Ustekinumab nella real life gastroenterologica

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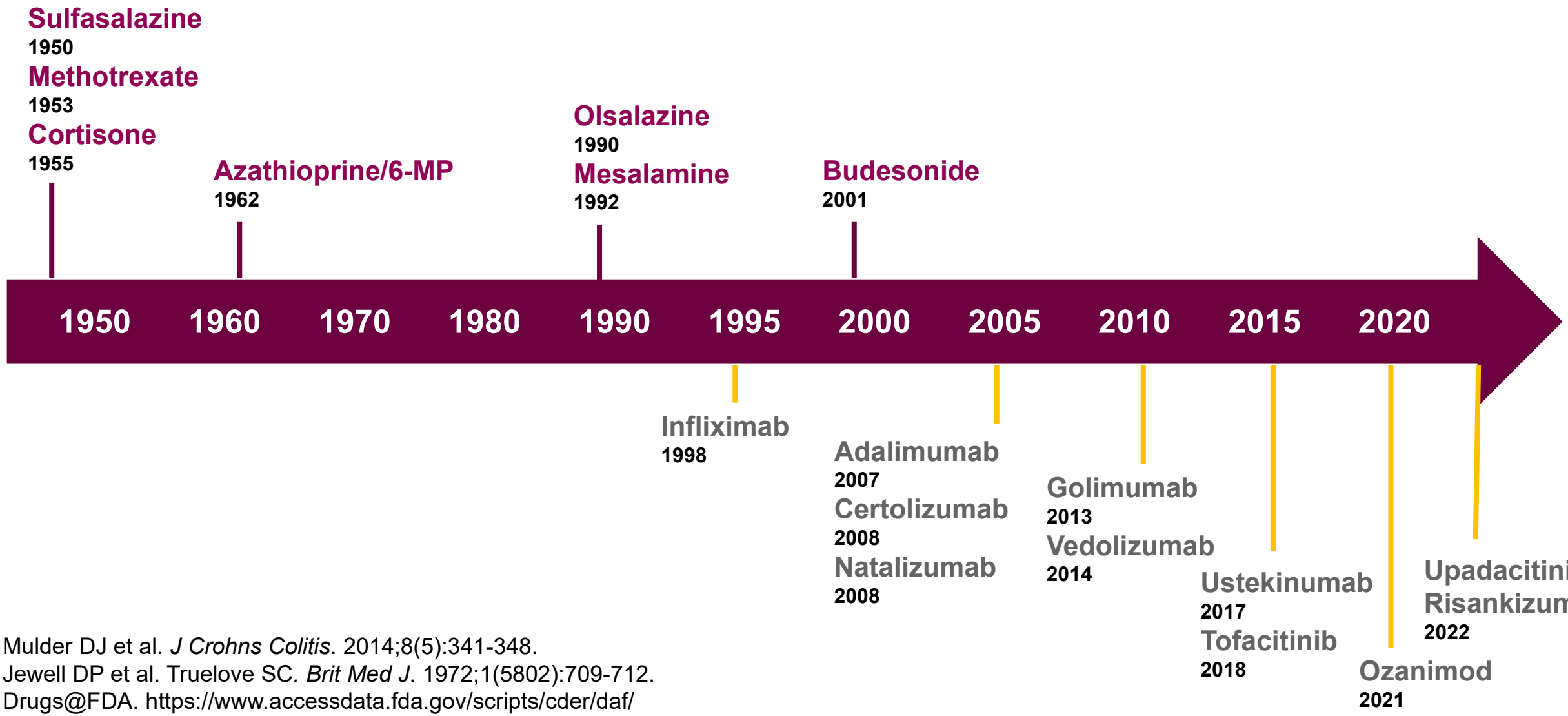
The evolution of treatment for IBD



Mulder DJ et al. *J Crohns Colitis*. 2014;8(5):341-348.
Jewell DP et al. Truelove SC. *Brit Med J*. 1972;1(5802):709-712.
Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/

Why anti TNF-α drugs are not enough?

1/3

Patients will not respond to induction therapy with anti-TNF inhibitors (primary nonresponse)[1,2]

≈50%

Patients who do respond may lose response within a few years[1,2]

Why?

Neutralizing anti-drug antibodies/low serum trough levels?

Other immune pathways are driving inflammation?

Immunogenicity:

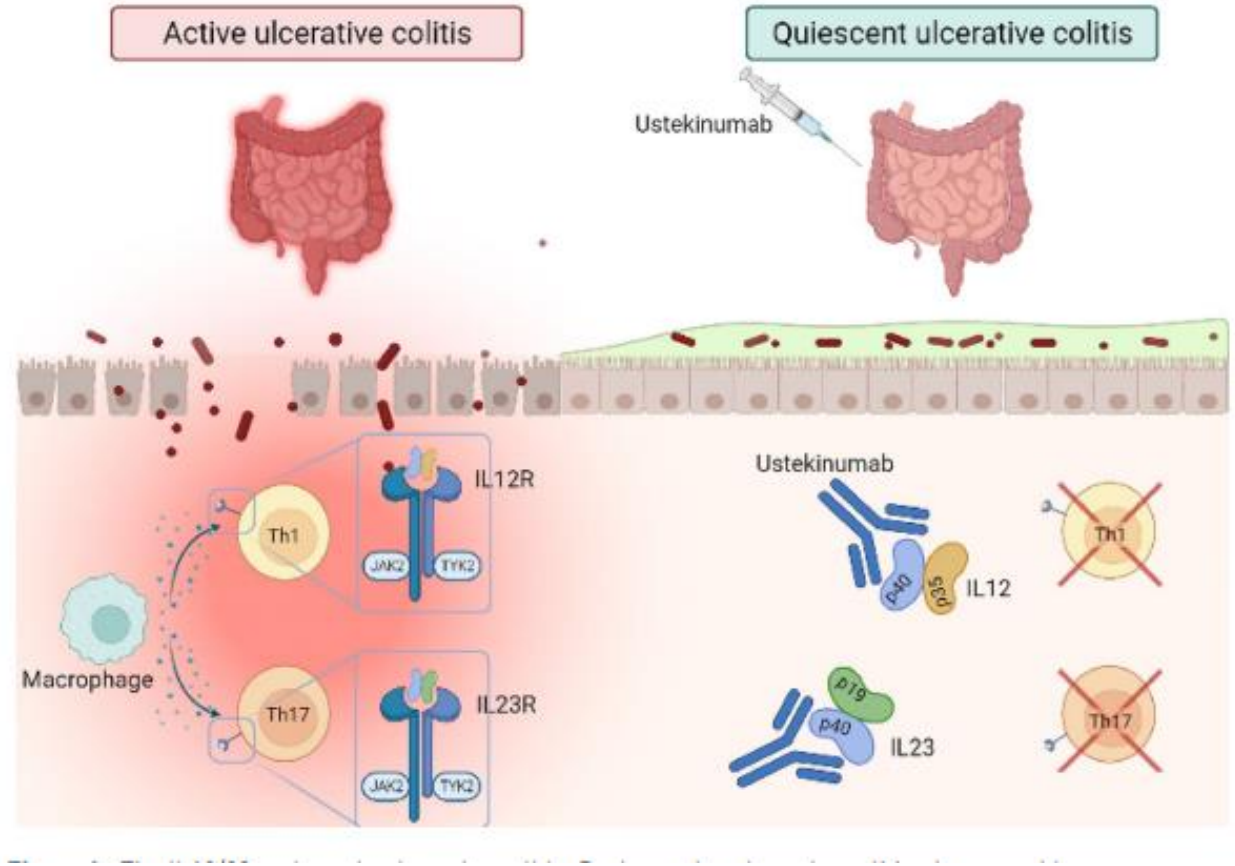
Vedolizumab 2.3%

Ustekinumab 0.77%

1. Cohen BL, Sachar DB, et al. *BMJ*. 2017;357:j25050; 2. Ford AC et al. *Am J Gastroenterol*. 2011;106:644-659.

- Patient factors:
  - Co-morbidities–e.g. cancer or cancer risk
  - Age
  - EIMs
  - Fistulas
  - Naïve patient versus previous biologic exposure
- Patient preference: IV, subc, oral
- Payers

Ustekinumab for IBD



- Ustekinumab is a fully human IgG1k monoclonal antibody that binds the p40 subunit of IL-12 & 23[1]
  - Prevents IL-12 and IL-23 from binding IL-12Rβ1
  - Inhibits IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production
- Approved for moderate to severe psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis[2,3]

Pugliese D, TAG 2022

1 Leung Y et al. *Gastroenterol Clin N Am*. 2014
2. Ustekinumab. Package insert. Janssen Biotech, Inc; 2016
3. Lichtenstewin GR et al. *Am J Gastroenterology*. 2018

The IBD population: clinical trial versus clinical practice

Retrospective study of patients with moderate-severe IBD at a US tertiary referral centre (n=206)

31% of patients were not eligible for participation in a clinical trial of biologic therapy*

Reasons for exclusion in CD

- **Strictures or abscesses** (62%)
- **Recent exposure or nonresponse to anti-TNF** (51%)
- **High-dose steroids** (18%)
- **Comorbidities** (26%)

Reasons for exclusion in UC

- **Current rectal therapy use** (57%)
- **Steroid and immunomodulator naïve** (45%)
- **Newly diagnosed** (17%)
- **Colectomy likely** (15%)

Non-eligible CD patients had a significantly lower response rate to biologics than eligible CD patients (60% vs 89%, *p*=0.03) **4–12 weeks after initial visit**

***Inclusion criteria based on those published for 9 trials of biologic therapy: ACCENT I, CLASSIC I, CHARM, PRECISE I, ENCORE, ENACT, SONIC, ACT 1, ACT 2**

Ha C, et al. Clin Gastroenterol Hepatol 2012

Clinical trial versus real-life studies

Control group
Pre-defined inclusion and exclusion criteria
RCT
Homogeneous follow-up
Validated clinical and endoscopic indices
Limited allowed concomitant medications

No control group
Small sample size
Unselected population
Retrospective design
Variability in follow-up intervals
Heterogeneity of measures
Free combination strategies

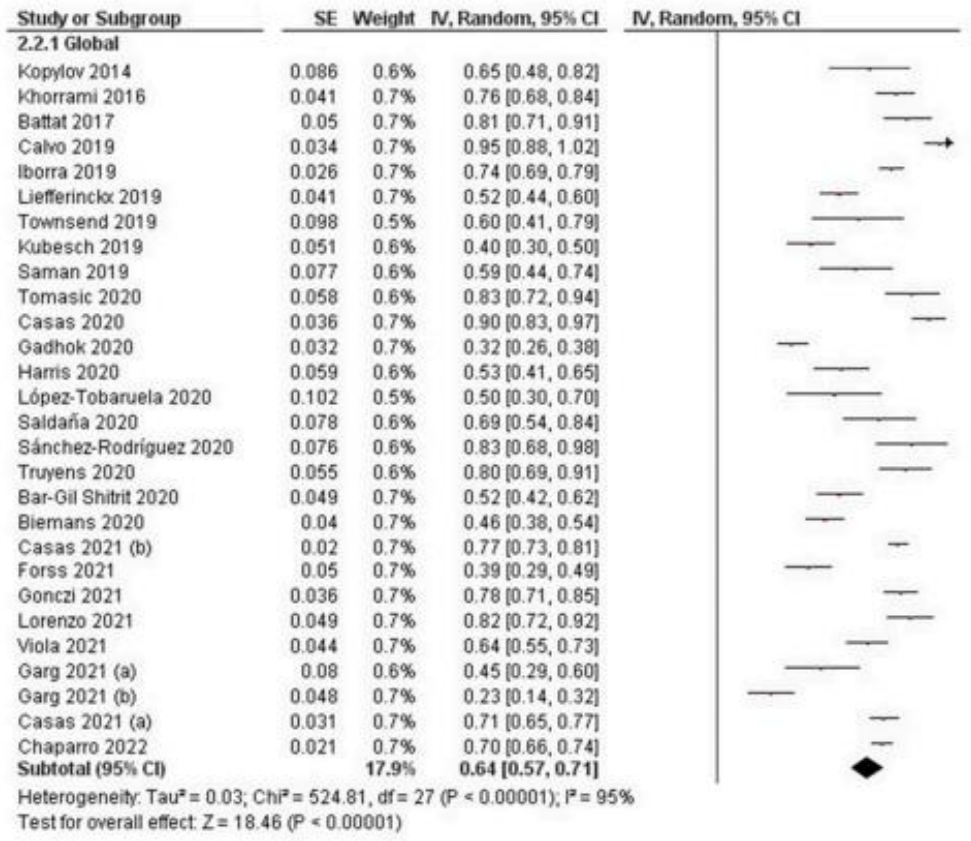
The PRO of RWE

- Wider range of population (disease severity, age, comorbidities)
- Combination therapies
- Exploration of «hard outcomes» in the long-term (surgery, bowel damage)
- Extrapolation from other indication
- Data on effectiveness on specific aspects (e.g. EIMs)
- Comparison between molecules (in absence of H2H trials)

