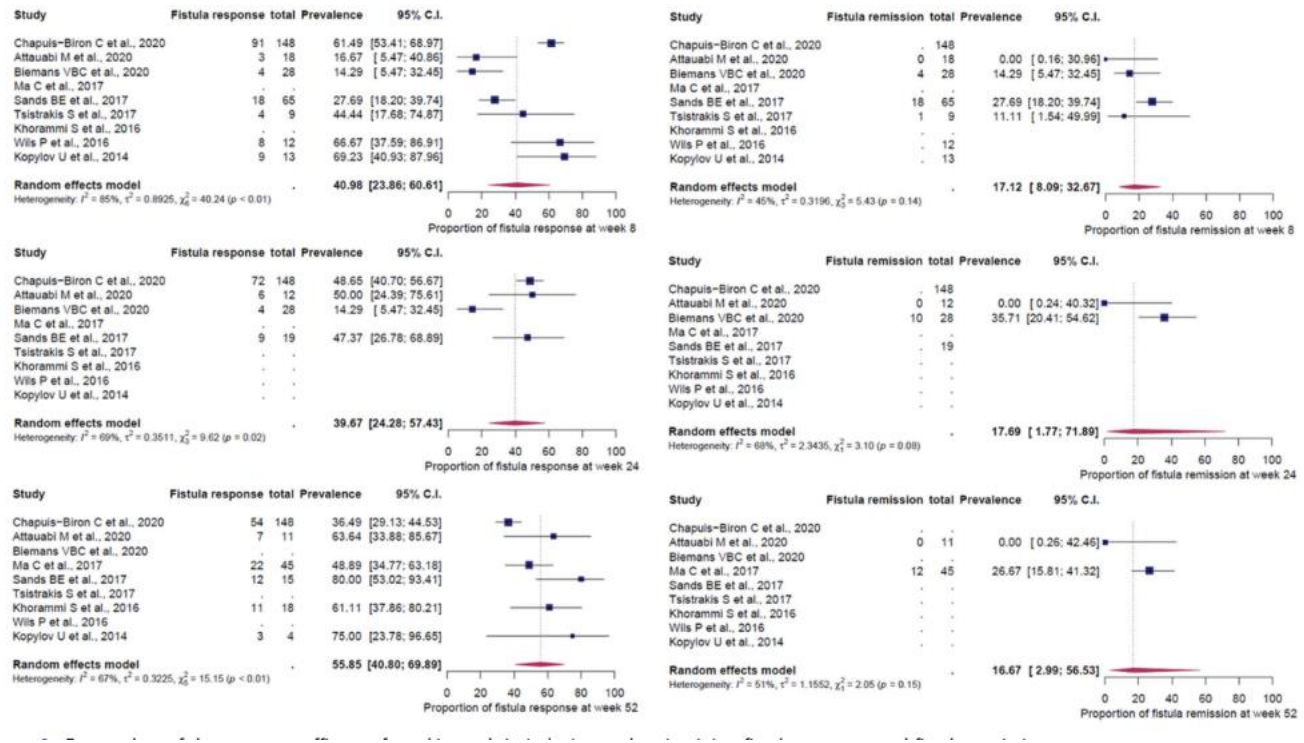
- ~~Perianal disease~~
- Operated patients
- Malignancies
- Cost-efficacy

D'Amico et al, JCC 2022

Efficacy of ustekinumab for active perianal fistulizing Crohn's disease: a systematic review and meta-analysis of the current literature

Mohamed Attauabi, Johan Burisch & Jakob Benedict Seidelin



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Ustekinumab: any weakness points?

