11ο ΚΡΗΤΟ-ΚΥΠΡΙΑΚΟ ΣΥΜΠΟΣΙΟ ΡΕΥΜΑΤΟΛΟΓΙΑΣ

Tofacitinib σε Ιδιοπαθείς Φλεγμονώδεις Νόσους του Εντέρου

Κωνσταντίνος Σουφλέρης

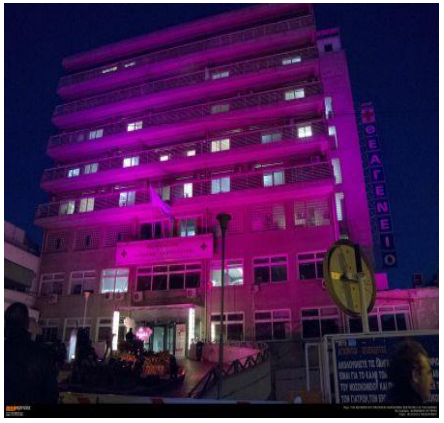
Γαστρεντερολόγος,

Επιμελητής Α΄Ε.Σ.Υ.,

Γαστρεντερολογική Κλινική,

Θεαγένειο Α.Ν.Θ.

Θεσσαλονίκη



ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

Abbvie

Enorasis

Janssen

Merck

Mylan

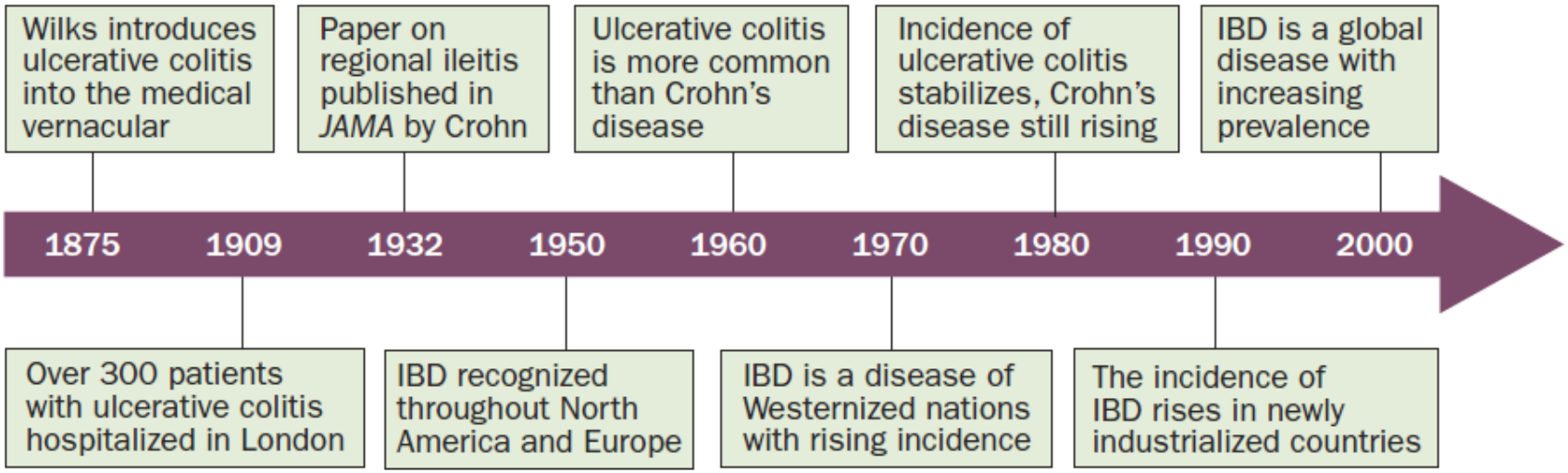
Pfizer

Roche

Takeda

Vianex

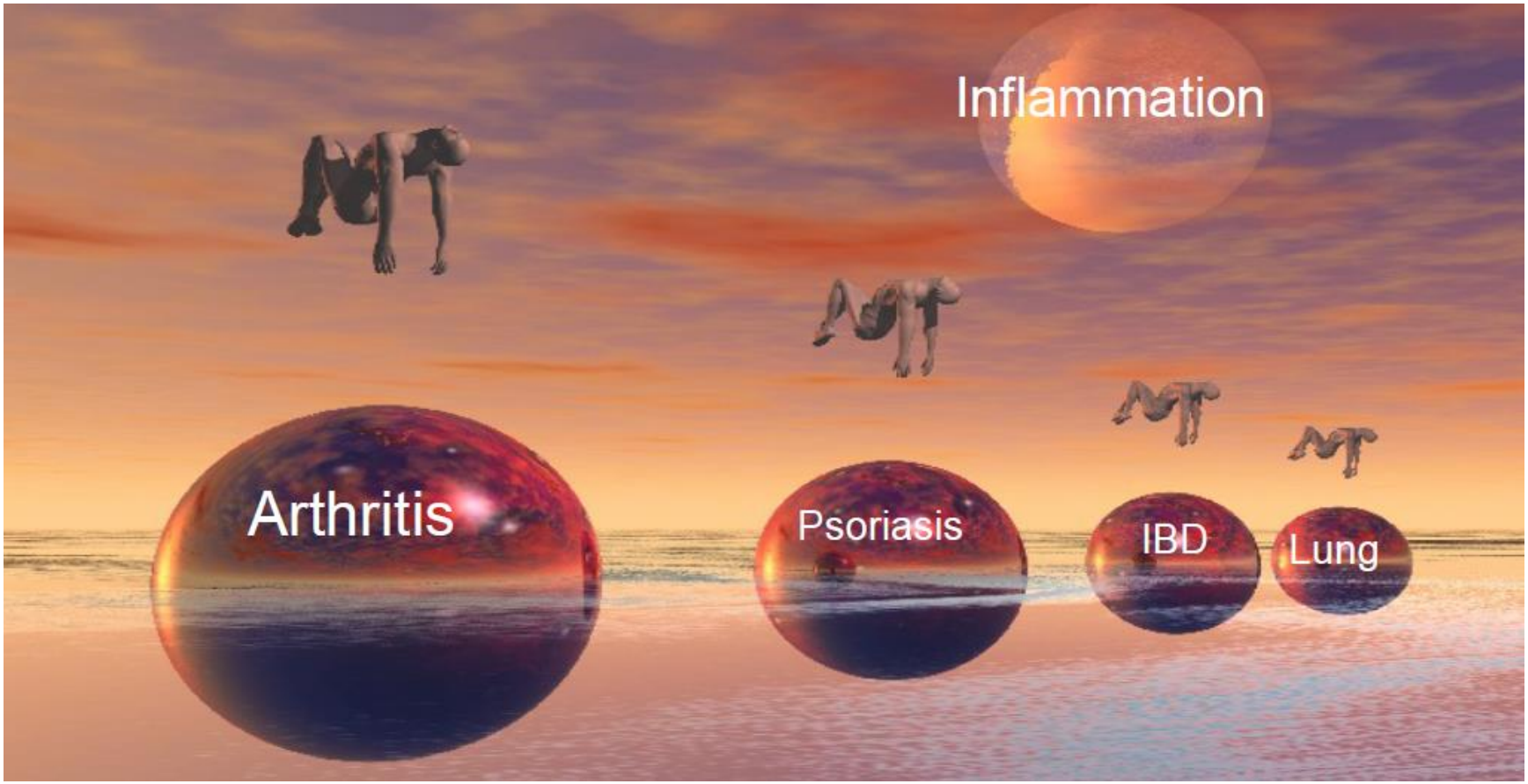
ΙΦΝΕ Επιδημιολογία: 1:200



Kaplan, Gastro 2015

Πόνος, Αυτοανοσία, Συνύπαρξη

ΙΦΝΕ Φλεγμονή διαφορετική ποιοτικά και ποσοτικά



Ο τέλειος Θεραπευτικός στόχος…

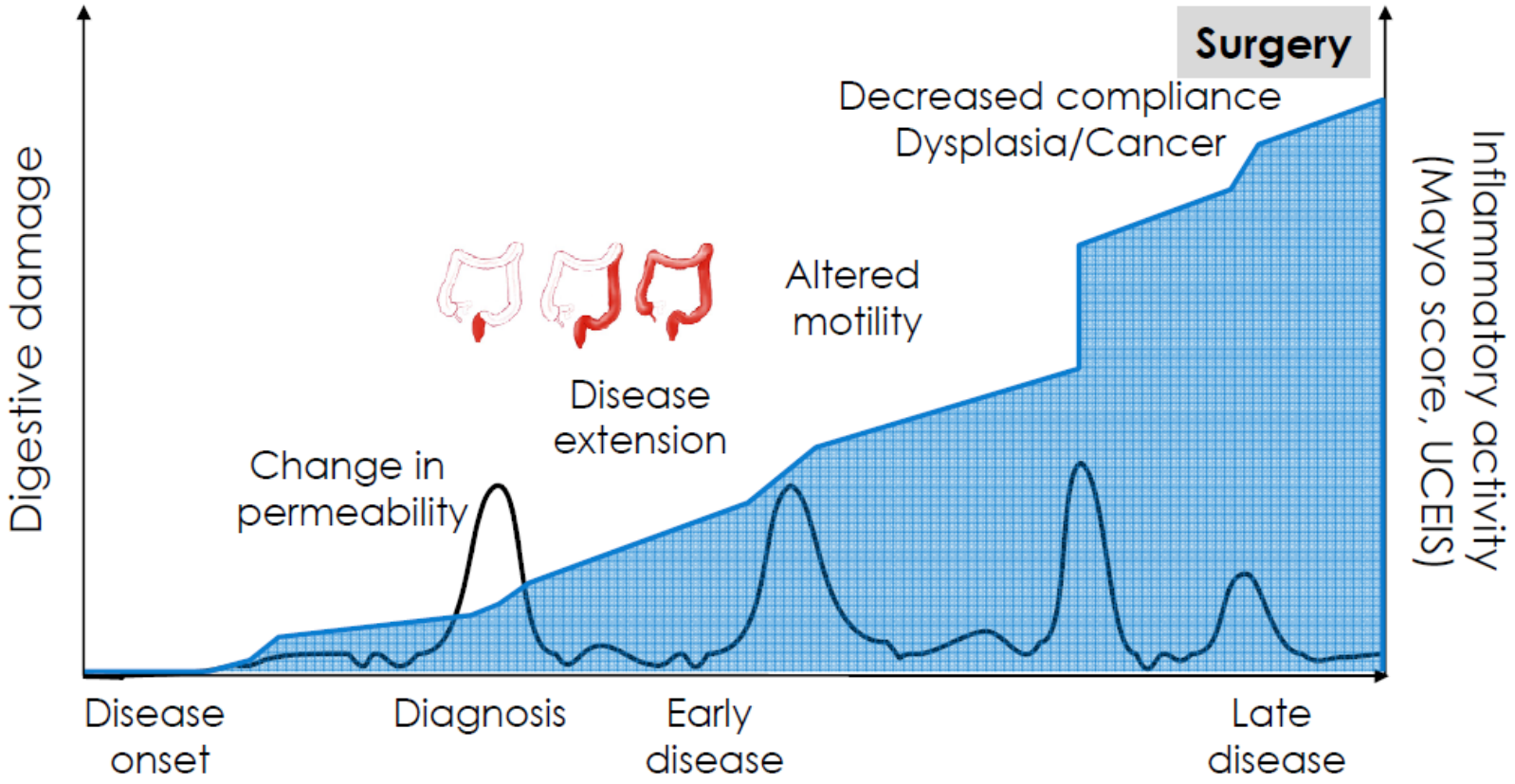
Aim of the treatment in IBD patients

« Returning to a normal life, the ultimate therapeutic goal in IBD »

Laurent Peyrin-Biroulet, UEGW Vienna, 2016

"Ulcerative Colitis, unlike Crohn's Disease, does not progress"

(narrowing; strictures; fibrosis; anorectal dysfunction; mural damage; pseudopolyps;)



Ως και 30 % με ενδοσκοπική και ιστολογική ύφεση έχουν παθολογική συχνότητα κενώσεων!