- Large cohort (ideal number > 1000 pts across multiple sites)
- Propensity score matching

Real-World Evidence of the Effectiveness and Safety of Ustekinumab for the Treatment of Crohn's Disease: Systematic Review and Meta-Analysis of Observational Studies (63)

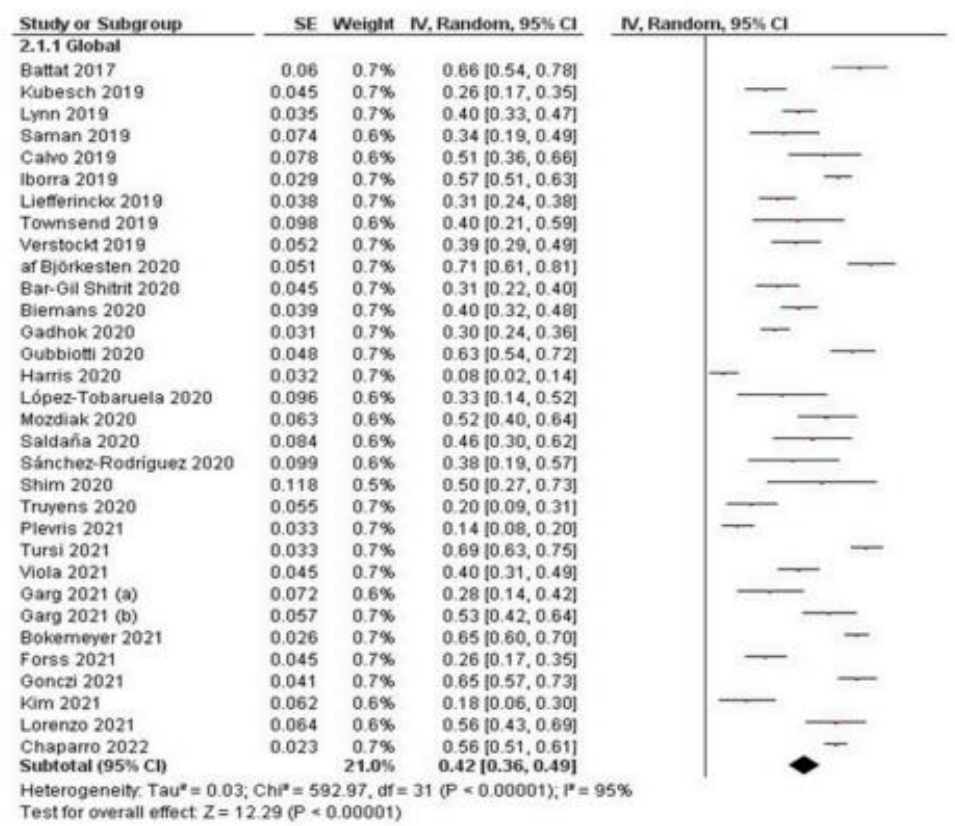
Short term clinical response (8-14w)



Study or Subgroup	SE	Weight	IV, Random, 95% CI
2.2.1 Global			
Kopylov 2014	0.086	0.6%	0.65 [0.48, 0.82]
Khorrami 2016	0.041	0.7%	0.76 [0.68, 0.84]
Battat 2017	0.05	0.7%	0.81 [0.71, 0.91]
Calvo 2019	0.034	0.7%	0.95 [0.88, 1.02]
Iborra 2019	0.026	0.7%	0.74 [0.69, 0.79]
Liefferinckx 2019	0.041	0.7%	0.52 [0.44, 0.60]
Townsend 2019	0.098	0.5%	0.60 [0.41, 0.79]
Kubesch 2019	0.051	0.6%	0.40 [0.30, 0.50]
Saman 2019	0.077	0.6%	0.59 [0.44, 0.74]
Tomasic 2020	0.058	0.6%	0.83 [0.72, 0.94]
Casas 2020	0.036	0.7%	0.90 [0.83, 0.97]
Gadhok 2020	0.032	0.7%	0.32 [0.26, 0.38]
Harris 2020	0.059	0.6%	0.53 [0.41, 0.65]
López-Tobaruela 2020	0.102	0.5%	0.50 [0.30, 0.70]
Saldaña 2020	0.078	0.6%	0.69 [0.54, 0.84]
Sánchez-Rodríguez 2020	0.076	0.6%	0.83 [0.68, 0.98]
Truyens 2020	0.055	0.6%	0.80 [0.69, 0.91]
Bar-Gil Shitrit 2020	0.049	0.7%	0.52 [0.42, 0.62]
Biemans 2020	0.04	0.7%	0.46 [0.38, 0.54]
Casas 2021 (b)	0.02	0.7%	0.77 [0.73, 0.81]
Forss 2021	0.05	0.7%	0.39 [0.29, 0.49]
Gonczi 2021	0.036	0.7%	0.78 [0.71, 0.85]
Lorenzo 2021	0.049	0.7%	0.82 [0.72, 0.92]
Viola 2021	0.044	0.7%	0.64 [0.55, 0.73]
Garg 2021 (a)	0.08	0.6%	0.45 [0.29, 0.60]
Garg 2021 (b)	0.048	0.7%	0.23 [0.14, 0.32]
Casas 2021 (a)	0.031	0.7%	0.71 [0.65, 0.77]
Chaparro 2022	0.021	0.7%	0.70 [0.66, 0.74]
Subtotal (95% CI)		**17.9%**	**0.64 [0.57, 0.71]**

Heterogeneity: Tau² = 0.03; Chi² = 524.81, df = 27 (P < 0.00001); I² = 95%
Test for overall effect: Z = 18.46 (P < 0.00001)

Longterm clinical remission (48-52w)



Study or Subgroup	SE	Weight	IV, Random, 95% CI
2.1.1 Global			
Battat 2017	0.06	0.7%	0.66 [0.54, 0.78]
Kubesch 2019	0.045	0.7%	0.26 [0.17, 0.35]
Lynn 2019	0.035	0.7%	0.40 [0.33, 0.47]
Saman 2019	0.074	0.6%	0.34 [0.19, 0.49]
Calvo 2019	0.078	0.6%	0.51 [0.36, 0.66]
Iborra 2019	0.029	0.7%	0.57 [0.51, 0.63]
Liefferinckx 2019	0.038	0.7%	0.31 [0.24, 0.38]
Townsend 2019	0.098	0.6%	0.40 [0.21, 0.59]
Verstockt 2019	0.052	0.7%	0.39 [0.29, 0.49]
af Björkesten 2020	0.051	0.7%	0.71 [0.61, 0.81]
Bar-Gil Shitrit 2020	0.045	0.7%	0.31 [0.22, 0.40]
Biemans 2020	0.039	0.7%	0.40 [0.32, 0.48]
Gadhok 2020	0.031	0.7%	0.30 [0.24, 0.36]
Gubbiotti 2020	0.048	0.7%	0.63 [0.54, 0.72]
Harris 2020	0.032	0.7%	0.08 [0.02, 0.14]
López-Tobaruela 2020	0.096	0.6%	0.33 [0.14, 0.52]
Mozdiak 2020	0.063	0.6%	0.52 [0.40, 0.64]
Saldaña 2020	0.084	0.6%	0.46 [0.30, 0.62]
Sánchez-Rodríguez 2020	0.099	0.6%	0.38 [0.19, 0.57]
Shim 2020	0.118	0.5%	0.50 [0.27, 0.73]
Truyens 2020	0.055	0.7%	0.20 [0.09, 0.31]
Plevris 2021	0.033	0.7%	0.14 [0.08, 0.20]
Tursi 2021	0.033	0.7%	0.69 [0.63, 0.75]
Viola 2021	0.045	0.7%	0.40 [0.31, 0.49]
Garg 2021 (a)	0.072	0.6%	0.28 [0.14, 0.42]
Garg 2021 (b)	0.057	0.7%	0.53 [0.42, 0.64]
Bokemeyer 2021	0.026	0.7%	0.65 [0.60, 0.70]
Forss 2021	0.045	0.7%	0.26 [0.17, 0.35]
Gonczi 2021	0.041	0.7%	0.65 [0.57, 0.73]
Kim 2021	0.062	0.6%	0.18 [0.06, 0.30]
Lorenzo 2021	0.064	0.6%	0.56 [0.43, 0.69]
Chaparro 2022	0.023	0.7%	0.56 [0.51, 0.61]
Subtotal (95% CI)		**21.0%**	**0.42 [0.36, 0.49]**

Heterogeneity: Tau² = 0.03; Chi² = 592.97, df = 31 (P < 0.00001); I² = 95%
Test for overall effect: Z = 12.29 (P < 0.00001)

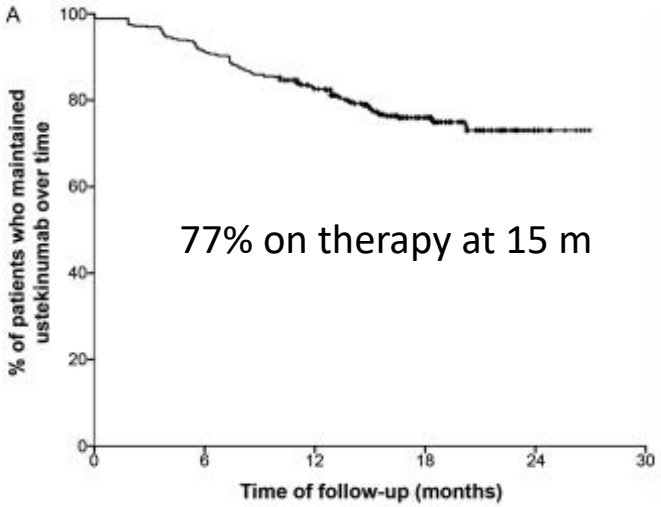
Longterm endoscopic remission: 33% (25–40%)
18% loss of response

Nearly one-third of the patients needed dose optimisation, with benefit in 59% of them

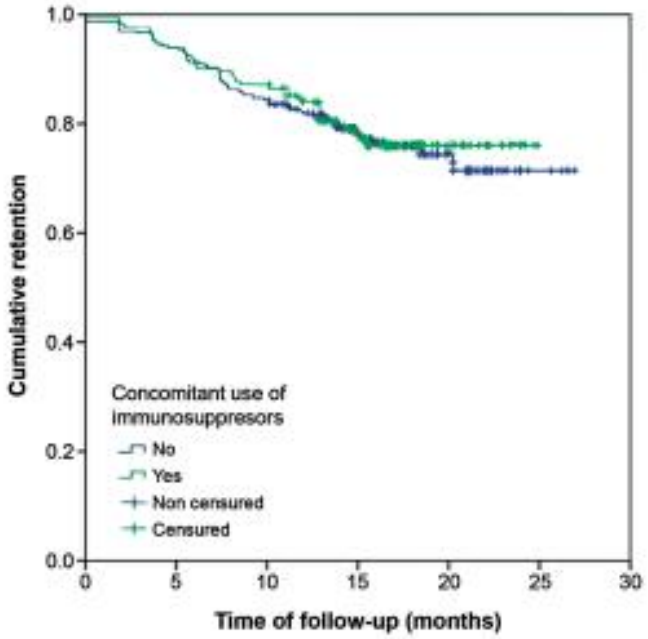
Rubín de Célix C, JCM 22

Demographics	463
Age, y	47.1 ± 13.4
Age at diagnosis, y	33.4 ± 14.5
Female	232 (50.1)
Smokers	118 (25.5)
Comorbidities	230 (49.7)
Disease characteristics at baseline	
Disease duration, y	14.1 ± 9
Time from diagnosis to UST initiation, y	12.6 ± 9
Age at UST initiation, y	45.6 ± 13.4
Extraintestinal manifestations	181 (39.1)
CD location	
Ileocolonic	218 (47.1)
Ileal	190 (41)
Colonic	55 (11.9)
Upper gastrointestinal tract	37 (8)
CD behavior	
Inflammatory	245 (52.9)
Stricturing	132 (28.5)
Penetrating	86 (18.6)
Active perianal disease	65 (14.0)
Harvey-Bradshaw Index score	8.4 ± 3.5
Prior use of biologics for CD treatment	447 (96.5)
Previous anti-TNF	
Adalimumab[a]	374 (83.7)
Infliximab[a]	348 (77.9)
Previous vedolizumab[a]	109 (24.4)
Previous surgery for CD[b]	281 (60.7)
Abdominal	218 (47.1)
Perianal	106 (22.9)
≥1 concomitant immunosuppressant	163 (35.2)
Azathioprine	106 (65)
Methotrexate	47 (28.8)
Mercaptopurine	13 (8)
Number of biologics for CD treatment	
1	138 (30.9)
2	168 (37.6)
≥3	141 (31.5)

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



77% on therapy at 15 m



The IR of ustekinumab discontinuation: 18% per patient-year of follow-up.