Challenges

- Pediatric patients
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- Operated patients
- Malignancies
- Cost-efficacy

pouchitis

D'Amico et al, JCC 2022

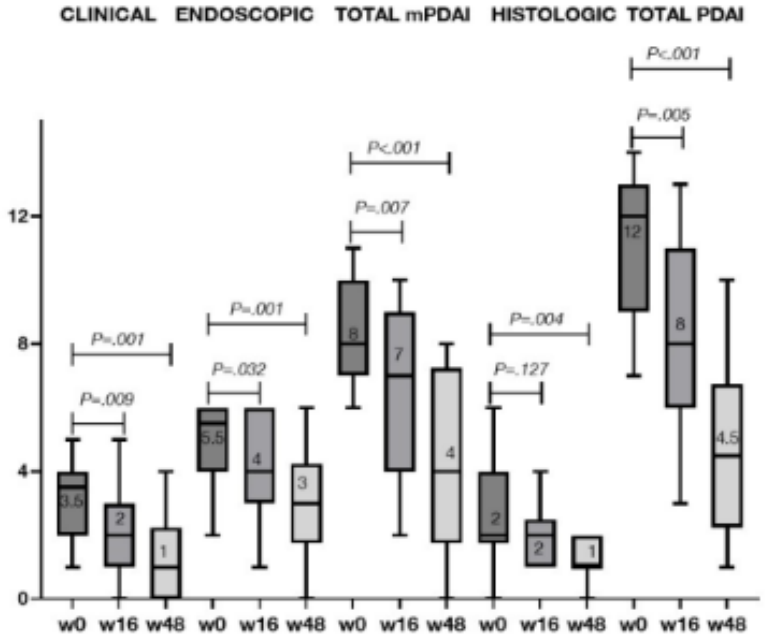

Table 1. Baseline disease characteristics (n=22)

Male, n (%)	13 (59)
Age at treatment initiation, years, median (IQR)	42.2 (32.2-52.3)
Time since colectomy, years, median (IQR)	8.2 (3.1-16.4)
Previous therapies prior to colectomy, n (%)	
Anti-TNF	15 (68.2)
Vedolizumab	5 (22.7)
Tofacitinib	3 (13.6)
Previous therapies for pouchitis, n (%)	
5-ASA (topical/systemic)	6 (27.3)
Steroids (topical/systemic)	17 (77.3)
Immunomodulators	8 (36.3)
Anti-TNF	9 (40.9)
Vedolizumab	7 (31.8)
Tofacitinib	1 (4.5)
Concomitant therapy during induction, n (%)	
Steroids (topical/systemic)	3 (13.6)
Immunomodulators	1 (4.5)

Ustekinumab showed a clinical and endoscopic effect in slightly more than half of the patients, remission in one third