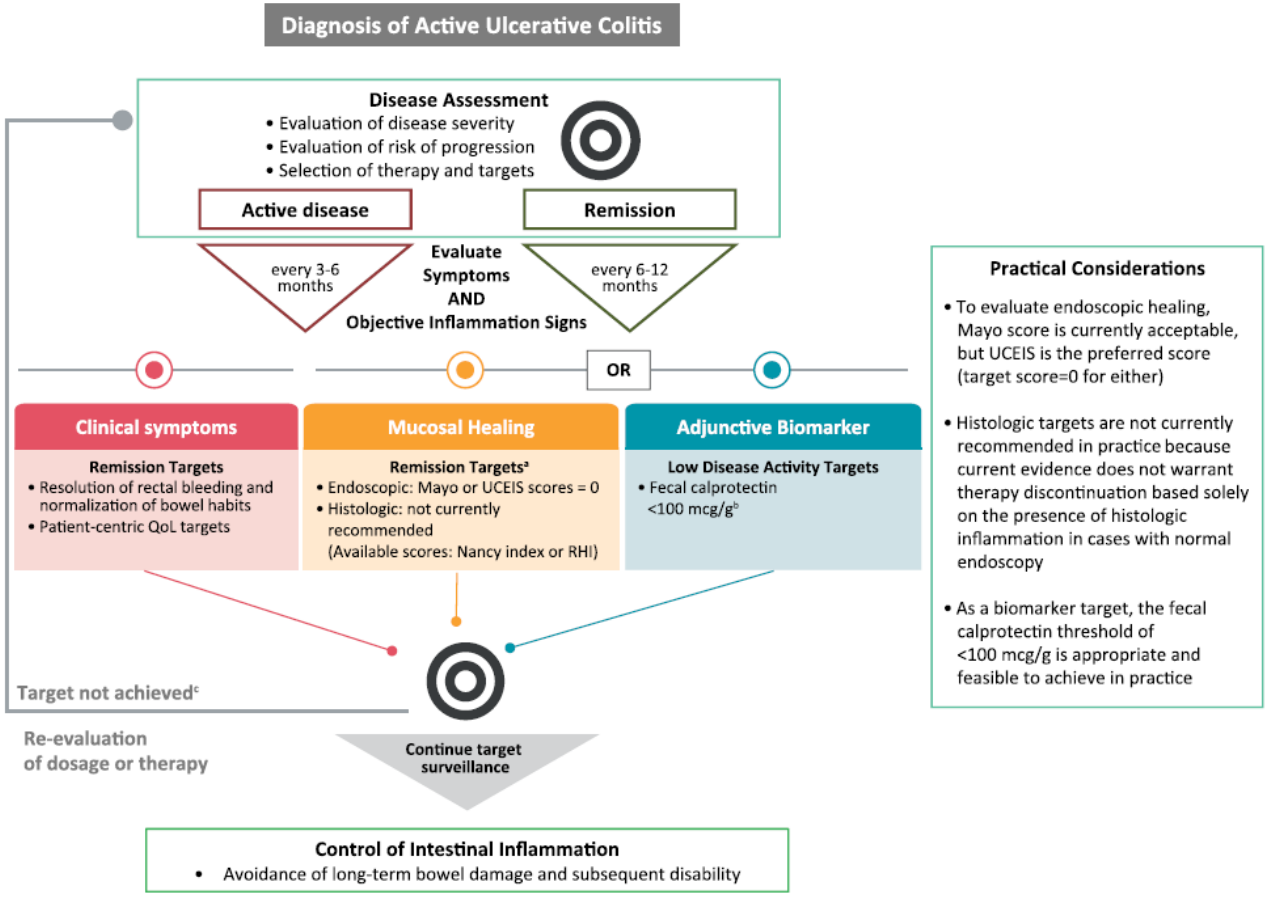
Torres, Inflamm Bowel Dis 2012

Treat To Target in Ulcerative Colitis

	STRIDE Consensus Targets	Accumulating Evidence	Optimized Targets
Clinical Targets and PROs	Resolution of rectal bleeding and normalization of bowel habits should be the target. Monitor every 3 months until symptom resolution and every 6 months thereafter.	Discrepancy between symptom normalization and endoscopic activity.	Validated PRO scores and tools/technologies for PRO reporting.
Endoscopic Targets	Absence of ulceration is the target (minimum score of 1). Assessments should be done every 3-6 months after start of therapy.	Utility of UCEIS and modified Mayo scores. More stringent endoscopic resolution associated with better outcomes (Mayo score = 0).	Validated UCEIS and Mayo scores. Mayo score = 0
Histological Targets	Not recommended as a target because of insufficient evidence.	Histological healing associated with endoscopic healing and can predict long-term outcomes.	Validated histological index. Nancy and Robarts scores as promising potential tools in clinical practice and clinical trials
Adjunctive Biomarker Targets	CRP and fecal calprotectin are adjunctive measures of inflammation but NOT treatment targets. Failure of CRP or fecal calprotectin normalization should prompt endoscopic evaluation.	Fecal calprotectin responsive to treatment induction and dose response.	Validated fecal calprotectin cut-off value with demonstrated specificity, sensitivity, and reliability. Home-based test development.
Novel Future Targets	Molecular evidence of inflammation (intestinal permeability) may be helpful with assessing disease activity in patients who demonstrate endoscopic healing but still experience symptoms. Methods for detecting molecular inflammation will require extensive research to demonstrate its association with disease short-term and long-term outcomes.		

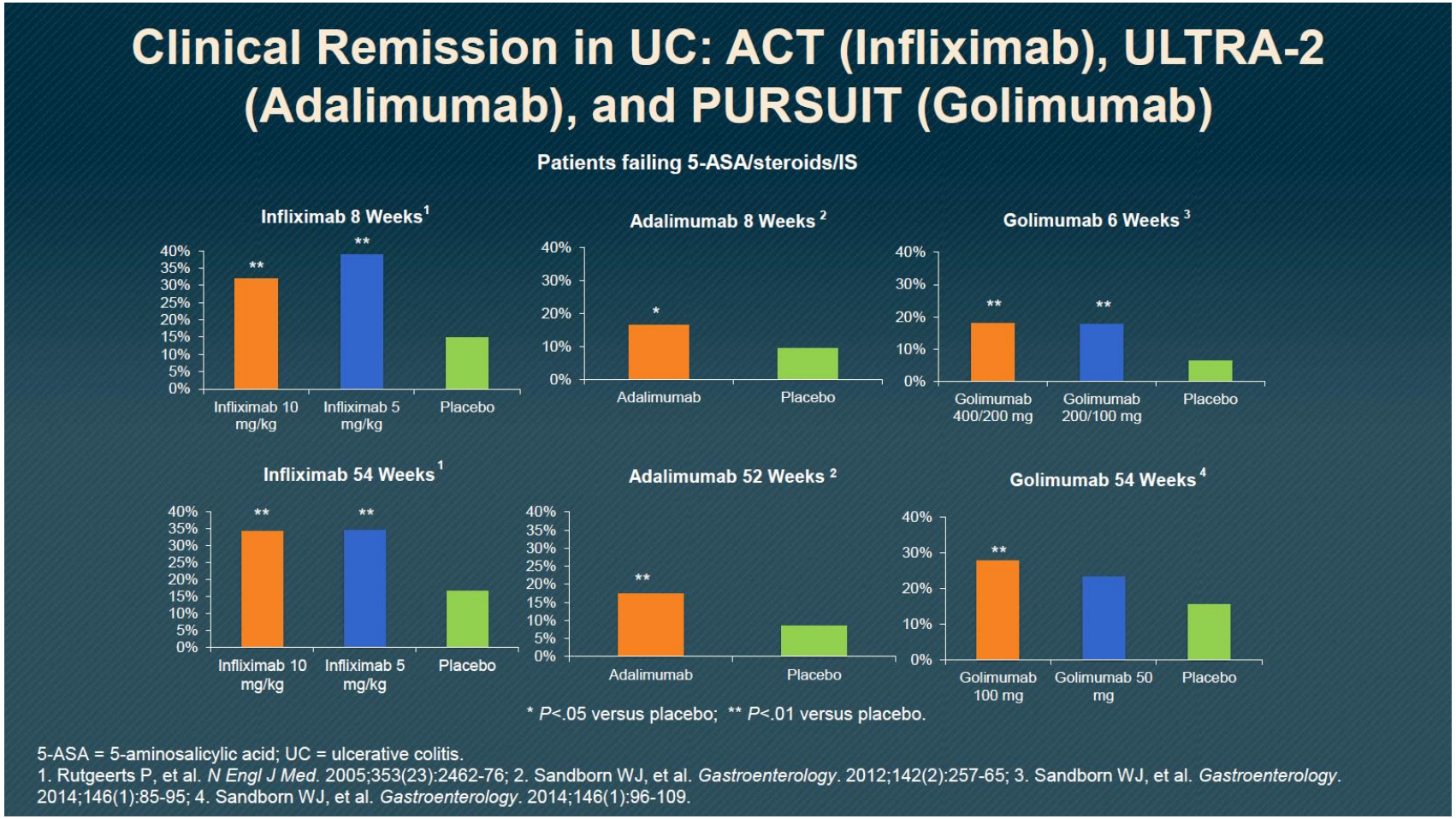
Ungaro, Am J Gastroenterol 2019

Treat To Target in Ulcerative Colitis



Ungaro, Am J Gastroenterol 2019

Anti-TNF και Ελκώδης Κολίτιδα



5-ASA = 5-aminosalicylic acid; UC = ulcerative colitis.

1. Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-76; 2. Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-65; 3. Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):85-95; 4. Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):96-109.