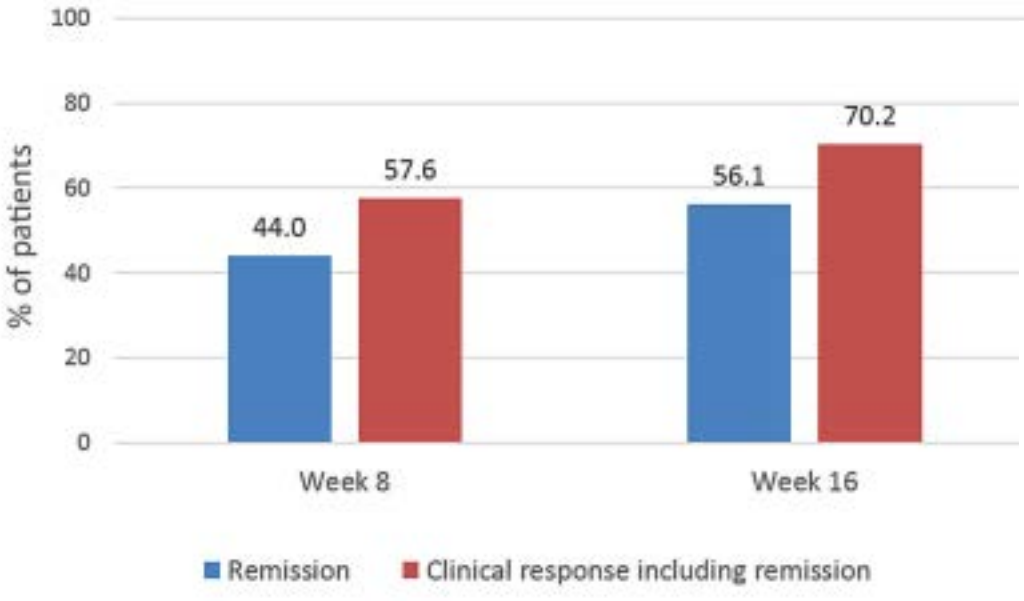
Table 3. Multivariate analysis of factors associated with ustekinumab discontinuation

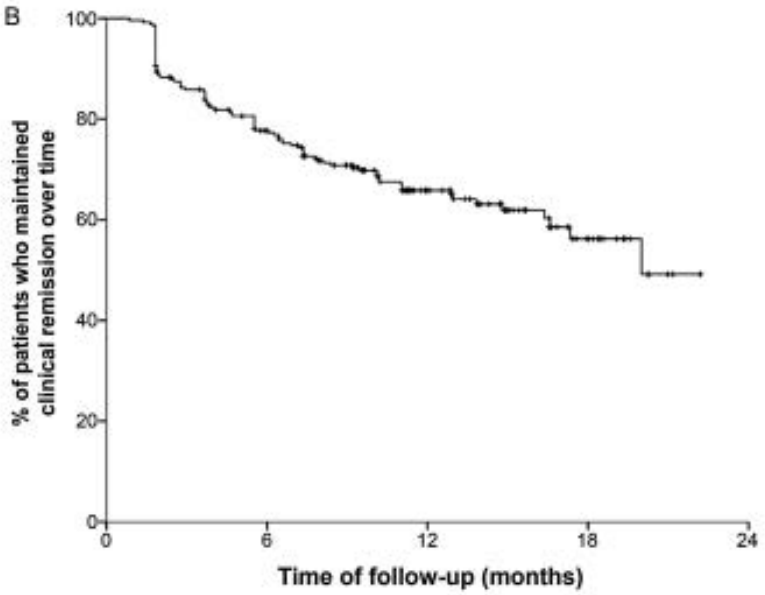
Factor	HR	95% CI
Previous abdominal surgery (yes vs no)	2.14	1.47-3.18
Concomitant steroid treatment (yes vs no)	1.82	1.24-2.67
Maintenance schedule (every 8 wk vs every 12 wk)	0.26	0.08-0.81

Abbreviations: CI, confidence interval; HR, hazard ratio.

Chaparro M, et al. IBD 2022

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





50 Aes reported by 39 (8.4%) patients (nly 17.9% of them stopped)
Only 4 severe

LoR: 29.7% per patient-year of follow-up

Number of previous biologics (HR 1.2; 95% CI, 1.0-1.5) andbaseline higher HBI (moderate vs mild [HR, 1.5; 95% CI, 1.0-2.3] and severe vs mild [HR, 4.0; 95% CI, 1.0-17.0]) were associated with a higher risk of LoR

Chaparro M, et al. IBD 2022

The Real-World Effectiveness of UST in the Treatment of CD – Results from SUCCESS

Objective: Examine the effectiveness of UST and assess predictors of response in a real-world cohort of CD patients.

Retrospective review of the US IBD Health Outcomes Consortium sub-study group (**SUCCESS**), a multicenter consortium of UST-treated CD patients in 16 centers across the US and Canada.

1,113 patients with median follow-up of 386 days

- 52% female, median disease duration 11 years

90% with prior biologic exposure

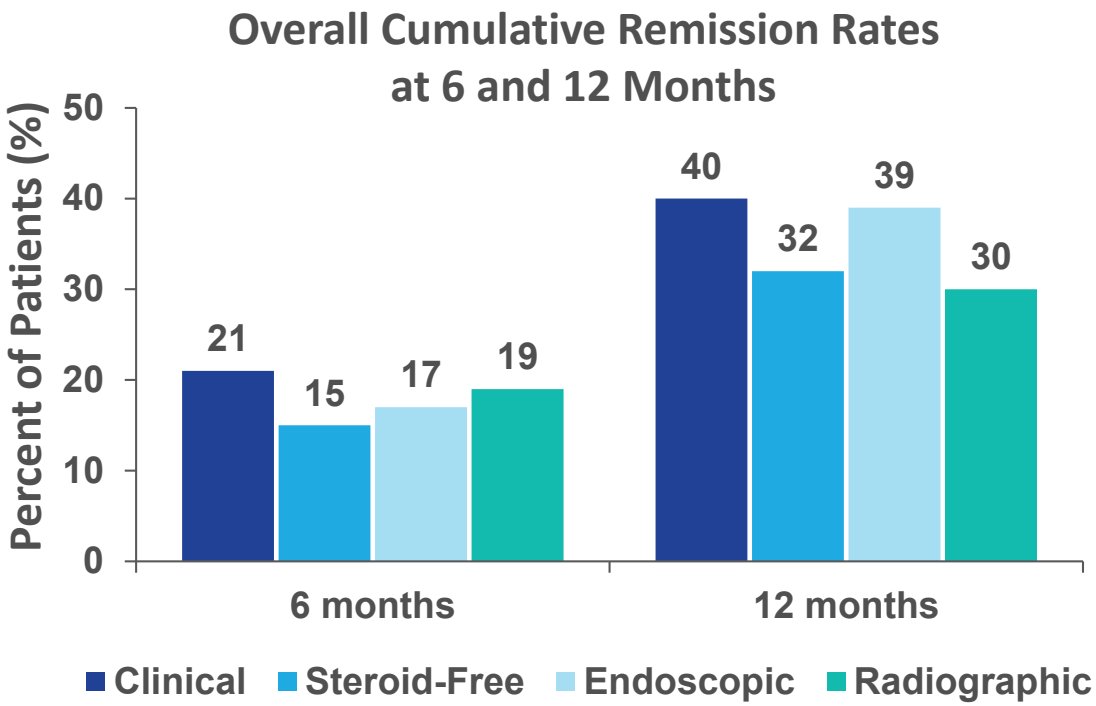
- 65% exposed to ≥ 2 biologics (23.8% prior VDZ)
- Majority (75%) discontinued anti-TNF for primary non-response or secondary loss of response

Clinical remission: Complete resolution of all CD-related symptoms, based on physician's global assessment (PGA);

Steroid-free remission: Achievement of clinical remission and no documented repeat corticosteroid prescription within four weeks of completing steroid taper;

Endoscopic remission: Absence of ulcers and/or erosions (limited to patients with documented mucosal ulcerations at baseline);

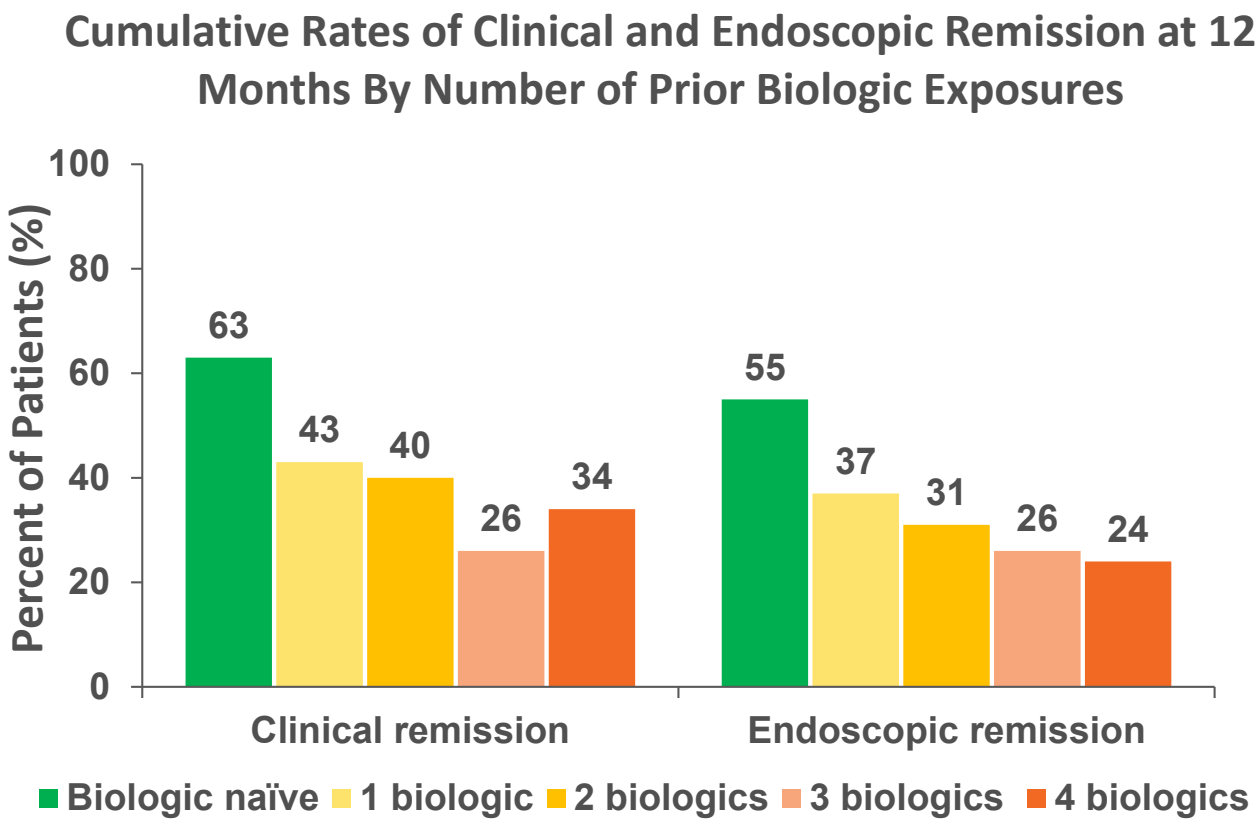
Radiologic remission: Based on discretion of each individual local reporting radiologist's review of CT or MR enterography.



UST: ustekinumab; CD: Crohn's disease; IBD: inflammatory bowel disease; VDZ: vedolizumab; TNF: tumour necrosis factor; CT: computed tomography; MR: magnetic resonance

Adapted from Johnson et al. AJG 2022

The Real-World Effectiveness of UST in the Treatment of CD – Results from SUCCESS



- Prior TNF-antagonist exposure and higher number of prior biologic exposures were associated with reduced likelihood of both clinical and endoscopic remission with UST.
- VDZ exposure associated with reduced likelihood of endoscopic, but not clinical remission.