Louis, Clinical Gastroenterology Hepatology 2024

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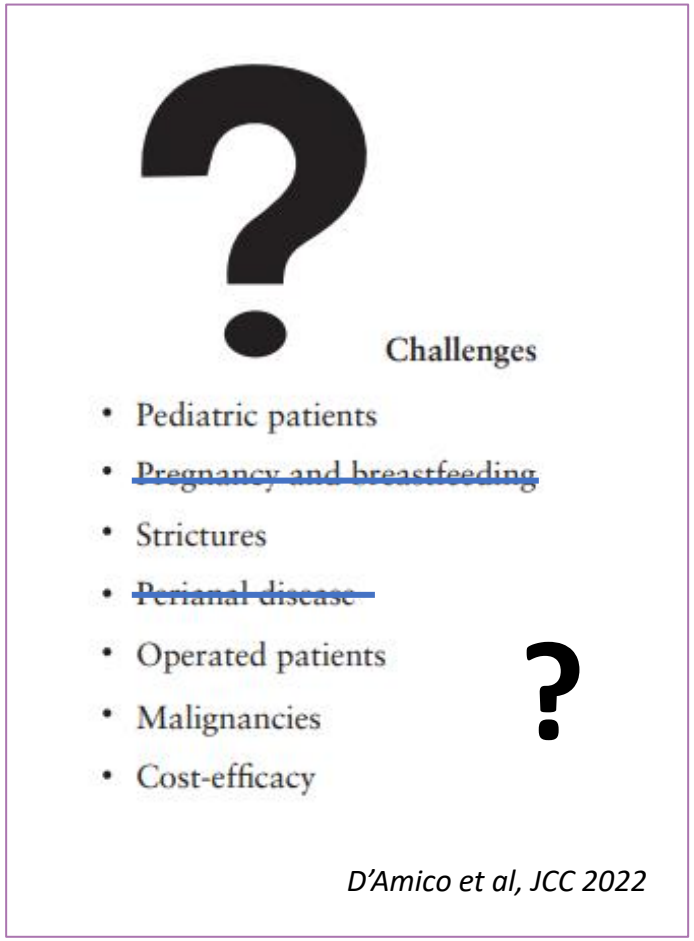
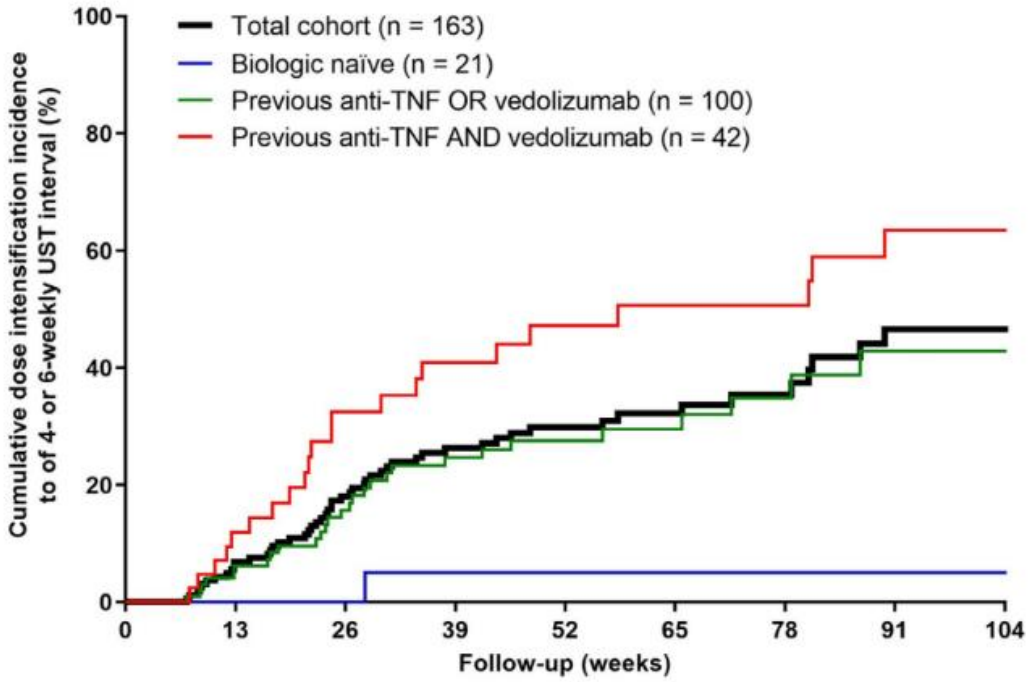
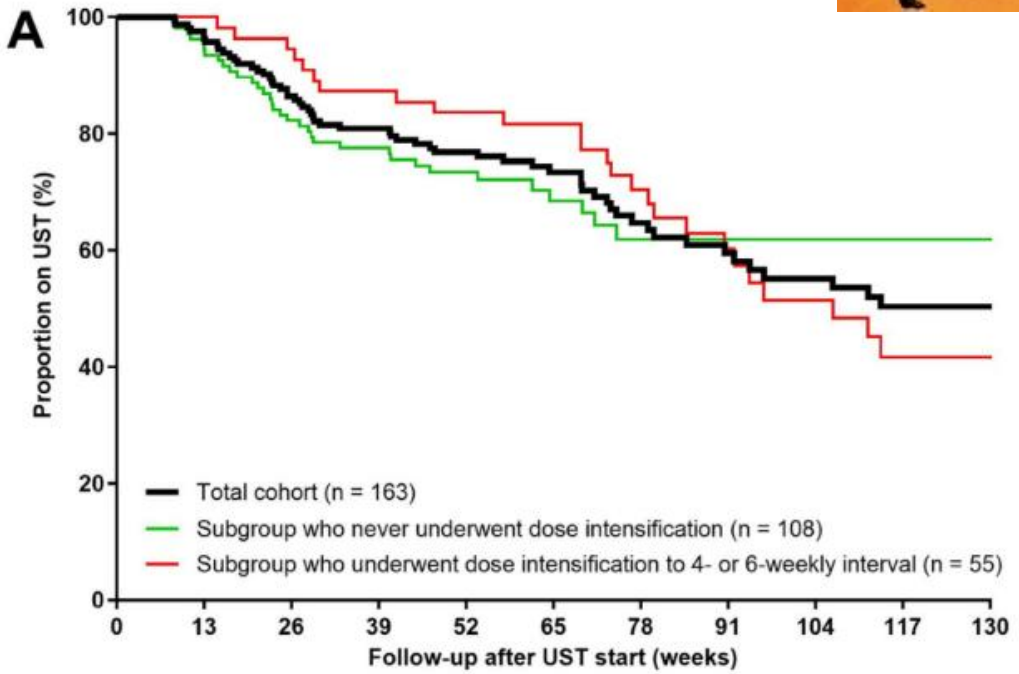
Ustekinumab: any weakness points?