Long term Infliximab in UC

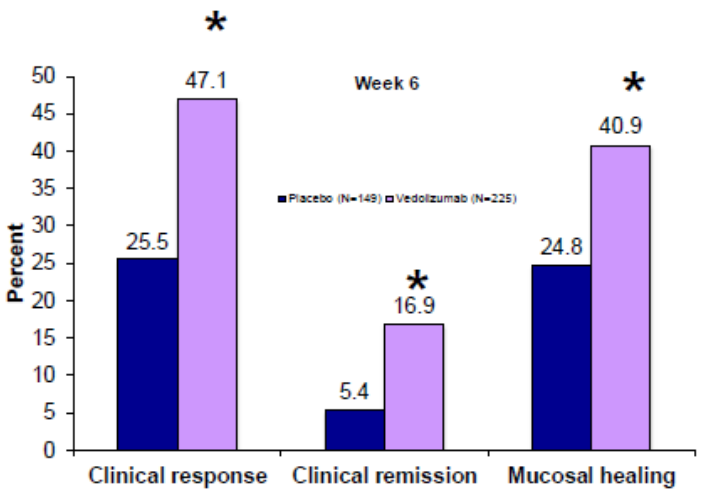
Infliximab Discontinuation Due to Treatment Failure

% Infliximab Discontinuation Due to Treatment Failure	Leeds 2012 n=210	Netherland 2011 n=152	Leuven 2009 n=614
Nonresponse	9	3	11
Loss of response	19	25	19
Adverse events	16	2	11
Total discontinuation	44	30	41

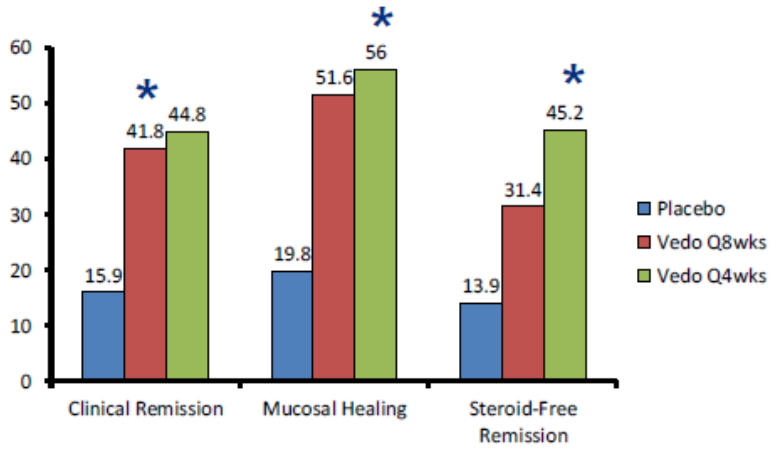
Sprakes MB, et al. *J Crohns Colitis*. 2012;6(2):143-53; de Bie CI, et al. *Aliment Pharmacol Ther*. 2011;33(2):243-50; Schnitzler F, et al. *Gut*. 2009;58(4):492-500

Anti-Integrins
Vedolizumab and Ulcerative Colitis

GEMINI 1



* p<0.001

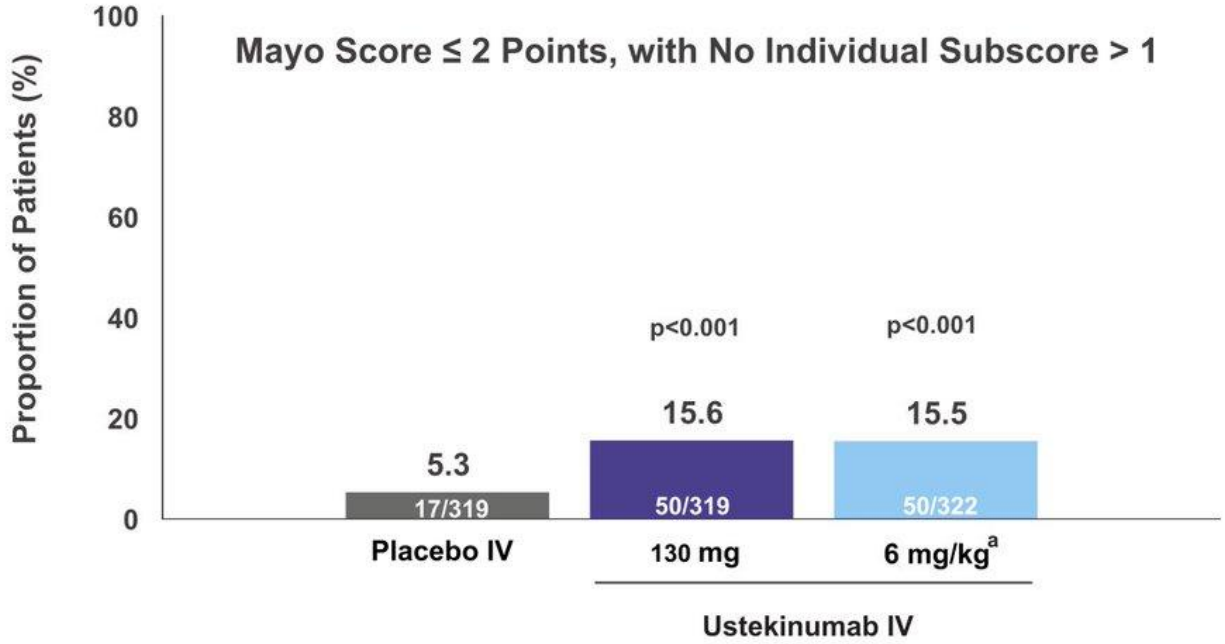


Randomized responders
Week 52

Feagan, NEJM 2013

Anti IL12/23:
Ustekinumab and Ulcerative Colitis-UNIFY

Primary Endpoint: Clinical Remission at Week 8

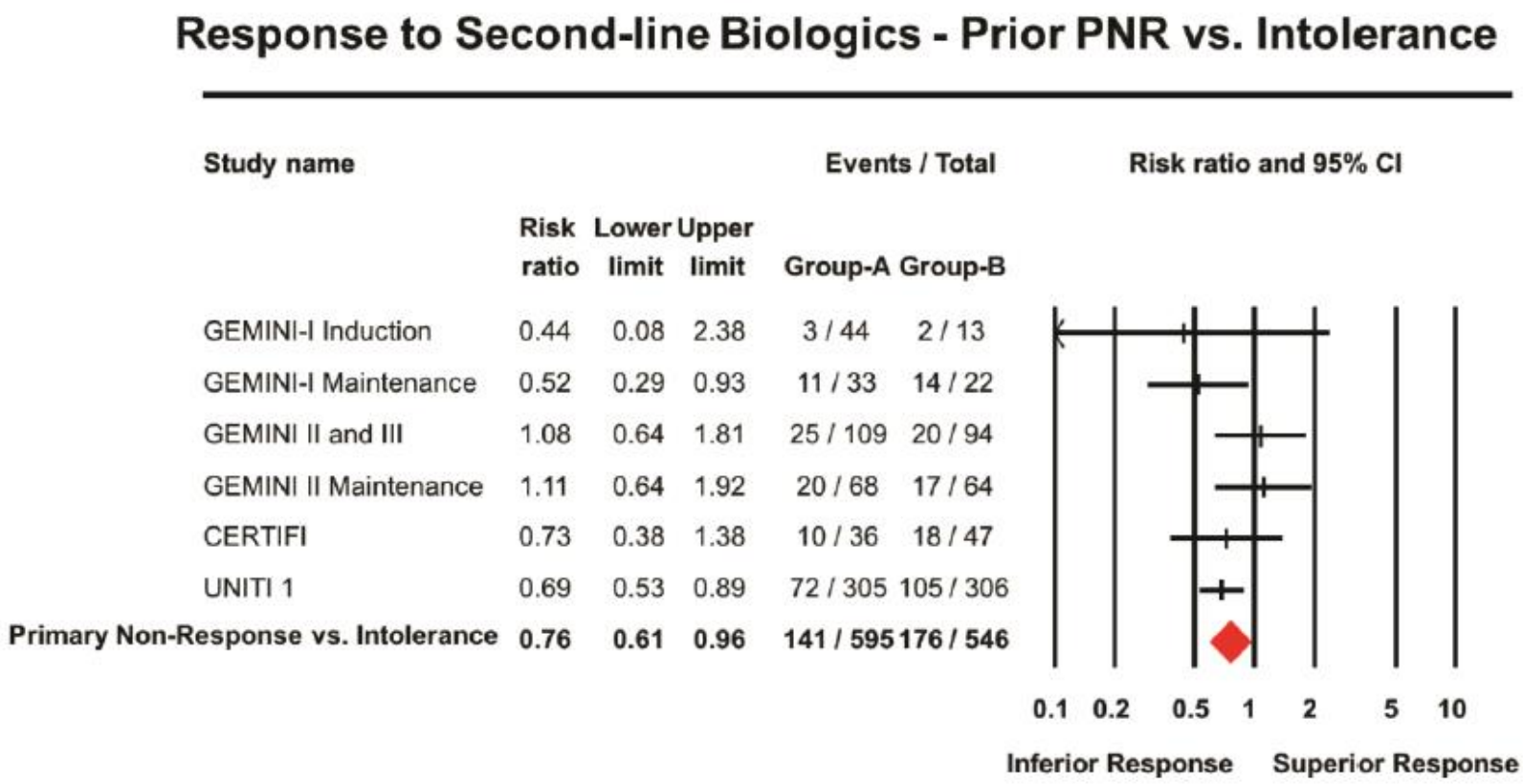


ACG 2018
October 5-10
Philadelphia, PA

[a]Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

Subjects who had a prohibited change in concomitant UC medication or an ostomy or colectomy prior to the Week 8 visit were considered not to be in clinical remission.
Subjects who had all 4 Mayo subscores missing at Week 8 were considered not to be in clinical remission. The p-values were based on the Cochran-Mantel-Haenszel (CMH) test.

Primary anti-TNF Non Response: Second Line Biologic…



Singh, J Crohns Colitis 2018

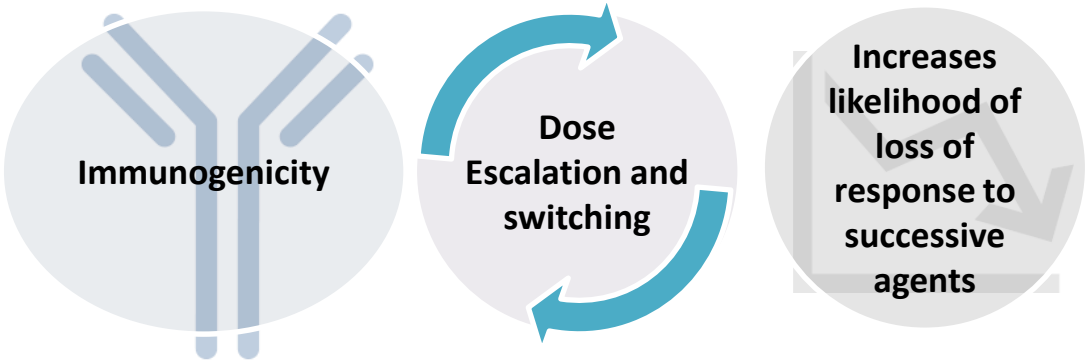
Ανεκπλήρωτες Θεραπευτικές Προσδοκίες στην Ελκώδη Κολίτιδα 2020 (βιολογικές θεραπείες)

Primary nonresponse: a lack of improvement in clinical signs and symptoms with induction therapy