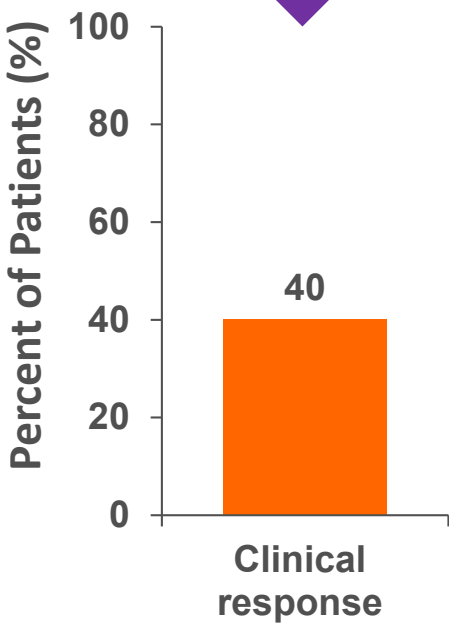
- Prior anti-TNF stopped for primary non-response reduced probability of clinical remission (HR 0.72)
- Prior anti-TNF stopped for intolerance increased probability of clinical remission (HR 1.45)

UST: ustekinumab; CD: Crohn's disease; HR: hazard ratio; TNF: tumour necrosis factor; VDZ: vedolizumab

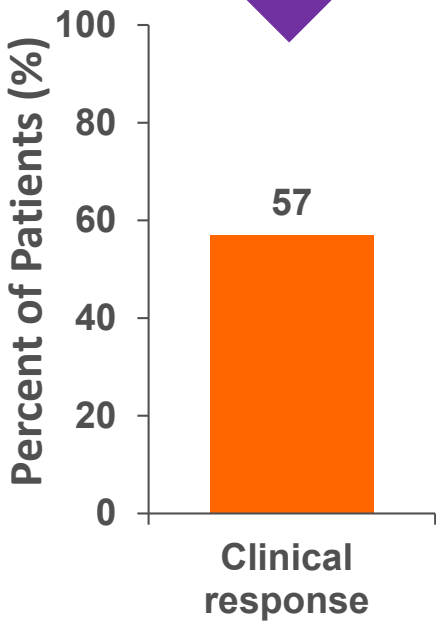
Adapted from Johnson et al. DDW 2021 #611.

The Real-World Effectiveness of UST in the Treatment of CD – Results from SUCCESS (4/4)

Primary non-response in 61.2% (681/1,113)
→ 22% (n=152) were **dose optimized**



Secondary loss of response in 9.2% (102/1,113)
→ 76% (n=77) were **dose optimized**



Types of dose optimization were: IV-reintroduction alone, increase interval to q4w alone or IV-reintroduction plus increase interval to q4w.

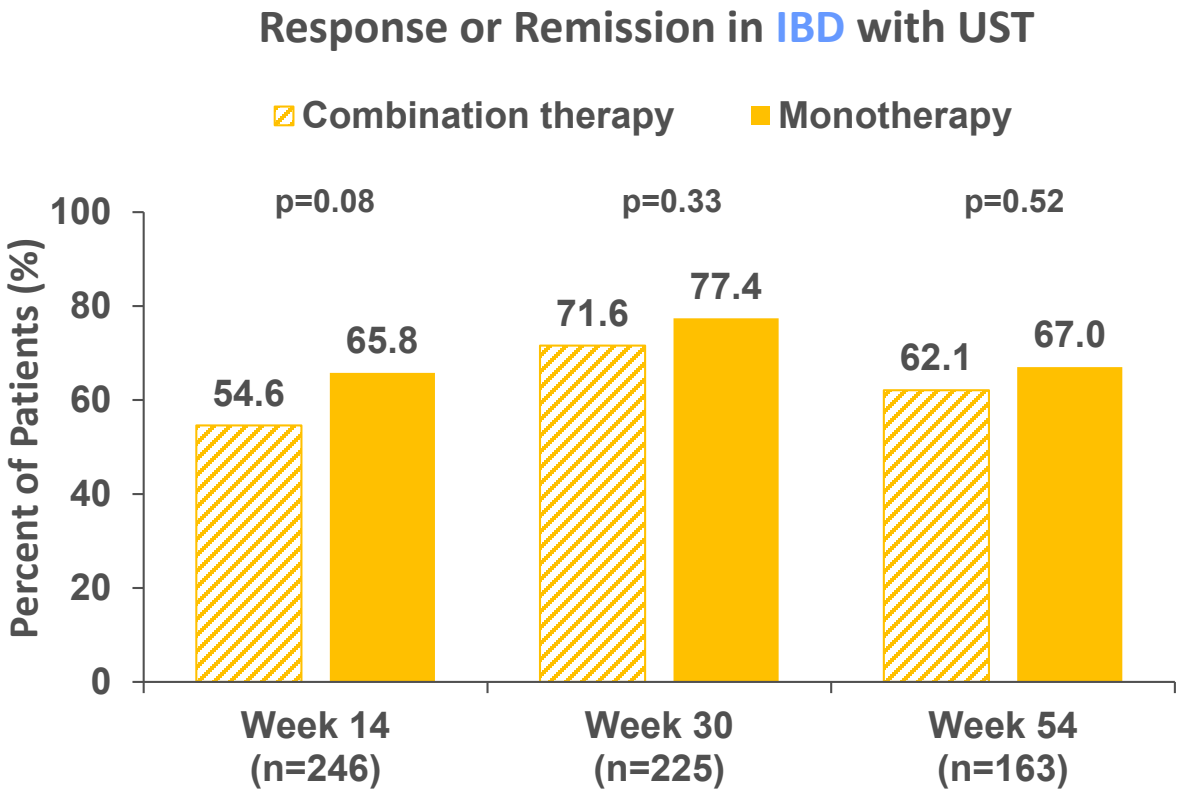
Dose optimization: IV-reintroduction alone, increased interval to q4w or IV-reintroduction plus increased interval to q4w.

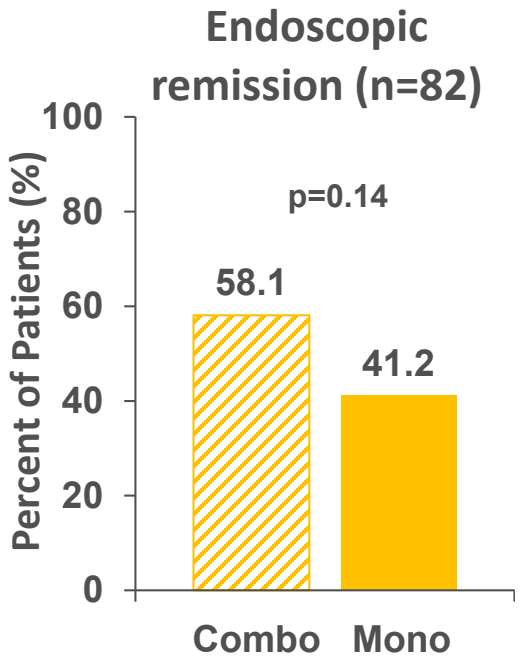
Adapted from Johnson et al. AJG 2022

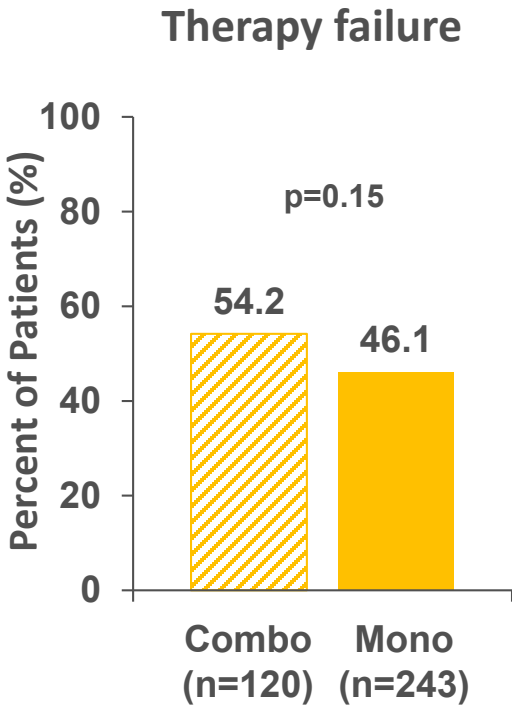
Impact of Combination Therapy on Clinical and Endoscopic Outcomes for UST Treated IBD Patients in a Retrospective Study – Outcomes

Mainly CD patients, at BL only four UC patients

”Combination therapy with immunomodulators did not increase rates of clinical remission/response, endoscopic remission, or persistence of therapy at 1 year”







Clinical response: Decrease in HBI ≥3 or Simple Clinical Colitis Activity Index (SCCAI)/partial Mayo score ≥2; Clinical remission: HBI ≤4 or SCCAI / Mayo <3; Endoscopic remission: Absence of ulcerations in CD, Mayo score 0 in UC. Colonoscopy 6-12 months. Therapy failure: Clinical relapse, defined by dose escalation, UST reinduction, addition of immunomodulator, need for rescue steroids, IBD related surgery/hospitalization during 1-year follow-up.

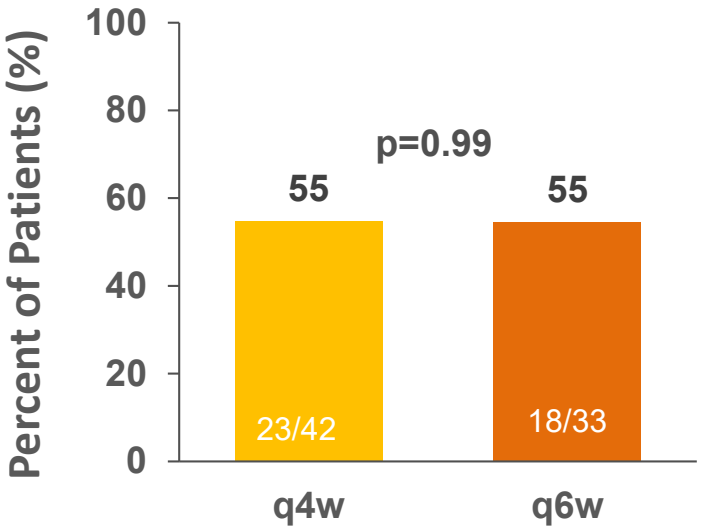
Adapted from Hu et al. Clin Gastroenterol Hepatol 2021;19:1366-76.

Predictors of UST Failure in CD After Dose Intensification (1/2)

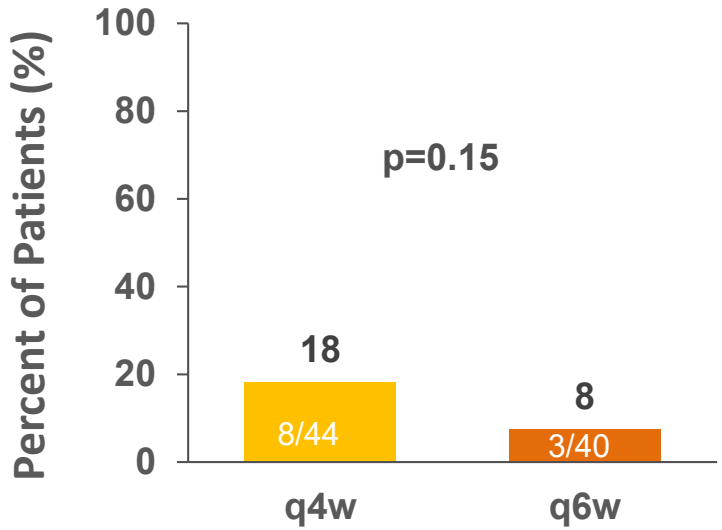
- Retrospective cohort study of adult CD patients undergoing UST dose intensification **N=123**; q4w (n=64), q5w (n=1), q6w (n=55), or q7w (n=3).
- Primary outcome: failure to achieve CS-free remission (HBI<5) within 12 months after intensification.
- Secondary outcome: discontinuation of UST with initiation of new biologic therapy.

Baseline characteristics between q4w and q6w groups were similar, except for cigarette smoking (4.7% q4w vs 18.2% q6w, p=0.02) and current CS use at time of intensification (31.3% q4w vs 14.6% q6w, p=0.03).

Primary Outcome: CS-Free Remission (HBI<5) at 12 months



Secondary Outcome: Change to New Biologic

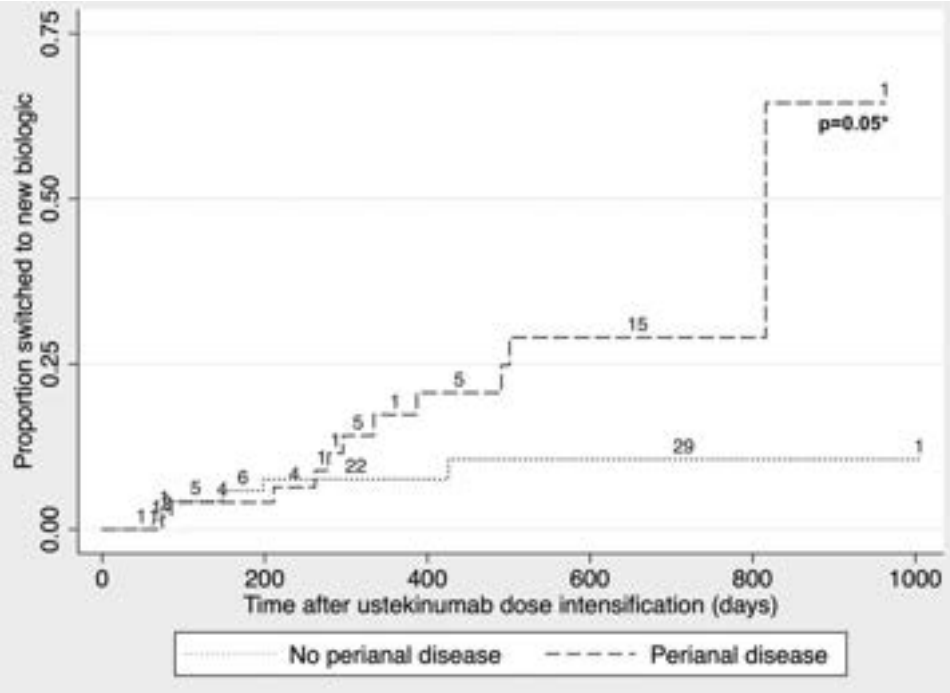


qxw: every x weeks; UST: ustekinumab; CD: Crohn's disease; CS: corticosteroid; HBI: Harvey-Bradshaw Index

Adapted from Dalal et al. Inflamm Bowel Dis 2021;27(8):1294-301.