D'Amico et al, JCC 2022

Optimization rate





Deriks, DLD 2023

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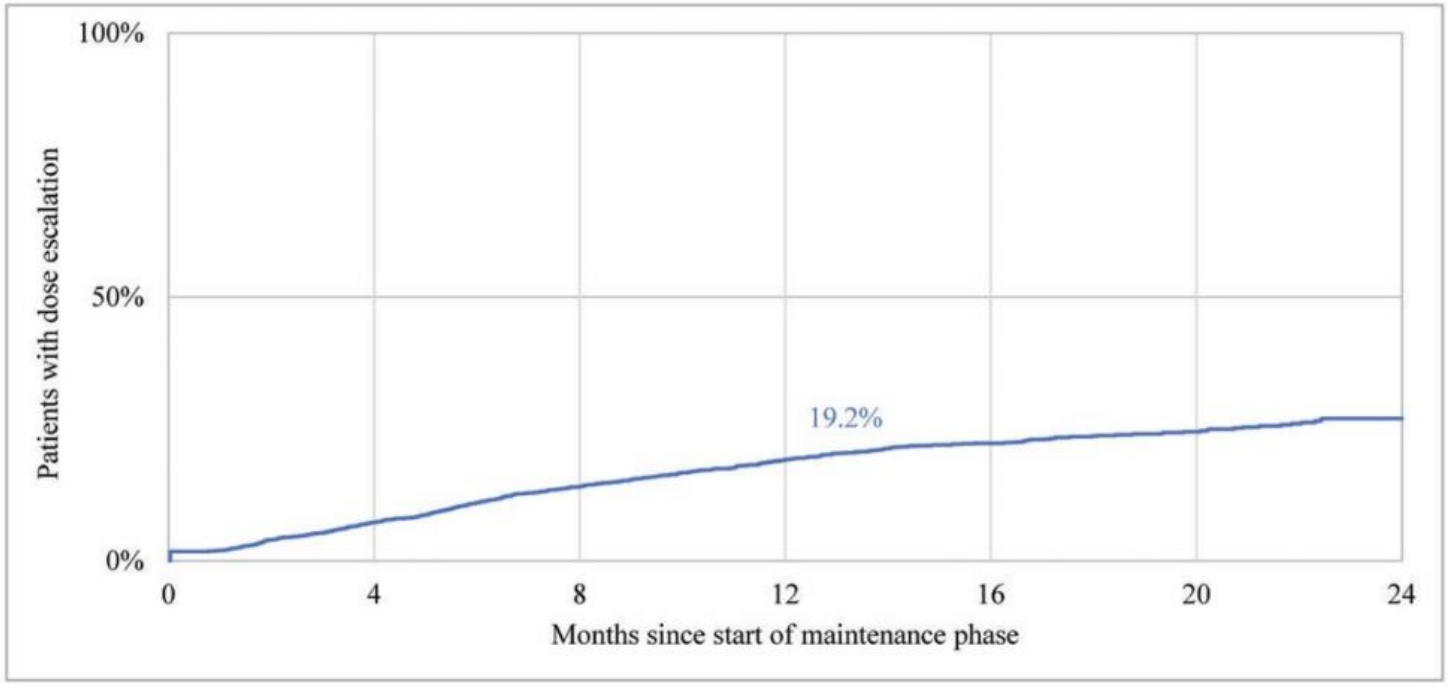
I R C C S