Primary failure with first-line infliximab ranges from **19% to 58%**

Secondary nonresponse: the eventual loss of an initial clinical response

Secondary loss of response occurs in **up to 40%** of patients



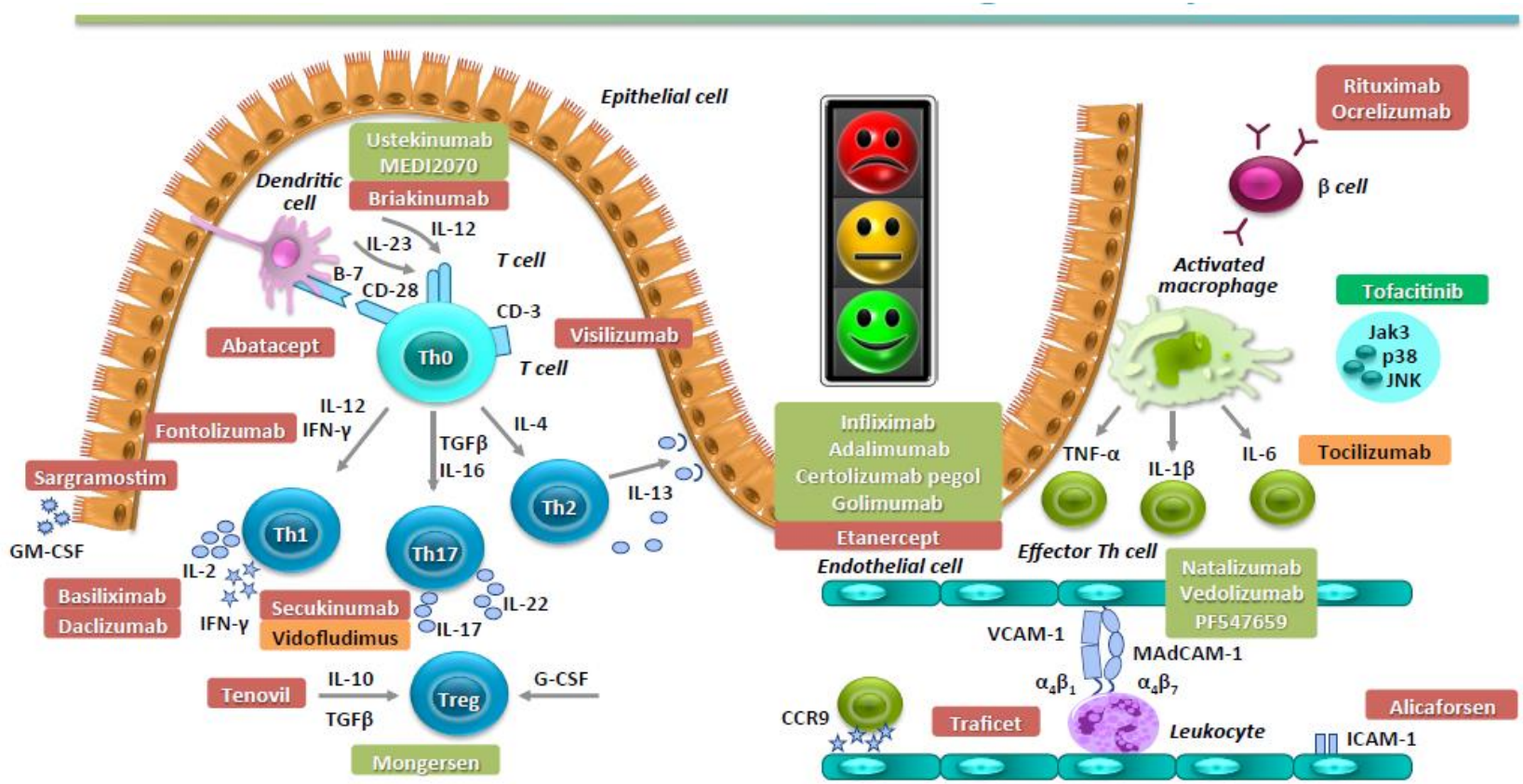
2020: Ασθενής και επιλογή θεραπείας

- ✓ (*Aminosalicylate compliance 45%)*
- ✓ *(Azathioprine missed doses 25%)*
- ✓ *(anti TNF adherence 82.6%)*
- ✓ ***effectiveness, long lasting action, rapid onset, few side effects…***
- ✓ ***ease of administration, time interval, fear of syringes, oral therapy****…*
- ✓ ***absence from work/home*** *(6,5 hours with infliximab)…*
- ✓ *different perception of disease impact between patients and physicians…*

48% dissatisfied with current treatment…

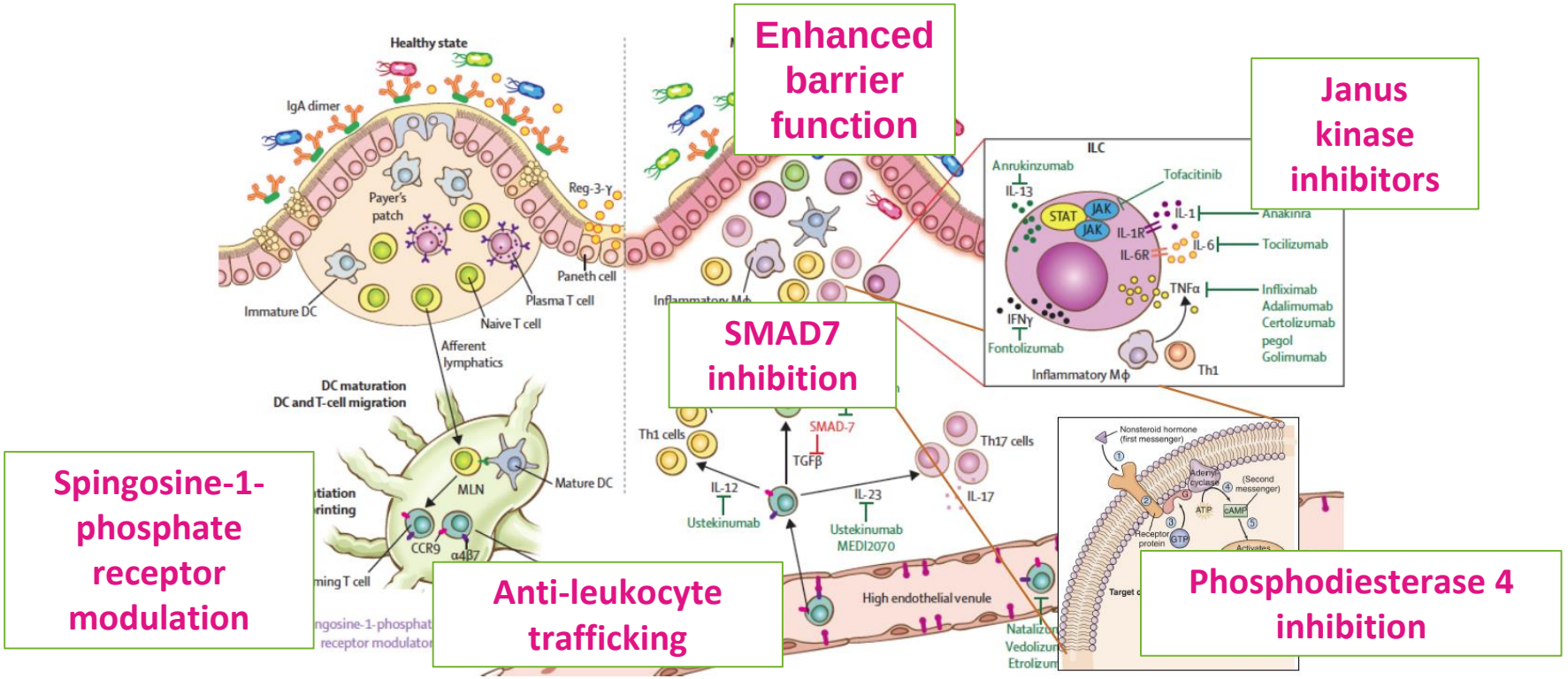
Danese, Dig Dis 2019

Νέες Θεραπείες στις ΙΦΝΕ



Adapted from Danese S, et al. Gut 2012;61:918–932

Νέοι Θεραπευτικοί στόχοι και Θεραπείες και ΙΦΝΕ



Ungaro, Lancet 2016

Μικρά Μόρια και Βιολογικοί Παράγοντες

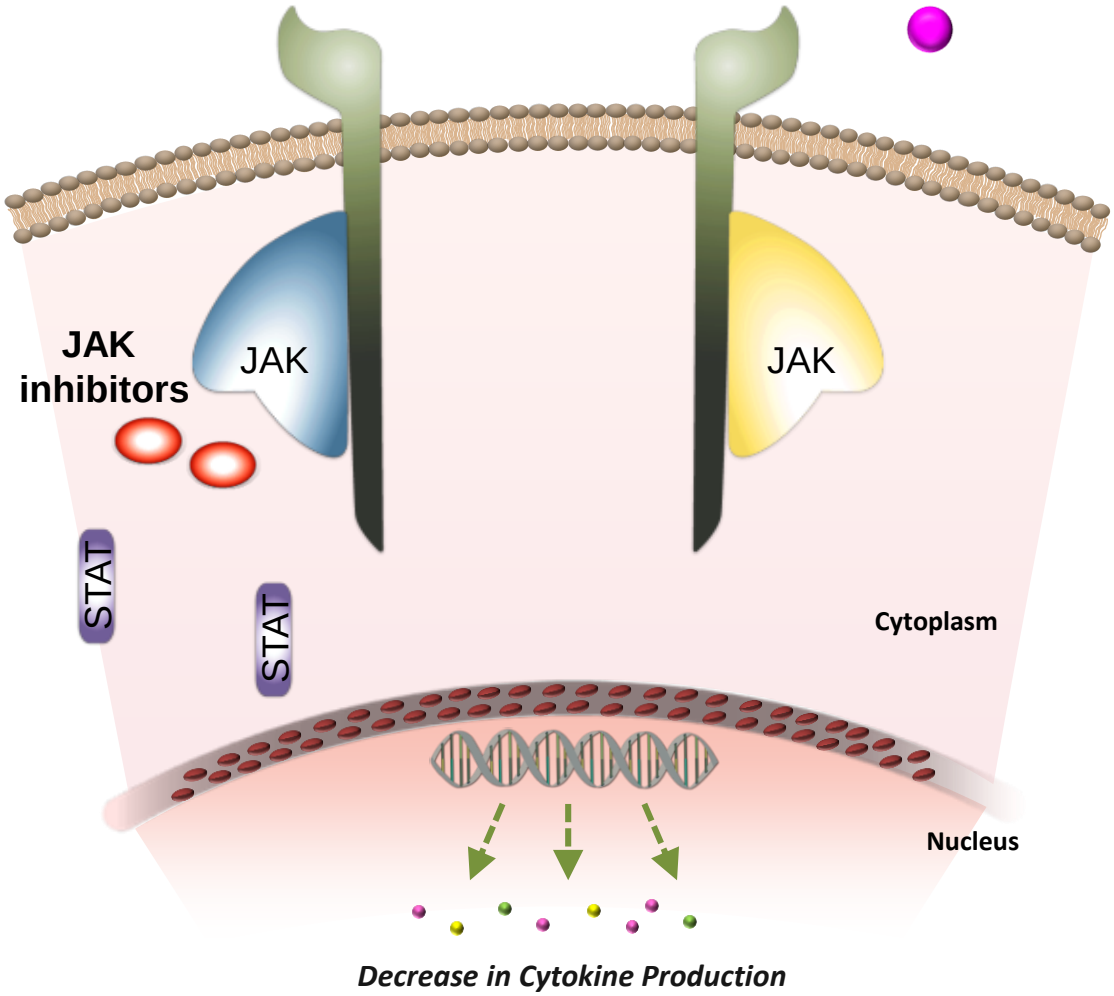
Table 1 Differences between small-molecule drugs (SMDs) and biologics[32 34 37]