Predictors of UST Failure in CD After Dose Intensification (2/2)

Kaplan-Meier Analysis of Time to New Biologic Therapy After UST Dose Intensification*



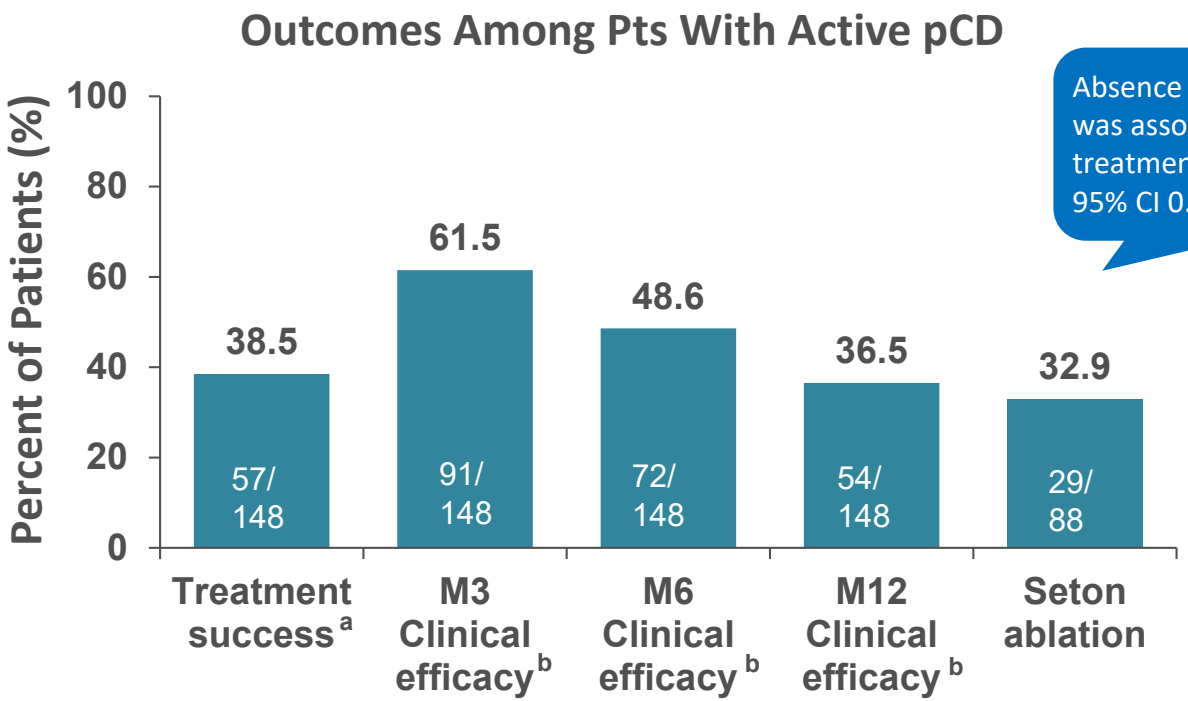
- Multivariable logistic regression demonstrated that perianal disease (odds ratio [OR], 3.2; 95% CI, 1.0–9.9), HBI as a continuous variable (OR, 1.3; 95% CI, 1.1–1.6), and current opioid use (OR, 3.4; 95% CI, 1.1–10.8) at time of intensification were associated with failure to achieve remission.
- Cox regression demonstrated that perianal disease (hazard ratio [HR], 3.0; 95% CI, 1.1–8.4) and current corticosteroid use (OR, 2.9; 95% CI, 1.0–7.9) at time of intensification were associated with shorter time to a new biologic.

*Calculated using log-rank test. Numbers represent censoring at loss of follow-up, time of UST discontinuation without initiation of new biologic therapy, or time of further UST dose intensification from q6w to q4w.

Adapted from Dalal et al. Inflamm Bowel Dis 2021;27(8):1294-301.

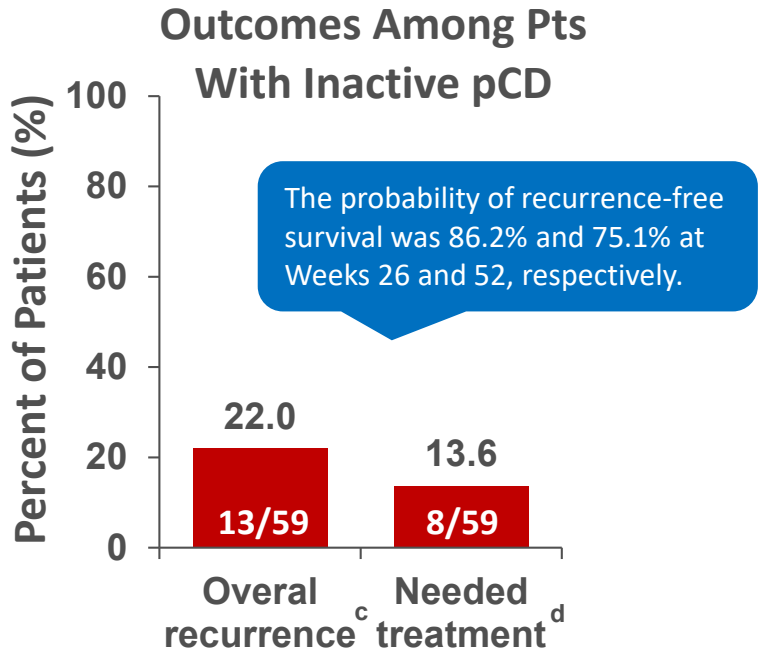
French data: BioLAP Study

UST for Perianal CD: The BioLAP Multicenter Study from GETAID - Outcomes



Absence of UST optimization was associated with treatment success (OR 2.74; 95% CI 0.96–7.82; p=0.044).

- Median follow-up time was 52.1 weeks (IQR: 19.6-69.4)
- Treatment optimization to q6w or q4w for 48 pts (32.4%)
- Treatment was discontinued in 38 pts (25.6%)



The probability of recurrence-free survival was 86.2% and 75.1% at Weeks 26 and 52, respectively.

- Median follow-up time was 47.7 weeks (IQR: 21.6-71.7)
- Median time to recurrence was 21.9 weeks (QIR: 13.0-34.6)
- Treatment optimization to q6w or q4w for 6 pts (10.2%)
- Treatment was discontinued in 18 pts (30.5%)

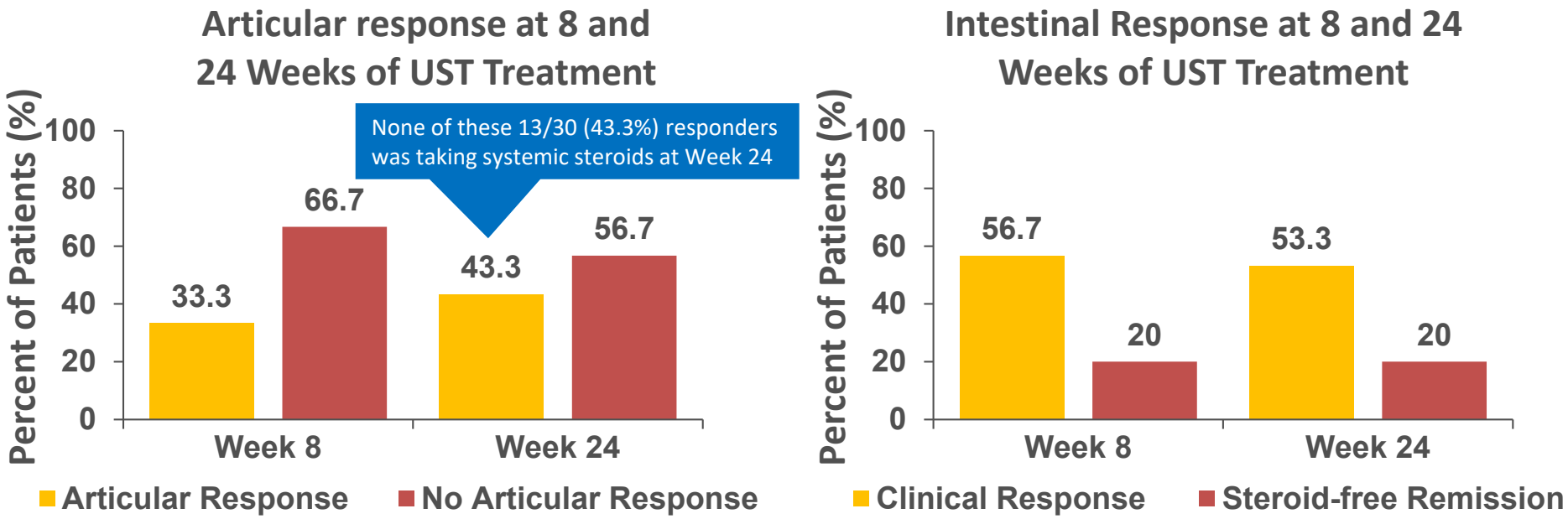
[a]Defined by (i) clinical success at 6 months of ustekinumab treatment assessed by the physician's appreciation, with (ii) no need to use medical treatment for perianal lesions nor (iii) unscheduled surgical treatment.
[b]Clinical efficacy according to physicians. M3, 3 months; M6, 6 months; M12, 12 months.
[c]Reccurrence among inactive pCD: Occurrence of perianal lesions and/or need of medical or surgical treatment.
[d]Antibotics and/or surgical treatment.

Adapted from Chapuis-Biron et al. Am J Gastroenterol 2020;115:1812-20.

Italian data

Effectiveness of UST on CD Associated Spondyloarthropathy: Real-World Data from the Sicilian Network for IBD (SNIBD)

- Multicentre, real-world assessment of the effectiveness of UST on CD-associated spondyloarthropathy (SpA); web-based data from the cohort of the SN-IBD (N=30 with active SpA).
- **30 CD patients had active SpA at baseline** (axial SpA: 3/30; peripheral SpA: 18/30; axial plus peripheral SpA: 9/30). All patients had a previous failure to at least one biological treatment.
- **Primary outcome**: articular response (disappearance of objective signs of arthritis (swelling and/or articular stiffness) and resolution of pain) at 8 and 24 weeks.



- The drop of mean HBI values from baseline to Week 24 was higher in patients with articular response compared with nonresponders (3.8 ± 2.4 vs. 1.3 ± 2.8, p = 0.02).
- The concomitant presence of a response on intestinal symptoms was the only factor associated with the articular response at 24 Weeks at univariable analysis (OR 5.14, CI 1.09-32.70, p = 0.038).

No patient with axial SpA experienced an articular response.