Optimization rate



Dose-escalation in one-fifth of patients (OFF label)

Zhdanava, Crohns and Colitis 2023

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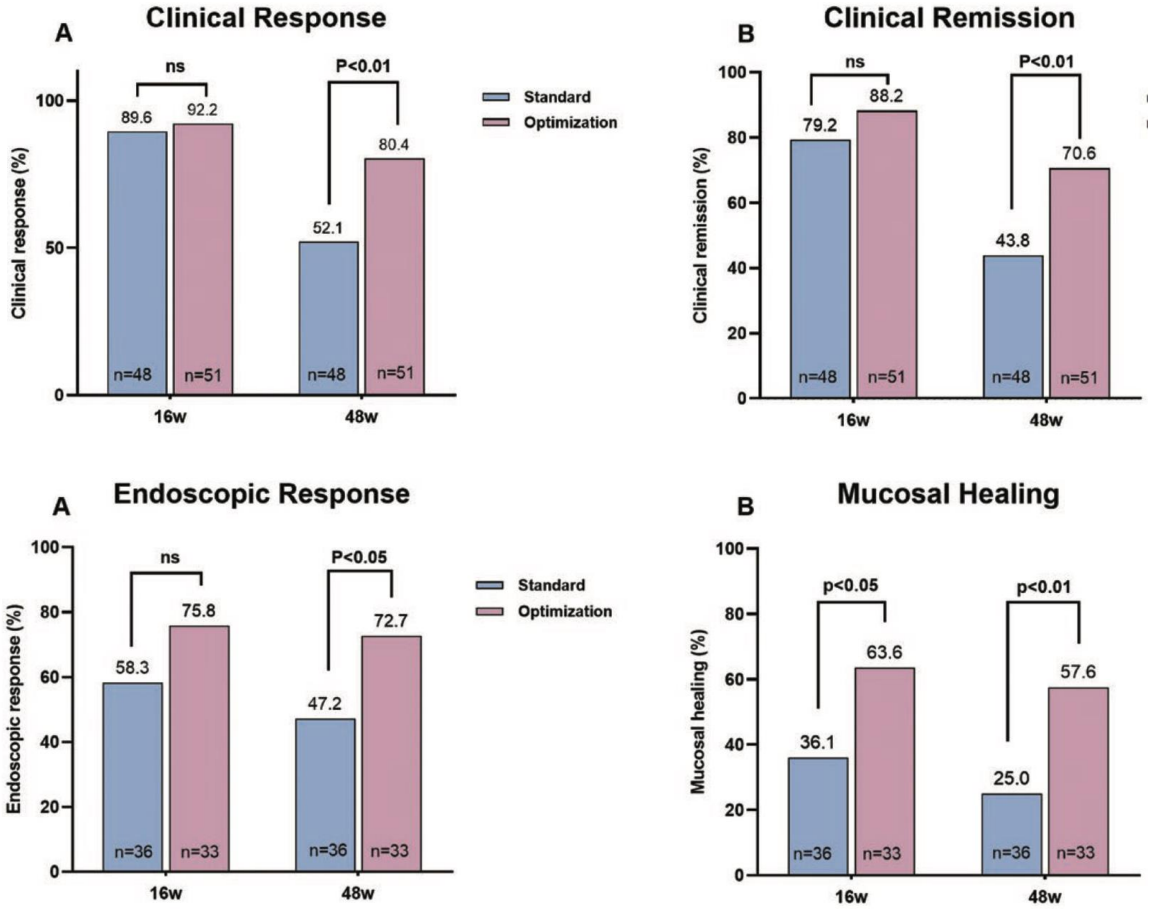
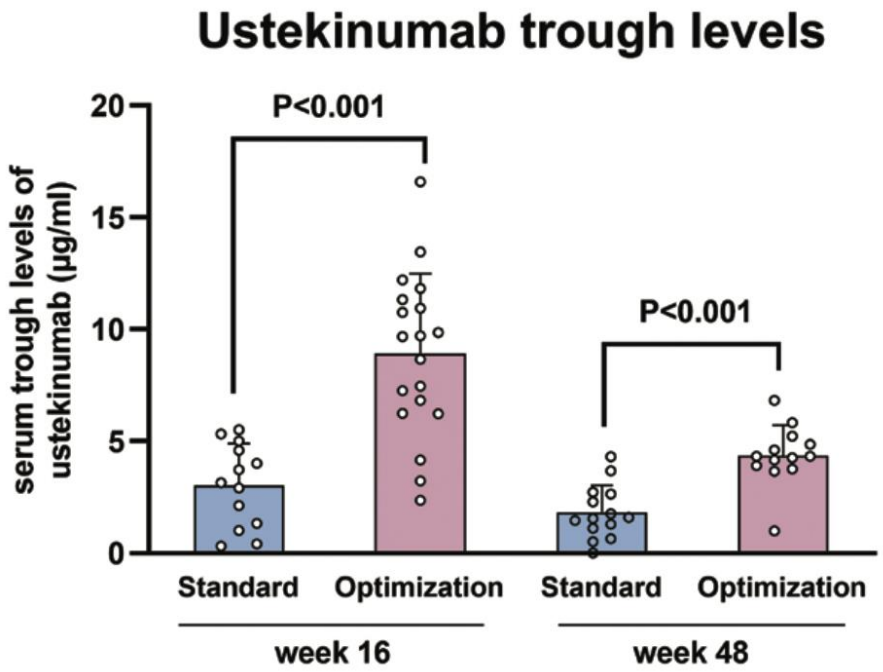
Optimization: strategy #1 (optimized induction)