	SMDs	Biologics
Molecular weight (Da)	<1000	>>1000
Chemical structure	Small organic compounds	Proteins
Location of target	Intracellular	Extracellular
Mechanism of action	Receptor or enzyme inhibition	Depletion
Route of administration	Oral	Parenteral
Distribution	Variable	Limited to plasma and extracellular fluids
Degradation	Metabolism	Proteolysis
Serum half-life	Short	Long
Antigenicity	Non-antigenic	Potentially antigenic
Drug–drug interactions	Possible	Infrequent
Toxicity	Specific toxicity due to the parent compound or metabolites. Possible 'off-target' effects	Receptor-mediated toxicity
Production	Chemical synthesis	Biological production
Cost of production	Variable	High
Generics	Identical	Biosimilar

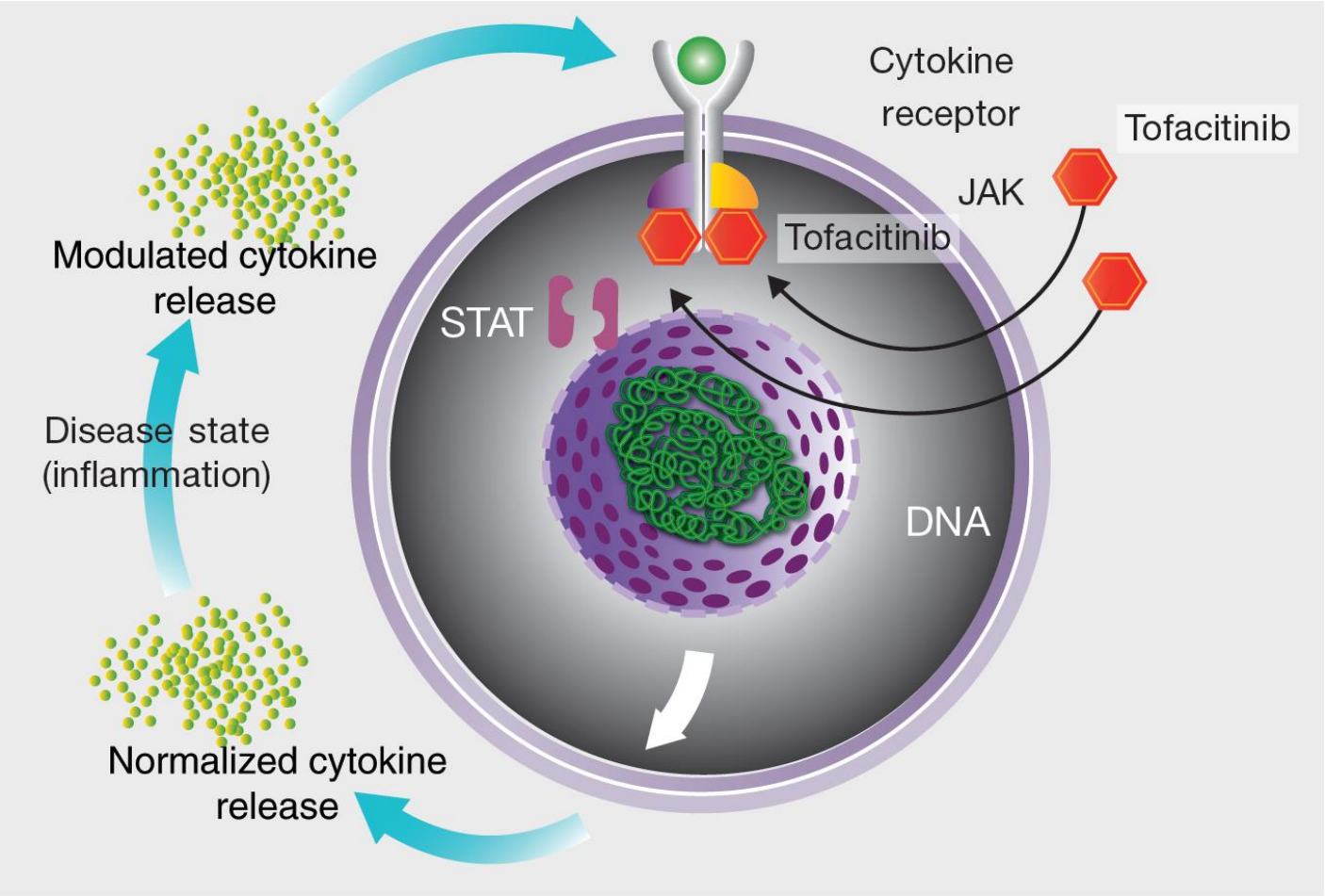
Olivera, Gut 2017

JAK Inhibitors: Μηχανισμός Δράσης

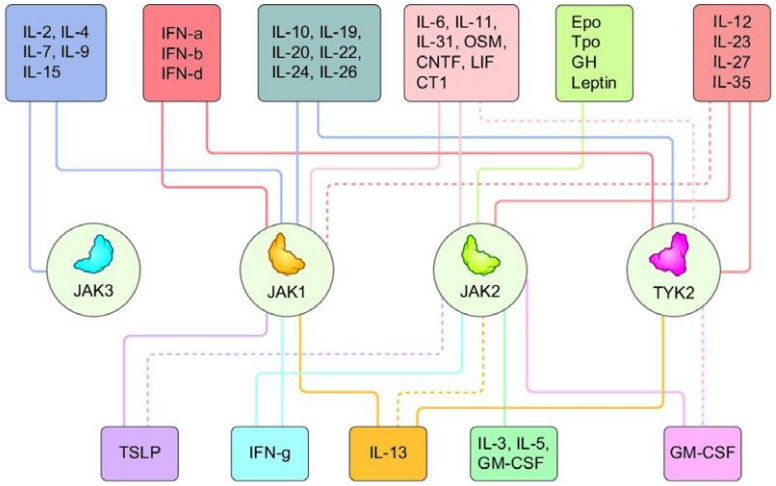
- Cytokines bind to cell surface receptors and activate JAKs
- JAK inhibitors work intracellularly to inhibit the phosphorylation and activation of JAKs
- Inactive JAKs prevent the phosphorylation and activation of STATs and activation of gene transcription
- Reduced production of inflammatory cytokines modulates the immune response



JAK inhibition (Tofacitinib) and Cytokines



JAKis and Ulcerative Colitis



JAK inhibitors currently approved or in development in patients with IBD.

Drug	Target	Gut selectivity	IBD type	Status
Tofacitinib	pan-JAK	No	CD UC	- FDA/EMA approved
Filgotinib	JAK1	No	CD[a] UC	Phase 3 recruiting (NCT02914600; NCT03077412; NCT03046056) Phase 3 recruiting (NCT02914535)
Upadacitinib	JAK1	No	CD UC	Phase 3 recruiting (NCT03345836) Phase 3 recruiting (NCT03006068)
TD-1473	pan-JAK	Yes	CD UC	Phase 2 recruiting (NCT03635112) Phase 2b/3 recruiting (NCT03758443)
Pf-06651600/ Pf-06700841	JAK3 JAK1/TYK2	No	CD UC	Phase 2a recruiting (NCT03395184) Phase 2b recruiting (NCT02958865)
BMS-986165	TYK2	No	CD UC	Phase 2 recruiting (NCT03599622) -

Danese, Gut 2019

JAK Inhibitors in Clinical Development for UC

JAK Inhibitor	Company	UC Status*	Target	Selectivity
Tofacitinib	Pfizer	Approved	JAK1 and JAK3 	• 20-fold selectivity for JAK3 over JAK2[3] • IC_{50} (nM): • JAK1=3.8; JAK2=10.7; JAK3=1.4; TYK2=24
Filgotinib	Gilead, Galapagos	Phase 3	JAK1 	• 30-fold selectivity for JAK1 over JAK2 • IC_{50} (nM): • JAK1=10; JAK2=28; JAK3=810; TYK2=110
Upadacitinib	AbbVie	Phase 2/3	JAK1 	• 74-fold selectivity for JAK1 over JAK2

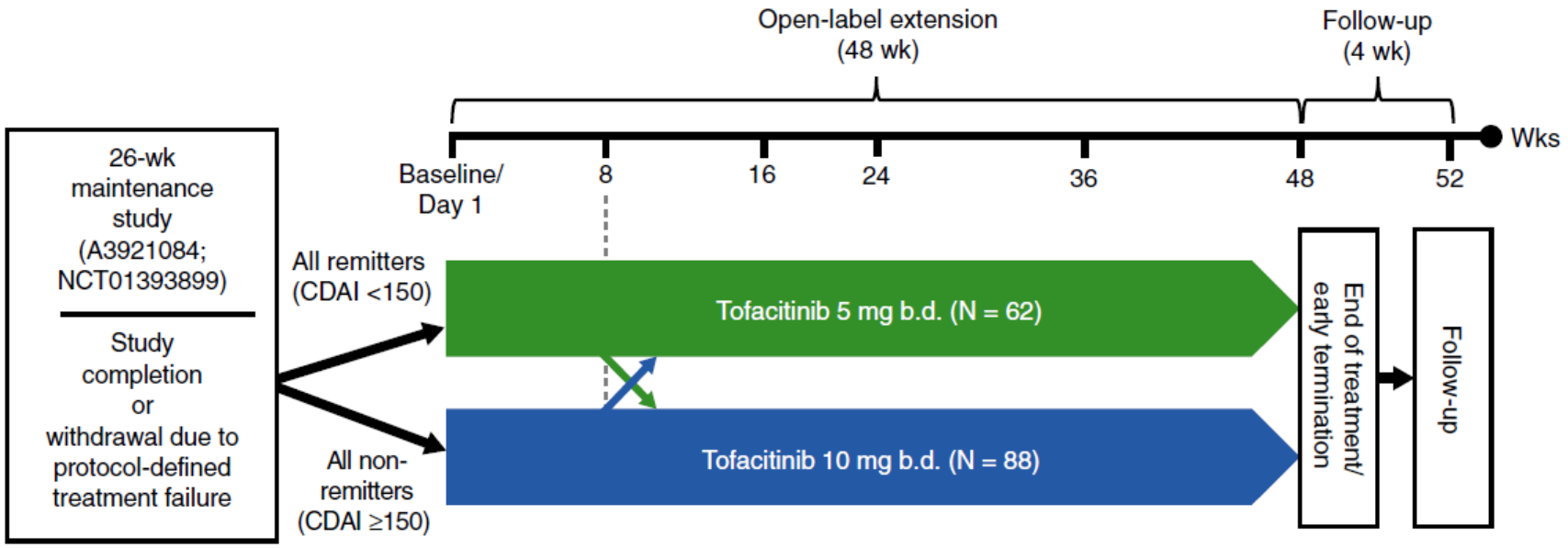
Tofacitinib (CP-690,550) an oral JAK inhibitor

Inhibits JAK1, JAK2, and JAK3 in vitro

Functional cellular specificity for JAK1 and JAK3 over JAK2

Modulates signaling for an important subset of pro-inflammatory cytokines: IL-2, -4, -7, -9, -15, and -21