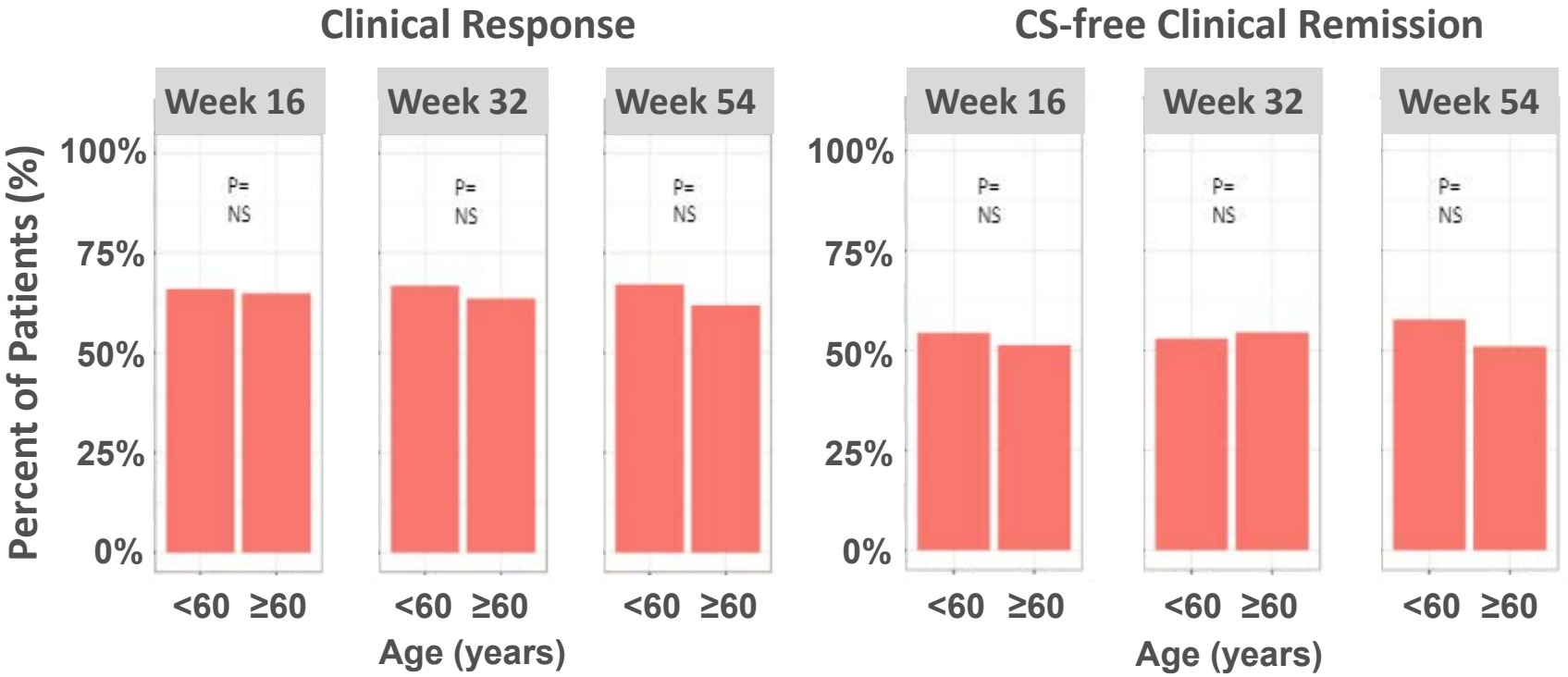
Clinical response: Reduction of Harvey-Bradshaw Index (HBI) ≥3 compared with baseline with a concomitant reduction of at least ≥50% of steroid dosage compared with baseline; Steroid- free clinical remission: Harvey-Bradshaw Index <5 without steroids use were reported.

Adapted from Macaluso et al. Expert Opin Biol Ther 2020;20(11):1381-4.

Effectiveness and Safety of Ustekinumab in Elderly Patients: Real World Evidence from ENEIDA Registry

Aim: To evaluate efficacy and safety in elderly patients with Crohn's disease in real-life practice (refractory patients).

- Retrospective analysis. Elderly patients (**n=212**): ≥60 years at start of treatment. Compared to young patients (<60 years) (**n=436**).
- Higher degree of comorbidity (1.00 vs 0.00) and less perianal disease (19.3% vs. 34.9%) in elderly patients (p<0.001). Baseline clinical and biochemical activity was similar in both groups.



Safety (elderly vs young)

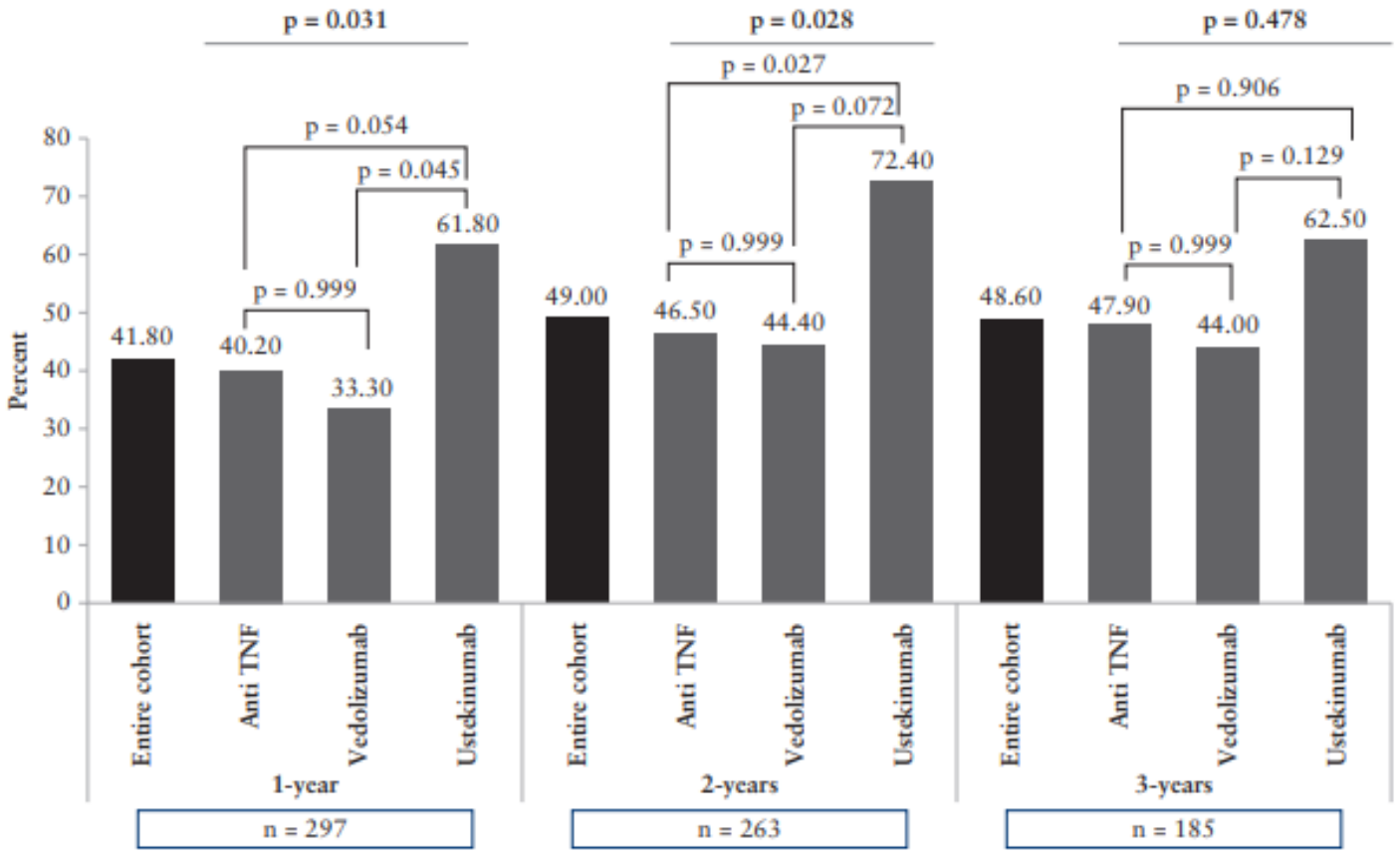
- Adverse effects (14.2% vs 11.2%, p=0.350)
- De novo neoplasms (4.25% vs 0.69%, p=0.003)
- Severe infections (7.08% vs 7.34%, p=1.000)
- Need for surgery (16.5% vs 20.0%, p=0.345)
- Need for hospital admission (21.7% vs 19.0%, p=0.489)

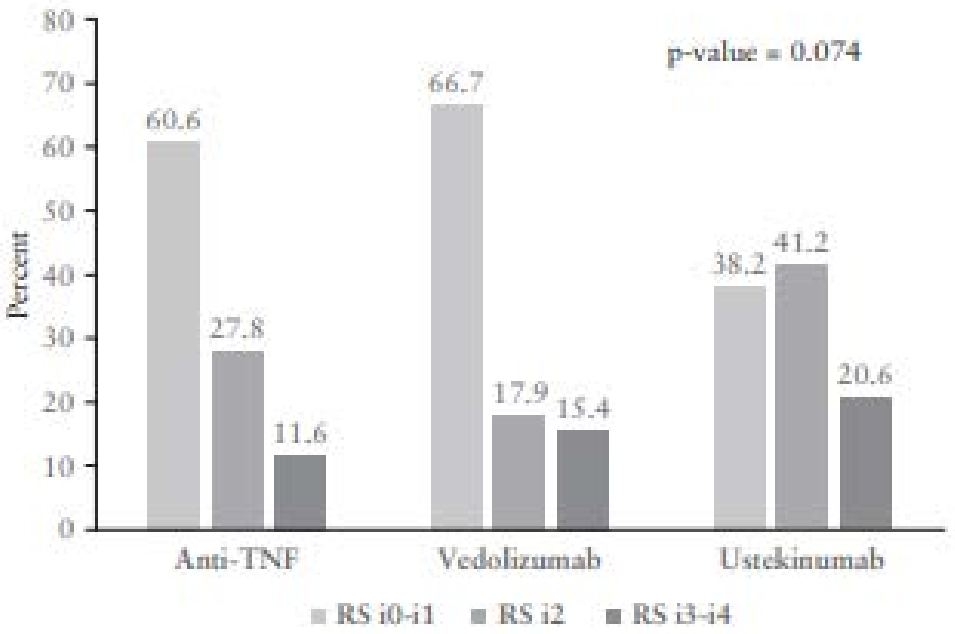
"Ustekinumab achieved clinical response in almost three-quarters of elderly patients, similar to the younger population, with no increase in the rate of infections or other adverse effects, with the exception of de novo neoplasms."

Clinical effectiveness were defined based on HBI.

Adapted from Casas-Deza et al. JCC 2022

Endoscopic Postoperative Recurrence in Crohn's Disease After Curative Ileocecal Resection with Early Prophylaxis by Anti-TNF, Vedolizumab or Ustekinumab: A Real-World Multicentre European Study





Yanai H, et al. JCC 2022

Table 1. Summary of real-life studies on ustekinumab for the treatment of ulcerative colitis.

Study	Ustekinumab dosage	Patients followed	Primary outcome	Results
Chaparro *et al.*[22]	IV induction 6 mg/kg, maintenance 90 mg sc every 8 or 12 weeks	95	Durability of ustekinumab treatment	63% at week 56
Amiot *et al.*[19]	IV induction 6 mg/kg (or sc induction 270 mg), maintenance 90 mg sc every 8 or 12 weeks	103	Steroid-free clinical remission at weeks 12–16	35%
Fumery *et al.*[52]	IV induction 6 mg/kg (or sc induction 270 mg), maintenance 90 mg sc every 8 or 12 weeks	103	Steroid-free clinical remission at week 52	32%
Dalal *et al.*[53]	Dose escalation to 90 mg every 4 or every 6 weeks	46	Steroid-free clinical remission after dose intensification	55%
Hong *et al.*[54]	IV induction, maintenance 90 mg sc every 8 weeks	47	Clinical remission at 3 months	42.6%
		20	Clinical remission at 12 months	45.0%
Chiappetta *et al.*[55]	IV induction, maintenance 90 mg sc every 12 or 8 weeks	68	Steroid-free clinical remission at week 24	31%
		68	Steroid-free clinical remission at week 52	50%
Ochsenkühn *et al.*[20]	IV induction 6 mg/kg, maintenance 90 mg sc every 8 or 12 weeks	19	Clinical remission at 1 year	53%
Dhaliwal *et al.*[21]	IV induction, maintenance 90 mg sc every 8 weeks	25 children	Steroid-free clinical remission at 52 weeks	44%
Dalal *et al.*[56]	90 mg every 8 weeks after weight-based induction	36	Steroid-free clinical remission at 12 to 16 weeks – comparison with tofacitinib	40% – *versus* 43.9% with tofacitinib ($p = 0.82$)

IV, intravenous.