A retrospective observational study
99 adult patients with severe CD
48 patients with standard and 51 with optimized induction treatment.

H Ren, IBD 2023

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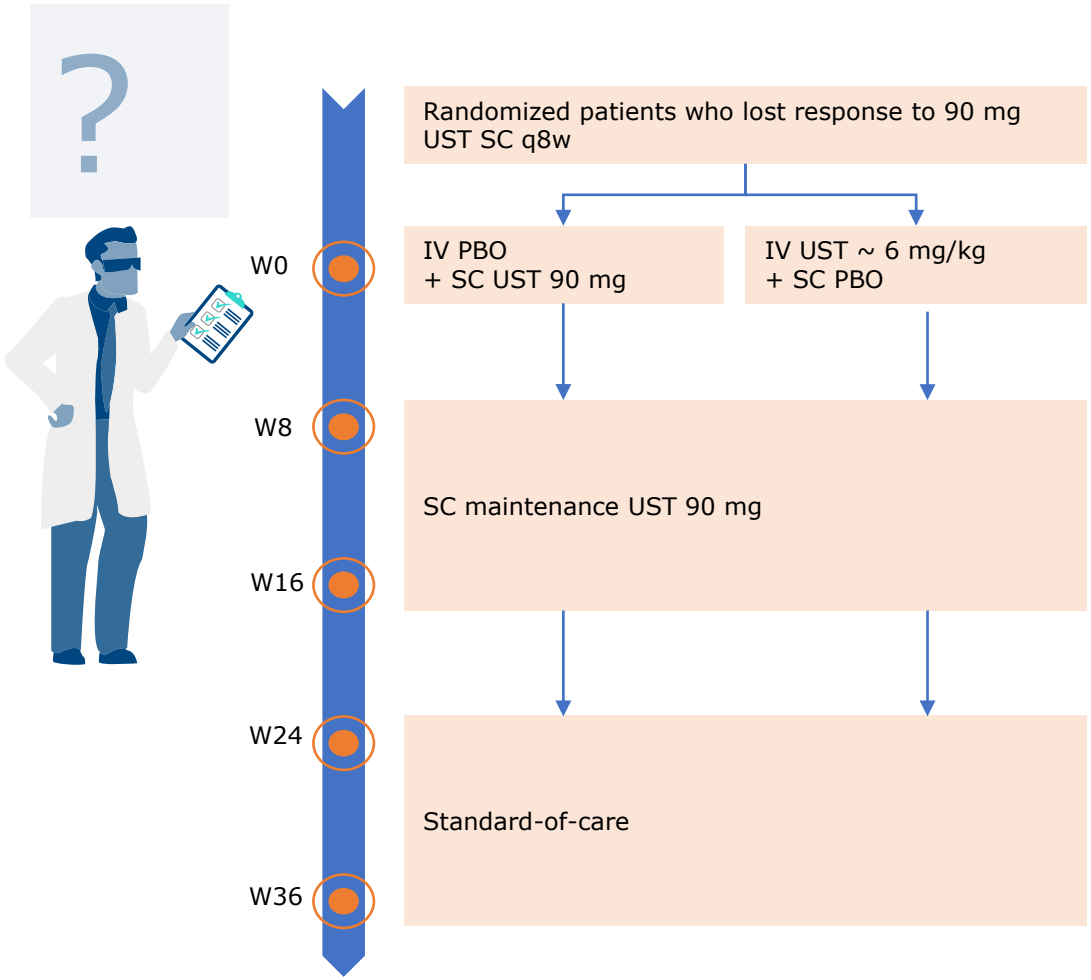
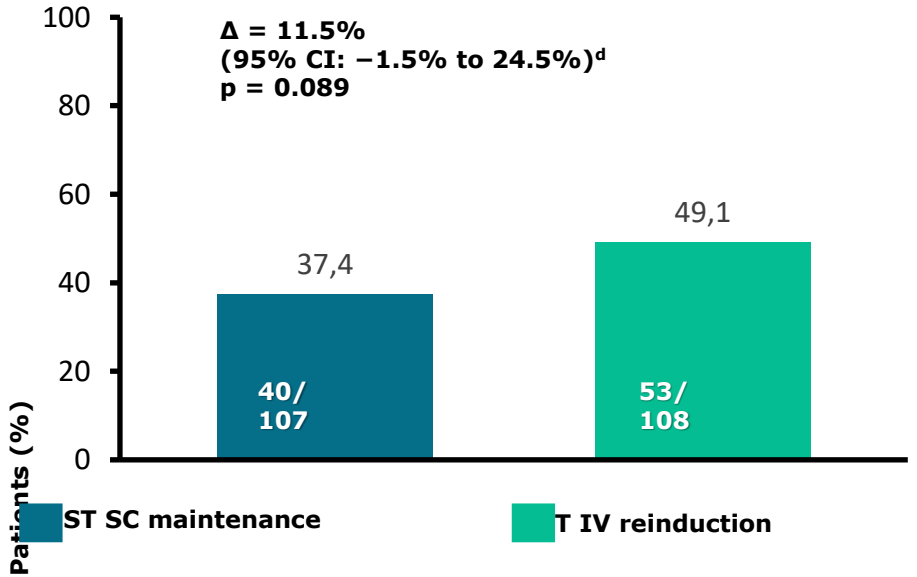
Optimization: strategy #2 (POWER STUDY)



Primary endpoint: clinical response



Schreiber S, et al. Poster presented at ECCO 2023; P436.

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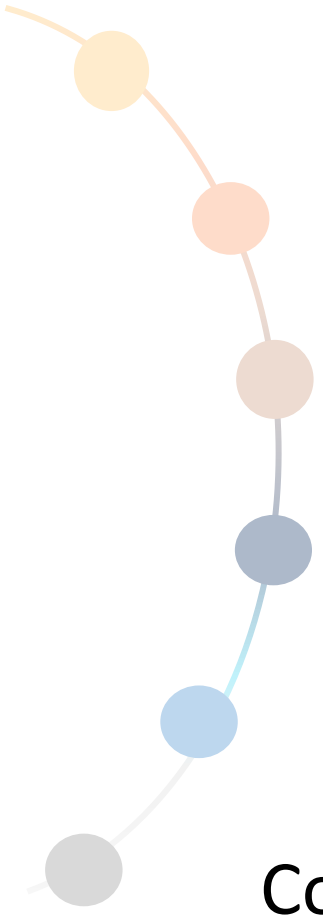
Outline



Background

Long-term outcomes

Real practice: ideal positioning

Real practice: ideal patient

Weakness points?

Conclusions

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- ✓ Efficacy and effectiveness with high persistence and durable remission
- ✓ Safety (even in special population)
- ✓ Evaluate EIMs
- ✓ Better in first lines
- ✓ In the future maybe pouchitis, POR, perianal disease
- ✓ In the future: potential role in dual therapy

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