Tofacitinib στη νόσο του Crohn: Αρνητική μελέτη…



Panes, Aliment Pharmacol Therap 2019

Tofacitinib στην Ελκώδη Κολίτιδα

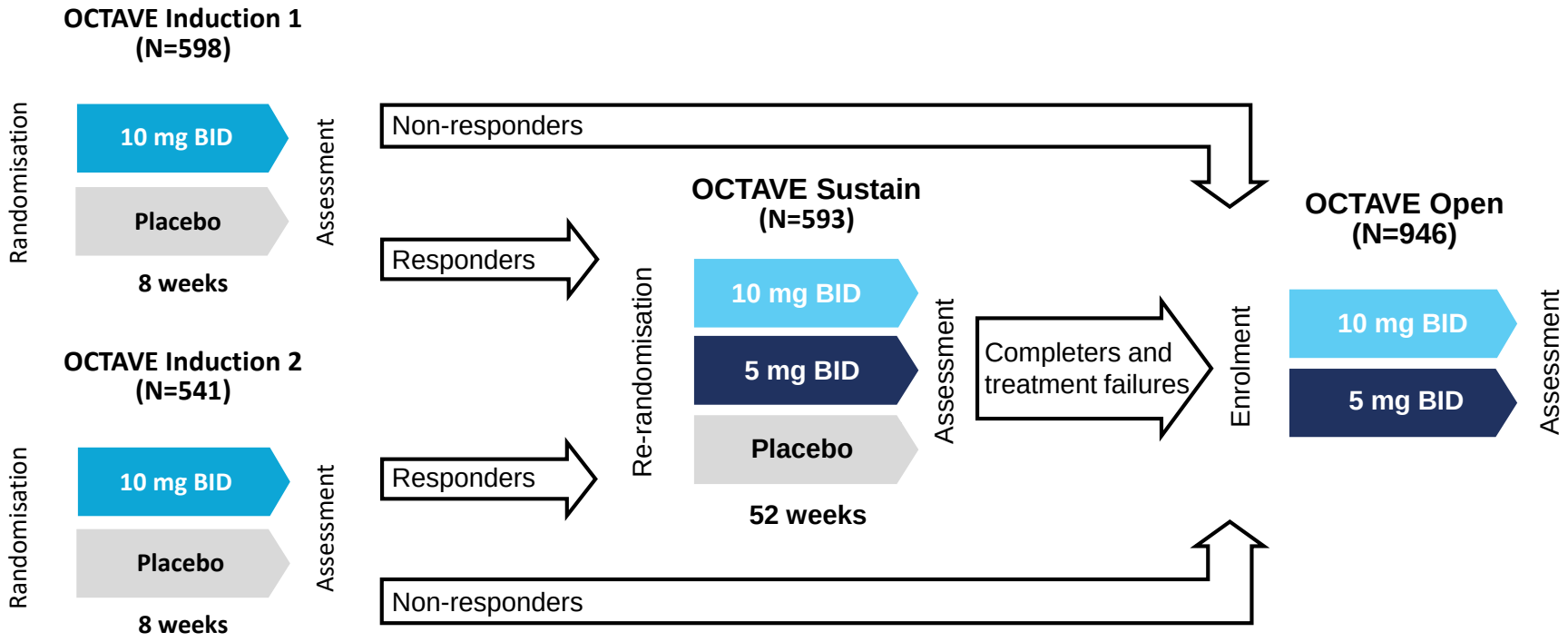
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

William J. Sandborn, M.D., Chinyu Su, M.D., Bruce E. Sands, M.D., Geert R. D'Haens, M.D., Séverine Vermeire, M.D., Ph.D., Stefan Schreiber, M.D., Silvio Danese, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Wojciech Niezychowski, M.D., Gary Friedman, M.D., Nervin Lawendy, Pharm.D., Dahong Yu, M.D., Ph.D., Deborah Woodworth, M.B.A., Arnab Mukherjee, Ph.D., Haiying Zhang, Ph.D., Paul Healey, M.D., and Julian Panés, M.D., for the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators*

OCTAVE clinical programme design



BID=twice daily.

Κριτήρια ένταξης του κλινικού προγράμματος OCTAVE

OCTAVE Induction 1 and 2: Key inclusion criteria
Adults with moderately to severely active UC for ≥4 months[1-3]
History of failure or intolerance to ≥1 of the following treatments:[1,2] • Oral or IV CS • AZA or 6-MP • TNF inhibitors: infliximab or adalimumab[3]
Permitted concomitant medications included stable doses of:[3] • Oral 5-ASA or SSZ • Oral CS (prednisone daily dose ≤25 mg equivalent; permissible in OCTAVE Induction 1 and 2 only)
OCTAVE Sustain: Key study criteria
Prohibited concomitant medications included oral immunomodulators or biologic therapies[3]
Only OCTAVE Induction 1 and 2 responders were eligible to enter OCTAVE Sustain[4]
Mandatory steroid taper from baseline[3]

5-ASA=5-aminosalicylic acid; 6-MP=6-mercaptopurine; AZA=azathioprine; CS=corticosteroid; IV=intravenous; SSZ=sulfasalazine; TNF=tumour necrosis factor.

1. ClinicalTrials.gov. NCT01465763 (OCTAVE Induction 1). 2. ClinicalTrials.gov. NCT01458951 (OCTAVE Induction 2). 3. Data on file. Pfizer Inc, New York, NY.
4. ClinicalTrials.gov. NCT01458574 (OCTAVE Sustain).

Πρόγραμμα Μελετών OCTAVE:
Οι μισοί ασθενείς σε στεροειδή, anti TNF αποτυχίες

Table 1. Baseline Demographic and Disease Characteristics of the Patients in the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Trials.*

Characteristic	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=197)
Male sex — no. (%)†	77 (63.1)	277 (58.2)	55 (49.1)	259 (60.4)	116 (58.6)	103 (52.0)	110 (55.8)
Age — yr‡	41.8±15.3	41.3±14.1	40.4±13.2	41.1±13.5	43.4±14.0	41.9±13.7	42.9±14.4
Induction-trial group assignment — no. (%)							
Placebo	—	—	—	—	24 (12.1)	22 (11.1)	24 (12.2)
Tofacitinib, 10 mg twice daily	—	—	—	—	167 (84.3)	170 (85.9)	167 (84.8)
Tofacitinib, 15 mg twice daily	—	—	—	—	7 (3.5)	6 (3.0)	6 (3.0)
Remission at maintenance-trial entry — no. (%)	—	—	—	—	59 (29.8)	65 (32.8)	55 (27.9)
Duration of disease — yr‡							
Median	6.0	6.5	6.2	6.0	7.2	6.5	6.8
Range	0.5–36.2	0.3–42.5	0.4–27.9	0.4–39.4	0.6–42.7	0.6–40.3	0.6–35.7
Extent of disease — no./total no. (%)¶¶							
Proctosigmoiditis	19/122 (15.6)	65/475 (13.7)	16/111 (14.4)	67/428 (15.7)	21/198 (10.6)	28/196 (14.3)	33/196 (16.8)
Left-sided colitis	37/122 (30.3)	158/475 (33.3)	39/111 (35.1)	149/428 (34.8)	68/198 (34.3)	66/196 (33.7)	60/196 (30.6)
Extensive colitis or pancolitis	66/122 (54.1)	252/475 (53.1)	56/111 (50.5)	211/428 (49.3)	108/198 (54.5)	102/196 (52.0)	103/196 (52.6)
Total Mayo score‡‖	9.1±1.4	9.0±1.4	8.9±1.5	9.0±1.5	3.3±1.8	3.3±1.8	3.4±1.8
Partial Mayo score‡‖	6.5±1.2	6.3±1.2	6.4±1.2	6.4±1.3	1.8±1.4	1.8±1.3	1.8±1.3
C-reactive protein — mg/liter‡							
Median	4.7	4.4	5.0	4.6	1.0	0.7	0.9
Range	0.1–82.5	0.1–208.4	0.2–205.1	0.2–156.0	0.1–45.0	0.1–33.7	0.1–74.3
Oral glucocorticoid use at baseline — no. (%)‡	58 (47.5)	214 (45.0)	55 (49.1)	198 (46.2)	100 (50.5)	101 (51.0)	87 (44.2)
Previous treatment with TNF antagonist — no. (%)§	65 (53.3)	254 (53.4)	65 (58.0)	234 (54.5)	92 (46.5)	90 (45.5)	101 (51.3)
Previous treatment failure — no. (%)§**							
TNF antagonist	64 (52.5)	243 (51.1)	60 (53.6)	222 (51.7)	89 (44.9)	83 (41.9)	93 (47.2)
Glucocorticoid	98 (80.3)	350 (73.5)	83 (74.1)	303 (70.6)	151 (76.3)	145 (73.2)	149 (75.6)
Immunosuppressant††	83 (68.0)	360 (75.6)	75 (67.0)	301 (70.2)	129 (65.2)	143 (72.2)	141 (71.6)