Pugliese D, TAG 2022

Effectiveness and Safety of Ustekinumab in UC: Real World Evidence From ENEIDA Registry

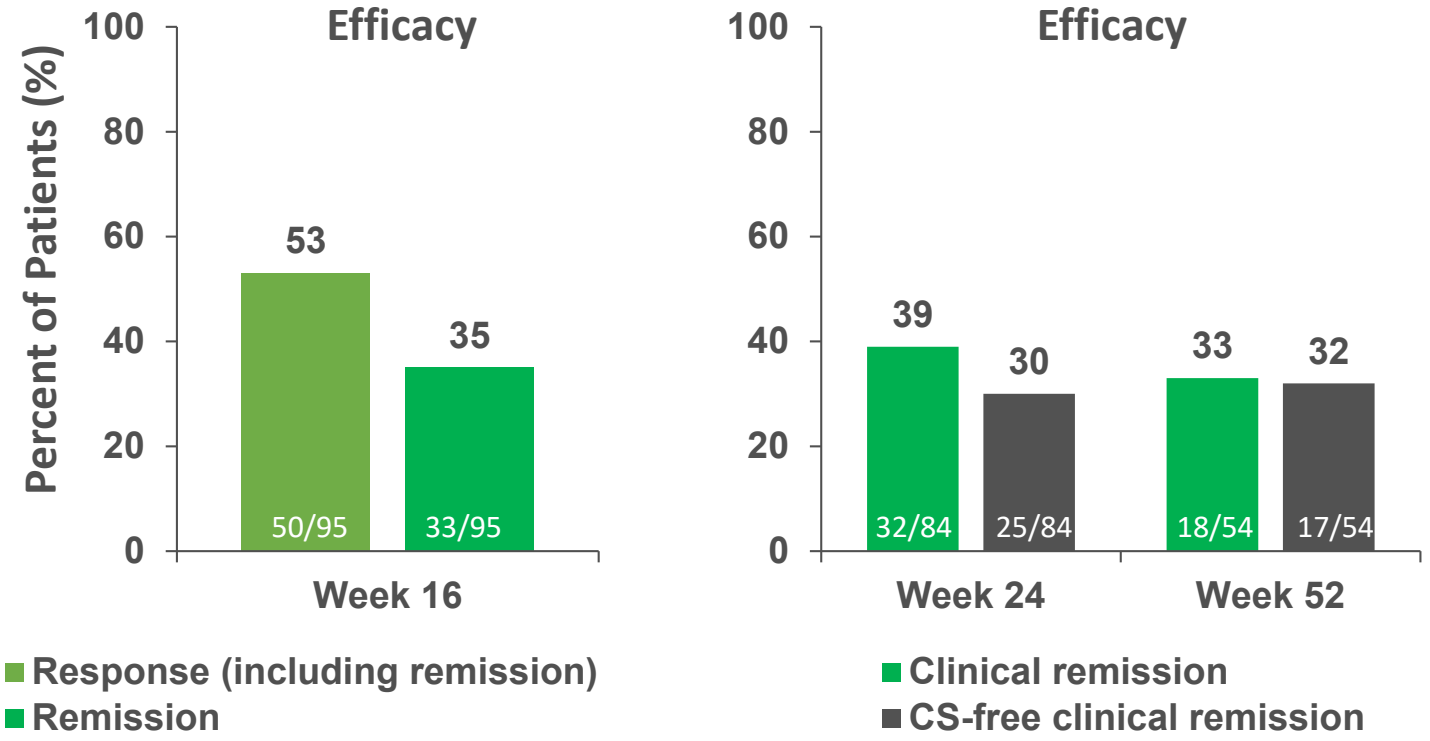
- Observational multicenter study including patients from the ENEIDA registry that received ≥1 dose of intravenous UST at least 16 weeks before data analysis due to active UC (partial Mayo score >2)**(n=95)**.
  - Dose adjustment was part of the treatment regimen (i.e., not included in treatment failure rules) unless otherwise indicated for dichotomous endpoints (remission vs. no remission at a certain time point).

- The schedule for the induction varied widely between patients:
  - 95 patients received a first IV dose of ~6 mg/kg.
  - 91 patients received a second dose of UST while four interrupted the treatment before administration of the second dose;
    - 51 of them (56%) received the second dose between Weeks 6 and 10, 8 (9%) before Week 6, 21 patients (23%) at Week 11, 5 (5%) at Week 12 and 6 (6%) after Week 12.
  - 84 patients received a third dose of UST;
    - In most of the cases (80%) administration was between Weeks 16 and 20. Fourteen patients (17%) received the third dose before week 16, and 3 patients (3.5%) after Week 20.

Baseline characteristics, n	(n=95)
Mean age (SD) (years)	47 (16)
Median time of follow-up (IQR) (weeks)	82 (41-153)
Female gender, n (%)	53 (56)
UC extent	
Extensive colitis, n (%)	55 (58)
Left-sided colitis, n (%)	37 (39)
Proctitis, n (%)	3 (3)
Extraintestinal manifestations, n (%)	27 (28)
Median partial Mayo score at baseline (IQR)	6 (4-8)
Endoscopic assessment at baseline, n (%)	68 (72)
Mild, n (%)	3 (4)
Moderate, n (%)	20 (30)
Severe, n (%)	45 (66)
Baseline CRP over the upper limit of normal range, n (%)	61 (64)
Median faecal calprotectin at baseline (IQR) (µg/g)	1,564 (795-2,998)
Prior biological treatment or tofacitinib, n (%)	95 (100)
Anti-TNF, n (%)	93 (98)
Vedolizumab, n (%)	78 (82)
Tofacitinib, n (%)	28 (30)
Anti-TNF and vedolizumab, n (%)	76 (80)
Anti-TNF, vedolizumab and tofacitinib, n (%)	27 (28)
Prior number of biological agents	
1-2 previous biologics, n (%)	40 (42)
≥3 previous biologics, n (%)	55 (58)
Concomitant immunosuppressants, n (%)	16 (17)
Steroids during induction, n (%)	53 (56)

Adapted from Chaparro et al. J Crohn Colitis 2021

Effectiveness and Safety of Ustekinumab in UC: Real World Evidence From ENEIDA Registry – Outcomes



- A total of 66 patients started maintenance with standard dose (q12w or q8w)
  - 18 patients intensified treatment (q6w/q4w): 10 due to primary failure (1 achieved remission after), 3 due to partial response, 5 due to LoR (2 achieved remission after)
  - 1 patient escalated q12w -> q8w due to LoR -> remission after.

- Lower probability of remission at Week 16 associated with:
  - CRP above the normal range limit at baseline (OR=0.3; 95% CI 0.1-0.7).
- The probability of maintaining UST treatment was 87% at week 16, 63% at week 56, and 59% at week 72; primary failure was the main reason for UST discontinuation.
- Approximately one-third of patients who were in remission at Week 16 relapsed during FU (median time of exposure to UST was 31 weeks). Dose was optimized in four patients, and 2 of them regained remission.
- Three AEs were reported: dry skin and itching (n=1), pneumonia (n=1), severe SARS-Cov-2 pneumonia leading to death.

Adapted from Chaparro et al. J Crohns Colitis. 2021

Effectiveness and Safety of UST Induction Therapy For 103 Patients With UC: A GETAID Multicenter Real-World Cohort Study

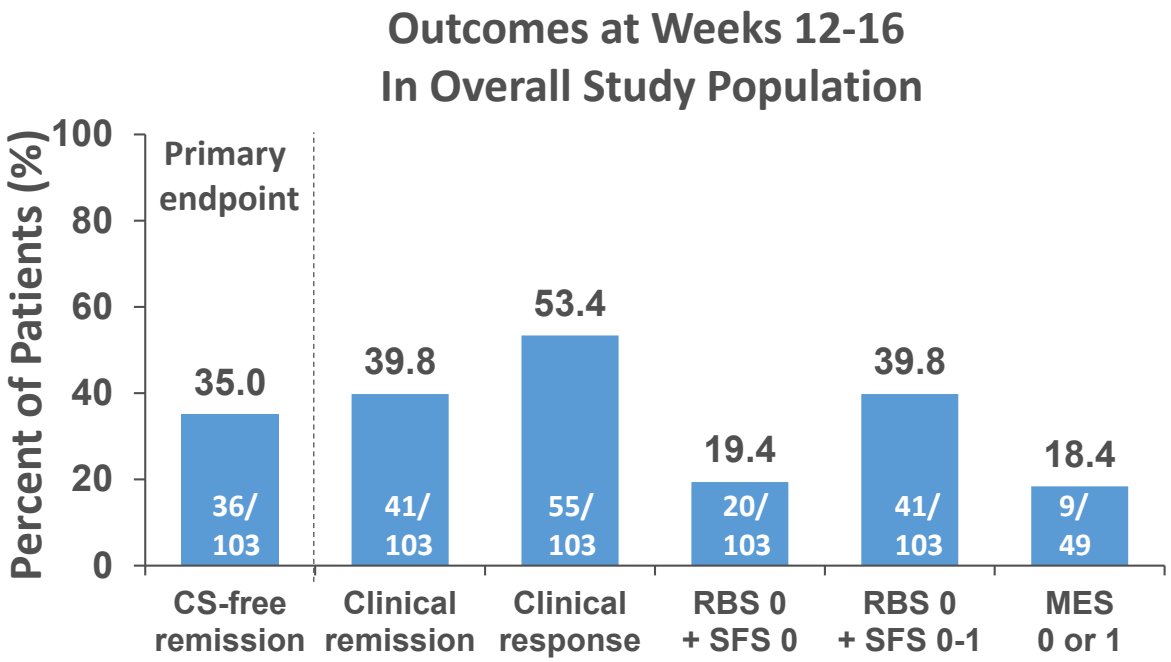
- Retrospective multicenter study including all UC patients treated with UST from January to September 2019 (n=103)
  - Maintenance therapy q8w or q12w
  - Dose optimization was allowed for insufficient response, according to the investigator's decision

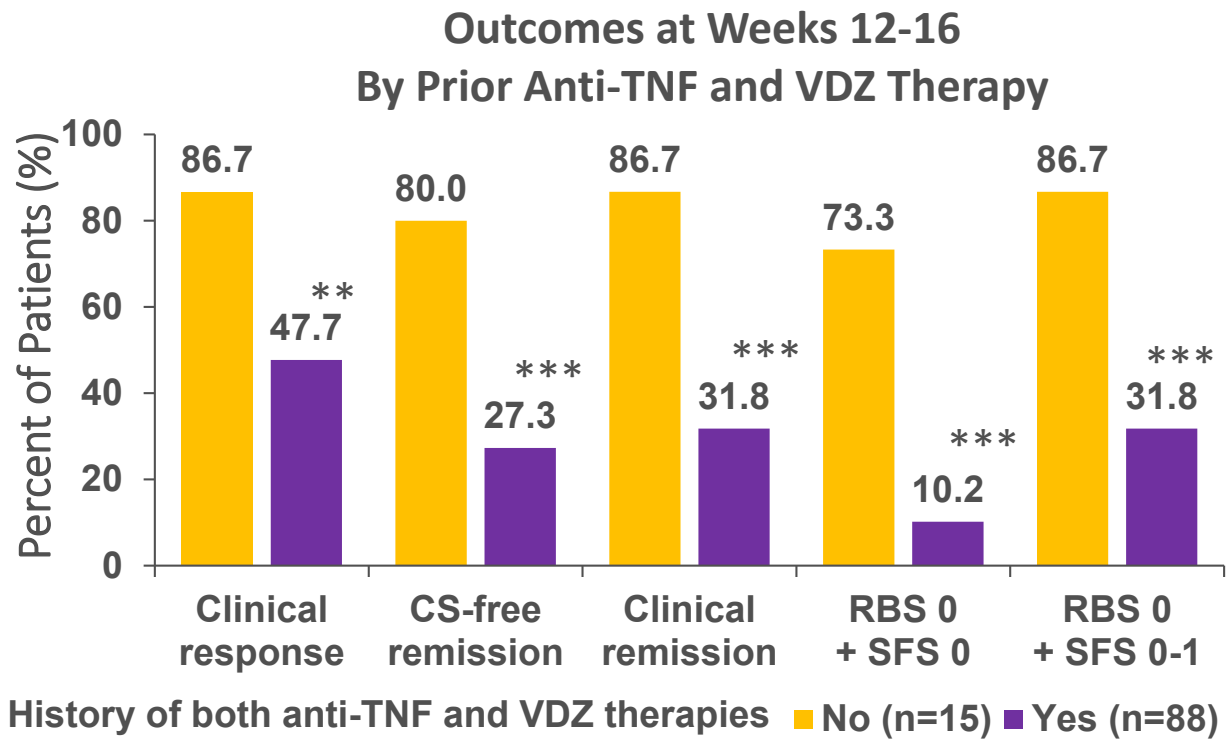
Baseline characteristics, n (%)	(n=103)
Median age, y (IQR)	39.3 (29.1-52.3)
Male gender	62 (60.2)
Disease duration, y (IQR)	7.6 (3.6-12.9)
Smoking:	
Past smoker	30 (29.1)
Active smoker	7 (6.8)
Age at diagnosis	
A1 (≤16)	8 (7.8)
A2 (17-40)	68 (66.0)
A3 (>40)	27 (26.2)
Location	
Proctitis	6 (5.8)
Left-sided colitis	43 (41.8)
Extensive colitis	54 (52.4)

Baseline characteristics, n (%)	(n=103)
Prior medications exposure	
Immunosuppressant (IMMs)	87 (84.5)
Purine analogues	85 (82.5)
Methotrexate	25 (24.3)
Anti-TNF therapy	102 (99)
- One anti-TNF agent	30 (29.1)
- ≥2 anti-TNF agents	72 (69.9)
VDZ	88 (85.4)
Tofacitinib	10 (9.7)
Clinical and endoscopic activity at BL, mean±SD	
Partial Mayo score	5.9±1.9
Mayo endoscopic subscore (MES) (n=93)	2.6±0.6
Total Mayo score (n=93)	8.5±2.1
UC Endoscopic Index of Severity (UCEIS) (n=93)	5.1±1.3
CRP level, mg/L	7.1 (3.1-15.0)
Concomitant medications	
Glucocorticoids only	41 (39.8)
IMMs only	15 (14.6)
Glucocorticoids and IMMs	9 (8.7)
None	38 (36.9)
UST therapy	
IV 6-mg/kg induction	93 (90.3)
SC 270-mg induction	10 (9.7)

Adapted from Amiot et al. Aliment Pharmacol Ther 2020

Effectiveness and Safety of UST Induction Therapy For 103 Patients With UC: A GETAID Multicenter Real-World Cohort Study – Outcomes





In multivariable analysis, CS-free remission at Weeks 12-16 was decreased in:
- Pts with a partial Mayo score >6 (OR = 0.10, 95% CI 0.01-0.90; P=0.04);
- Pts with history of both exposure to anti-TNF and VDZ therapies (OR=0.03, 95% CI 0.01-0.42; P=0.01).