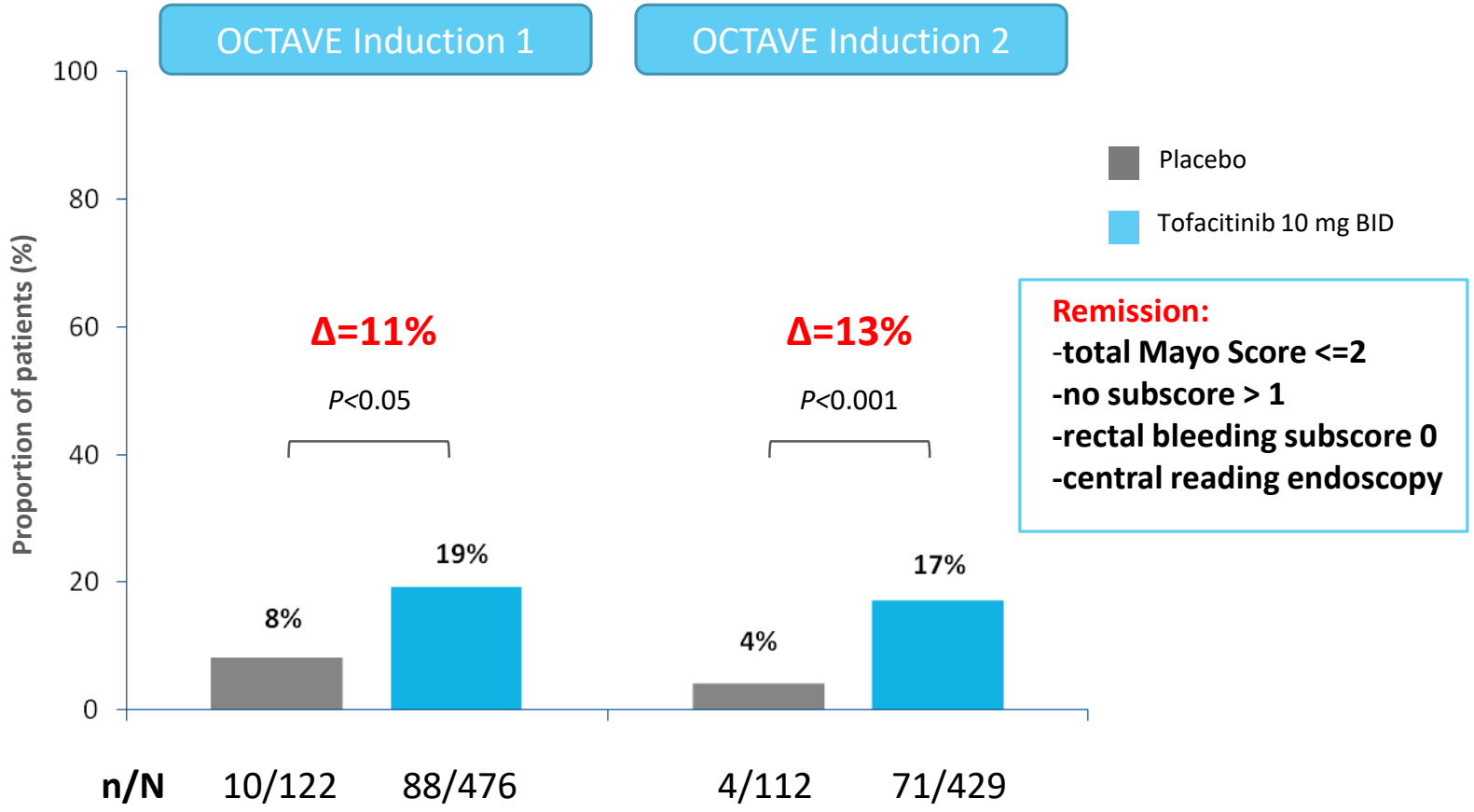
* Plus–minus values are means ±SD. There were no significant differences between groups within each trial unless otherwise noted. TNF denotes tumor necrosis factor.
† In the OCTAVE Induction 2 trial, there was a significant difference between groups in the proportion of male patients (P=0.03).
‡ For the OCTAVE Sustain trial, the baseline values were obtained at the time of entry in the OCTAVE Sustain trial.
§ For the OCTAVE Sustain trial, the baseline values were obtained at the time of entry into one of the induction trials (OCTAVE Induction 1 or 2).
¶ Data on extent of disease are missing for three patients.
‖ The total Mayo score ranges from 0 to 12 and the partial Mayo score (i.e., the total Mayo score excluding the endoscopic subscore) ranges from 0 to 9, with higher scores indicating more severe disease.
** Previous treatment failure was determined by the investigator.
†† Immunosuppressants included agents such as azathioprine and mercaptopurine and did not include biologic agents (e.g., TNF antagonists) or glucocorticocoids.

Πρωτεύοντα και δευτερεύοντα καταληκτικά σημεία

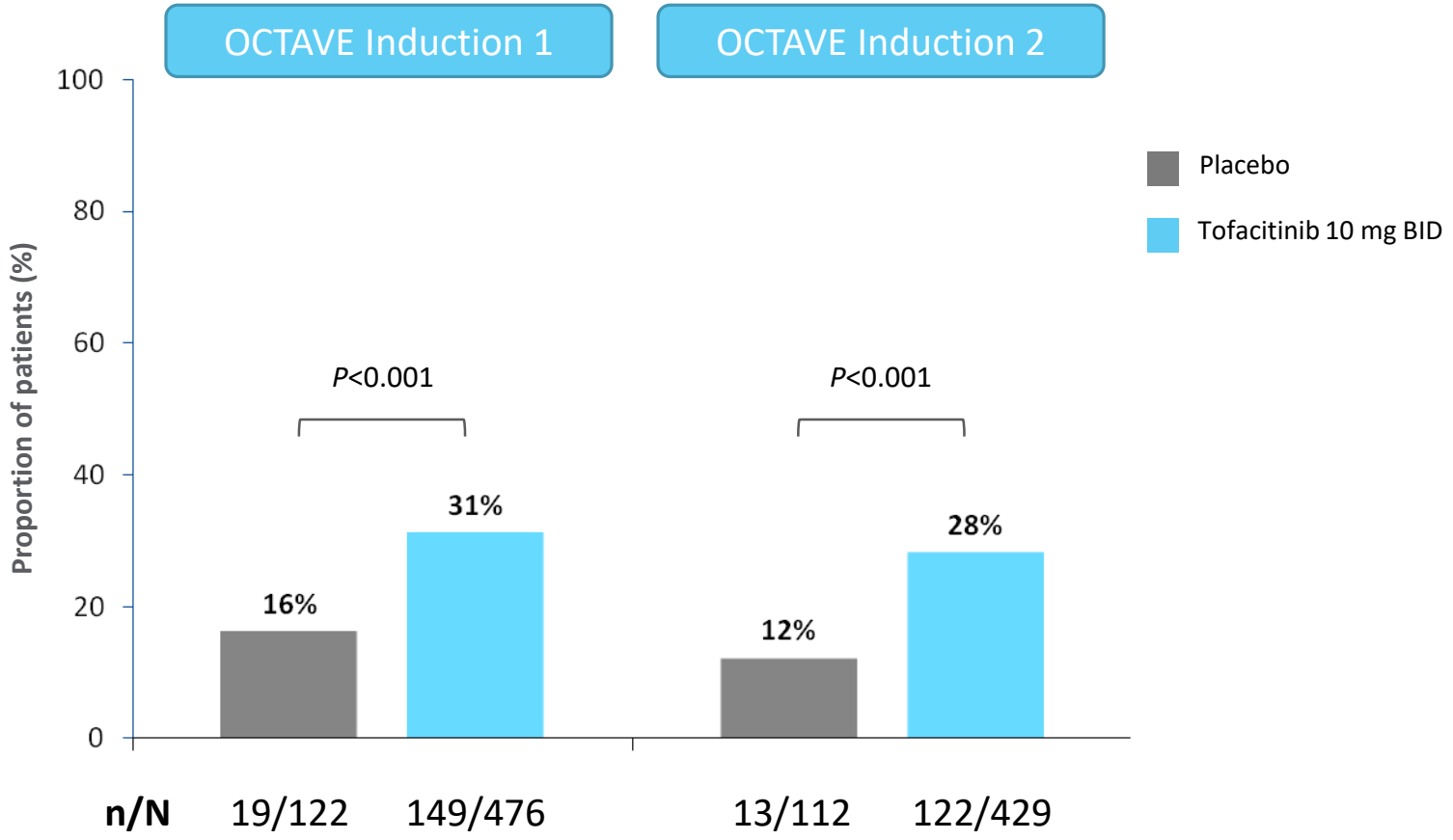
Endpoint		Definition
OCTAVE Induction 1 and Induction 2		
Primary endpoint	• Remission at week 8	• Total Mayo score ≤2 • No subscore >1 • Rectal bleeding subscore =0
Key secondary endpoint	• Mucosal healing at week 8	• Endoscopic subscore ≤1
OCTAVE Sustain		
Primary endpoint	• Remission at week 52	• Total Mayo score ≤2 • Rectal bleeding subscore =0
Key secondary endpoints	• Mucosal healing at week 52	• Endoscopic subscore ≤1
	• Sustained CS-free remission	• CS-free and in remission at weeks 24 and 52, in patients who were in remission at baseline

CS=corticosteroid

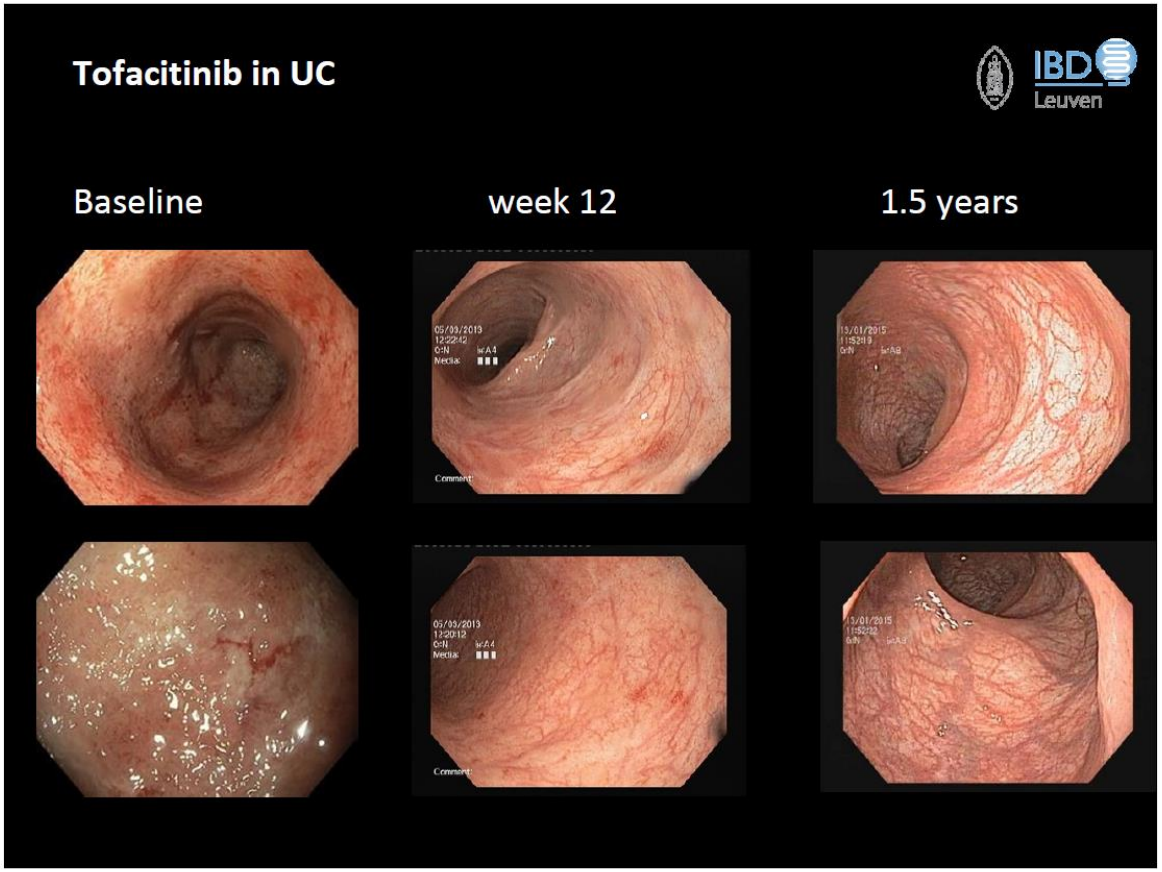
Πρωτεύον καταληκτικό σημείο : Ύφεση την εβδομάδα 8