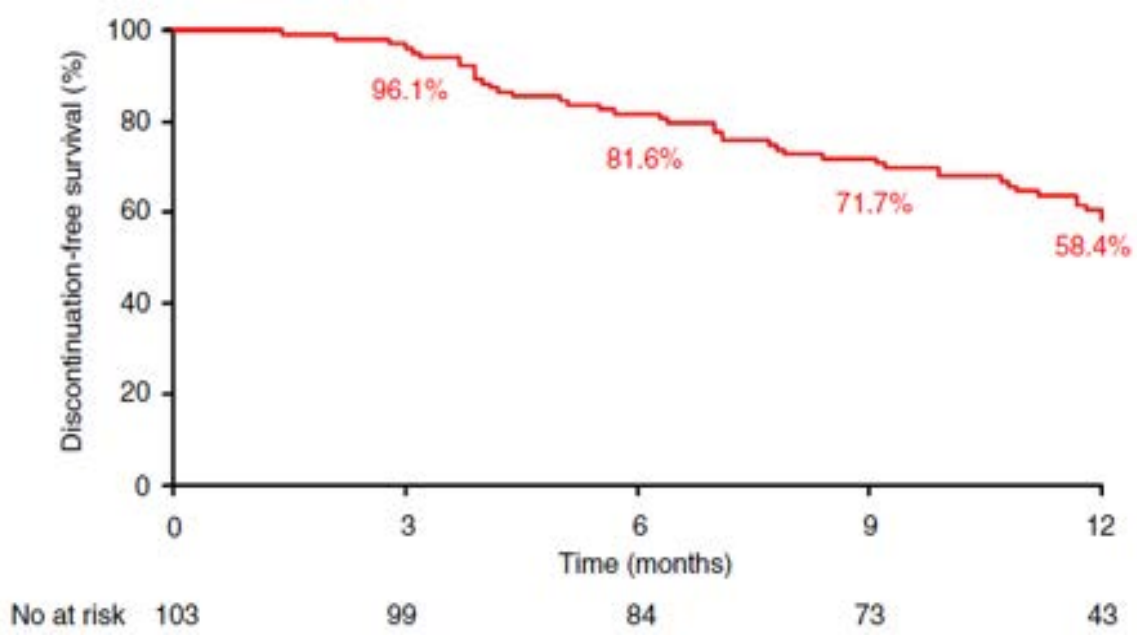
- Optimization to q4w in 16 pts,
- Discontinuation due to lack of efficacy in 10 pts,
- AEs occurred in 7.8% and SAEs in 3.9%.

Clinical remission: PMS ≤2, with a combined SFS and RBS ≤1; Clinical response: Reduction in PMS ≥3 points and a decrease of ≥30%, with a decrease of ≥1 point on RBS OR absolute RBS of 0 or 1.
PMS, Partial Mayo score; RBS, Rectal bleeding score; SFS, Stool frequency score; MES, Mayo endoscopic subscore.
**p=0.005; ***p<0.001.

Adapted from Amiot et al. Aliment Pharmacol Ther 2020

Effectiveness and Safety of UST Maintenance Therapy in 103 Patients With UC: A GETAID Cohort Study – Outcomes

Probability of UST Discontinuation



Safety Results During Maintenance Period

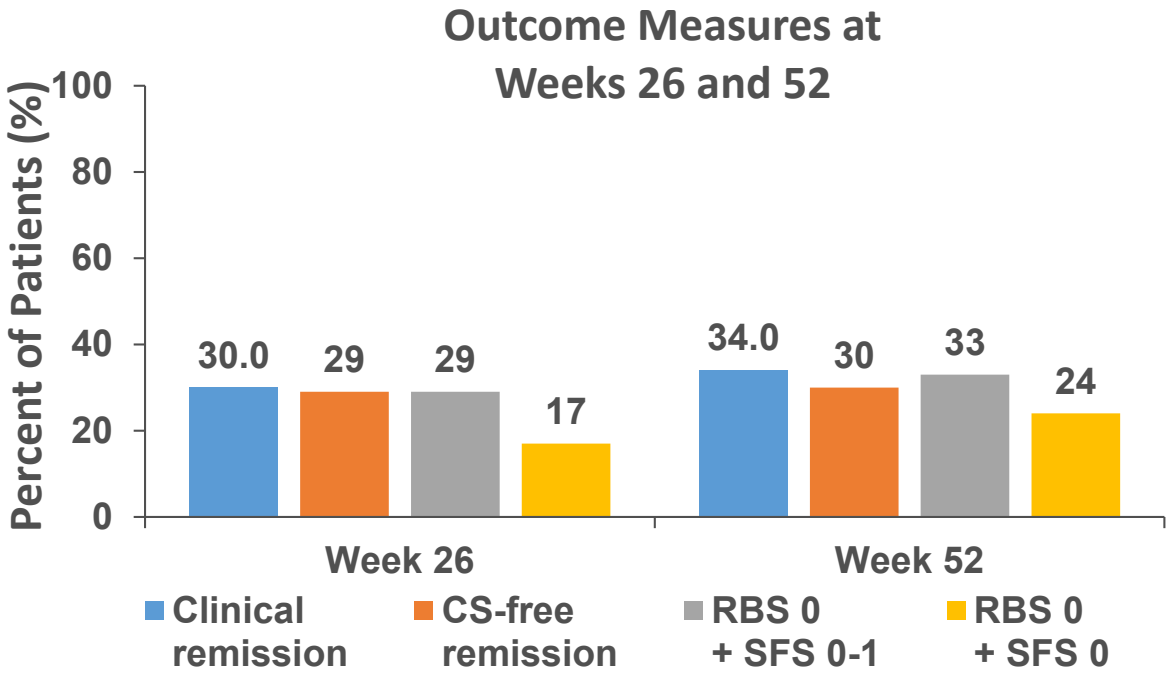
Event	Maintenance Period (n=103)
Number of adverse events	
Arthralgia	4
IBD exacerbation	3
Dental abscess	1
Skin rash	2
Gastroenteritis	2
Rhinopharyngitis	1
Myocardial infraction	1
***Clostridioides difficile* infection**	1
Fatigue	1
Any serious adverse event[a]	4 (3.9%)
Any cancer	0
Death	1 (0.9%)

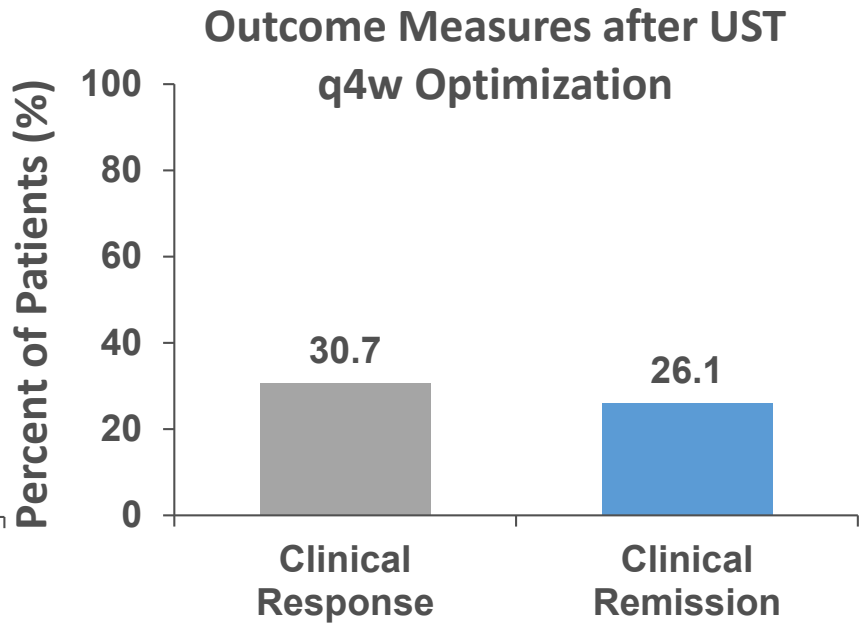
[a]A serious adverse event was defined as any adverse event when leading to treatment interruption, hospitalization, disability or persistent damage, colectomy and death.

Adapted from Fumery et al. Aliment Pharmacol Ther 2021

Effectiveness and Safety of UST Maintenance Therapy in 103 Patients With UC: A GETAID Cohort Study – Outcomes

- Long-term effectiveness and safety of UST maintenance therapy in a multicenter cohort study from the GETAID





Sixty-five (63.1%) patients were optimized to q4w 90 mg SC regimen during the whole follow-up period including six who were further de-escalated to prior q8w regimen.

- Among the 93 patients with an assessment of endoscopic activity at Week 0, 65 (63.1%) were also re-evaluated between Week 26 and Week 52.
  - Mean UCEIS decreased from 5.0 ± 1.1 at baseline to 3.6 ± 1.1 between week 26 and 52 ($p < 0.001$).
  - The mean Mayo endoscopic subscore also decreased from 2.7 ± 0.5 at baseline to 2.0 ± 1.0 between week 26 and 52.

Clinical remission: pMC score <3 and a combined SFS and RBS of ≤1; SFS: stool frequency subscore; RBS: rectal bleeding subscore

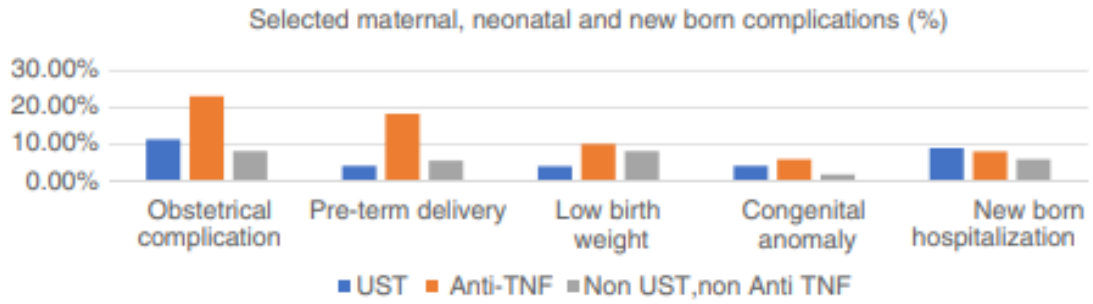
Adapted from Fumery et al. Aliment Pharmacol Ther 2021

Ustekinumab during pregnancy in patients with inflammatory bowel disease: a prospective multicentre cohort study

129 pregnant patients:
UST 27; anti-TNF 52; non-UST, nonanti-TNF 50
(thiopurine or mesalazine 30, no therapy 20)

TABLE 3 Maternal, obstetrical, neonatal and newborn outcomes

	UST n = 27	Anti-TNF n = 50	Non-UST non-anti-TNF n = 50	p
Maternal obstetrical complications (%)	3 (11.5)	12 (23.1)	4 (8.2)	0.095
Maternal hospitalisations (%)	3 (11.5)	8 (15.7)	5 (10.0)	0.769
Spontaneous abortions (%)	2 (7.4)	0	0	0.002
Caesarean section (%)	10 (41.7)	15 (29.4)	10 (20.8)	0.178
Delivery week Median, [IQR]	38 [38.00-39.00]	38 [37.00-40.00]	39 [38.00-40.00]	0.200
Pre-term delivery (%)	1 (4.3)	9 (18.4)	4 (5.7)	0.133
Birth weight Median, [IQR]	3090 [2955.00-3306.00]	3118 [2871.00-3369.00]	3262 [2807-3584.00]	0.201
Low birth weight <2500gr (%)	1 (4.2)	5 (10.2)	4 (8.3)	0.679
5-Min Apgar score Median, [IQR]	10 [9.00-10.00]	9 [9.00-10.00]	9 [9.00-10.00]	0.143
5-Min Apgar <7	0	2 (4.1)	0	0.239
Congenital anomaly (%)	1 (4.3)	3 (6.1)	1 (2.0)	0.596
Breastfeeding (%)	10 (53)	31 (77.5)	33 (86.8)	0.082
Newborn hospitalisation 1st year (%)	2 (9.1)	4 (8.2)	3 (6.1)	0.885
Newborn infections 1st year (%)	0 (0)	0 (0)	0 (0)	0
Newborn malignancy 1st year (%)	0 (0)	0 (0)	0 (0)	0
Vaccination (%)	18 (100)	42 (97.7)	37 (94.9)	0.540
Newborn developmental delay (%)	0	0	2 (4.8)	0.227



Avni-Biron I, et al. APT 2022

Conclusions

- Real-life studies confirmed effectiveness and safety of ustekinumab for both CD and UC patients, also for special categories of patients
- Different variables (previous biologic exposure, perianal disease, etc..) have been identified as predictors of poor clinical response among studies
- Future studies will hopefully help us to best address our treatment choices (ideally biomarkers driven)

Grazie per l’attenzione!