Δευτερεύον καταληκτικό : Mucosal Healing την εβδομάδα 8

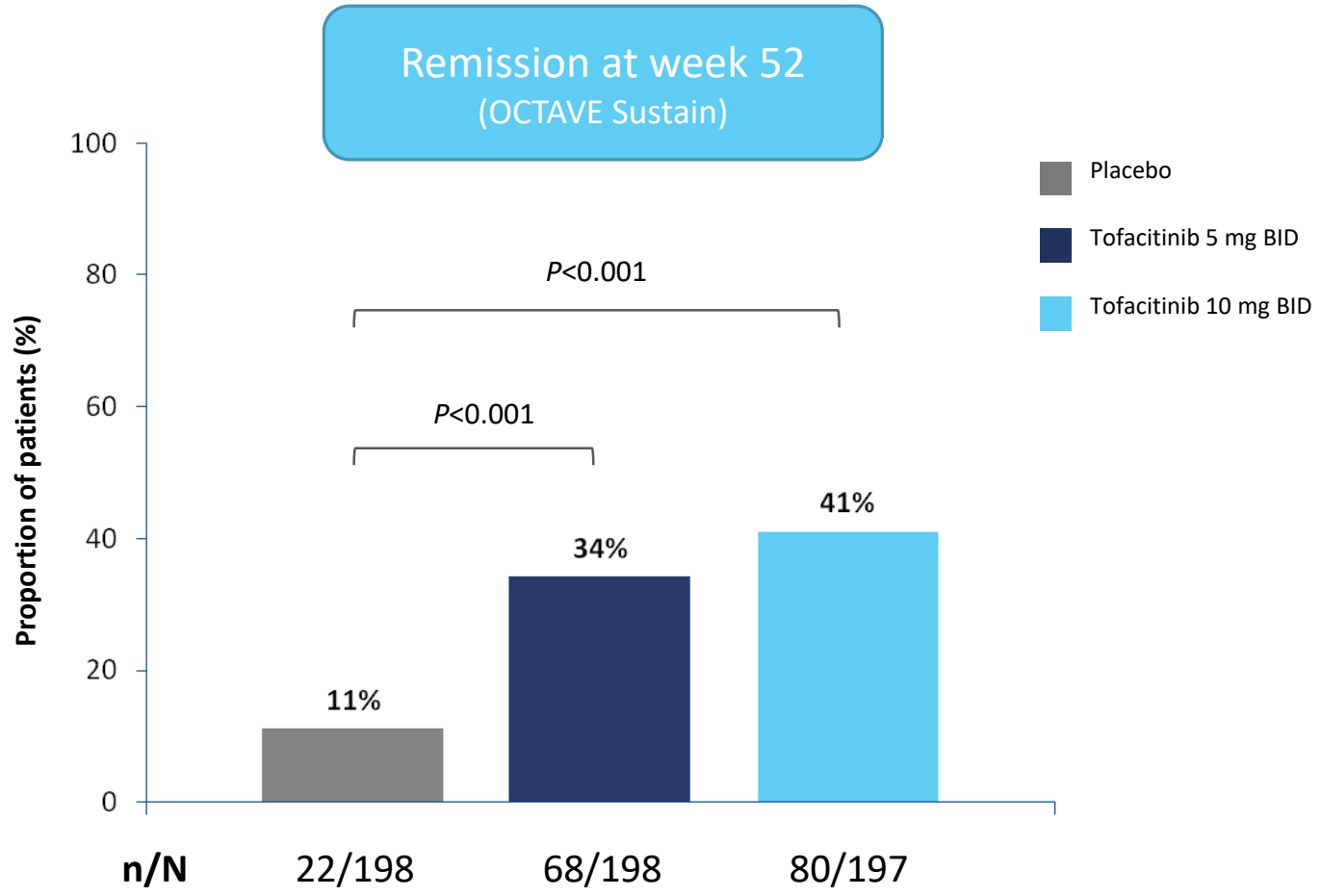


Mucosal Healing with Tofacitinib

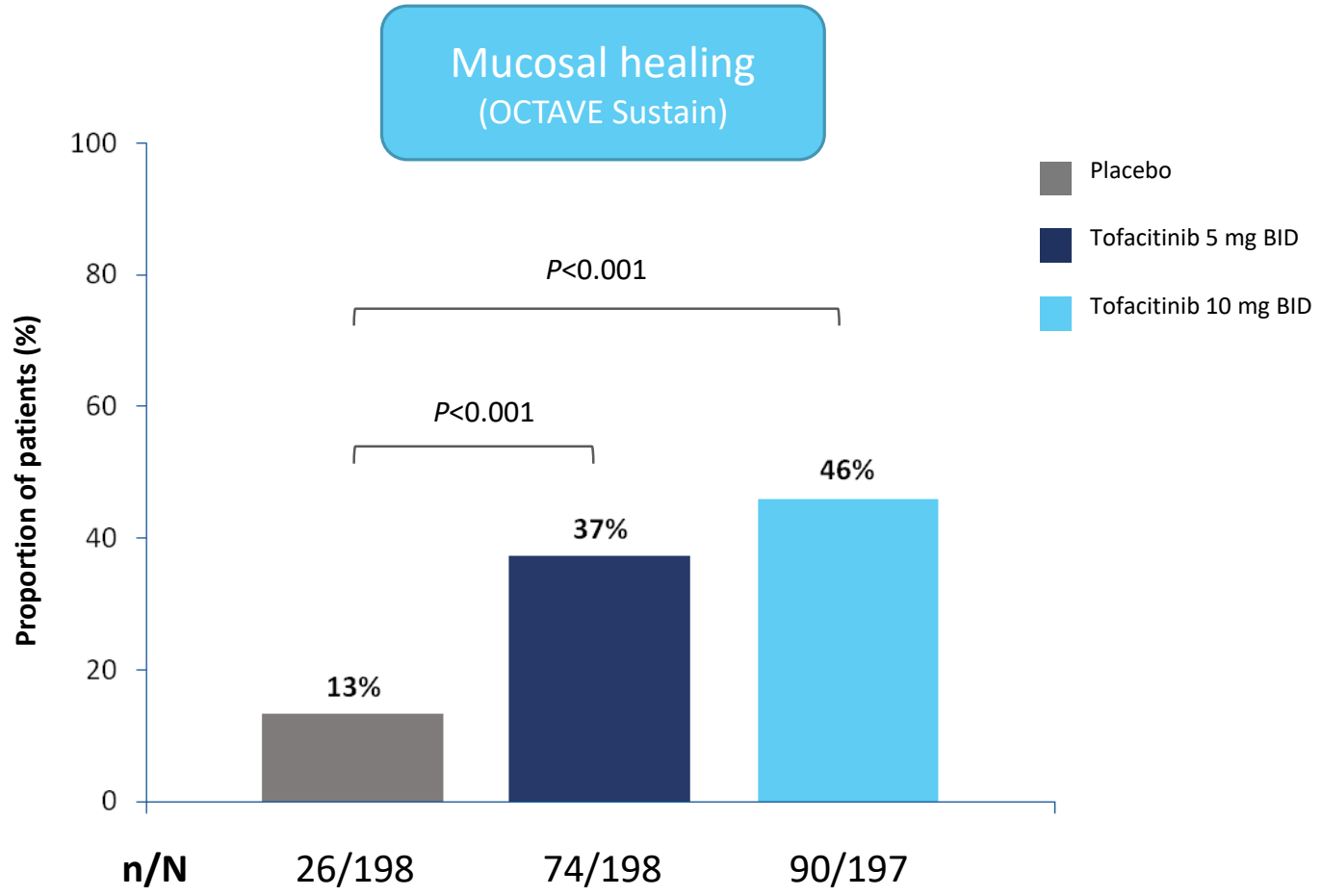


Από Vermeire, ECCO IBD Masterclass 2018

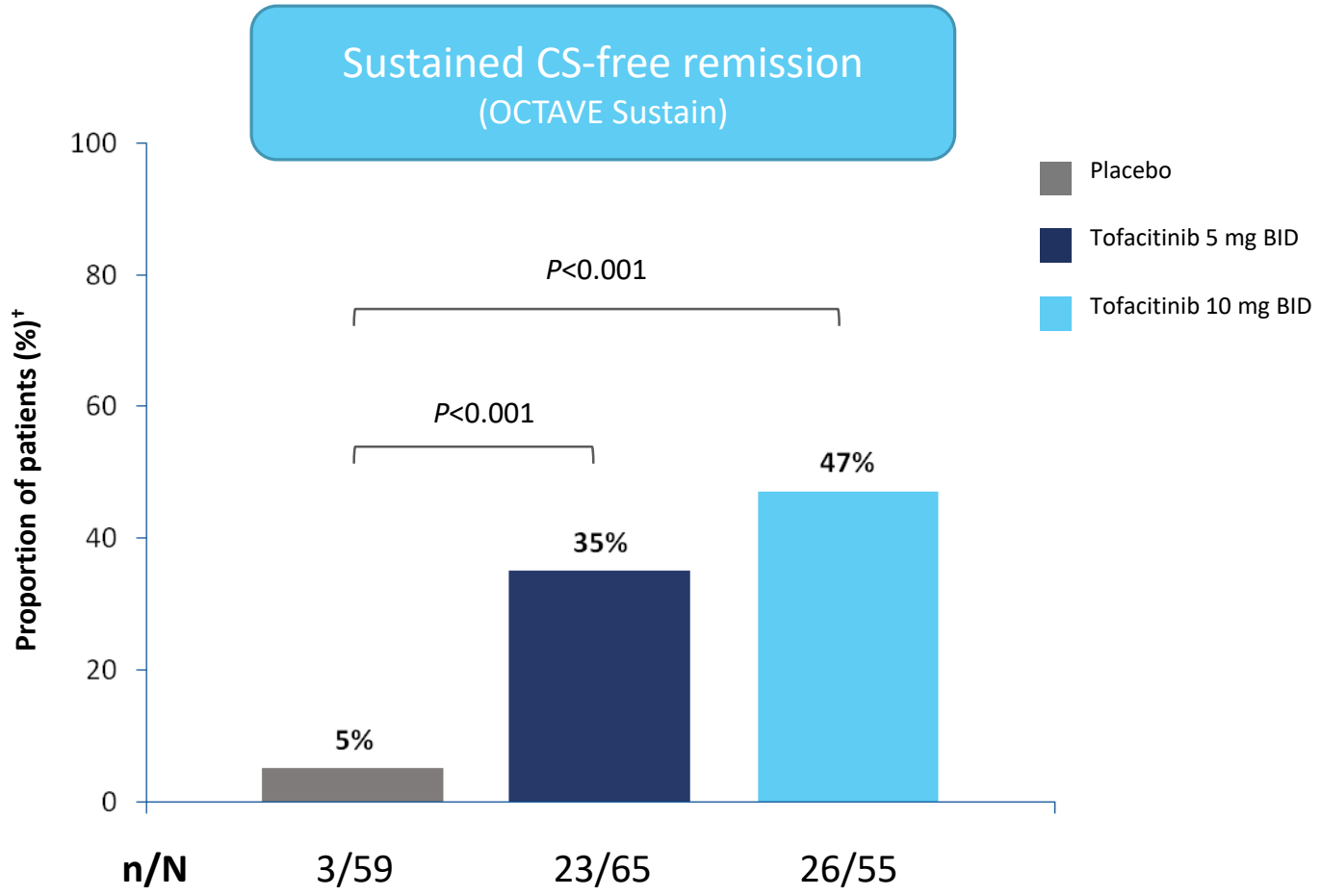
OCTAVE SUSTAIN
Διατήρηση της Ύφεσης την Εβδομάδα 52



OCTAVE Sustain:
Δευτερεύον καταληκτικό: Mucosal Healing την εβδομάδα 52



OCTAVE Sustain:
Ύφεση χωρίς στεροειδή την εβδομάδα 24 και 52



†Among those who were in remission at OCTAVE Sustain entry.
BID=twice daily; CS=corticosteroid.

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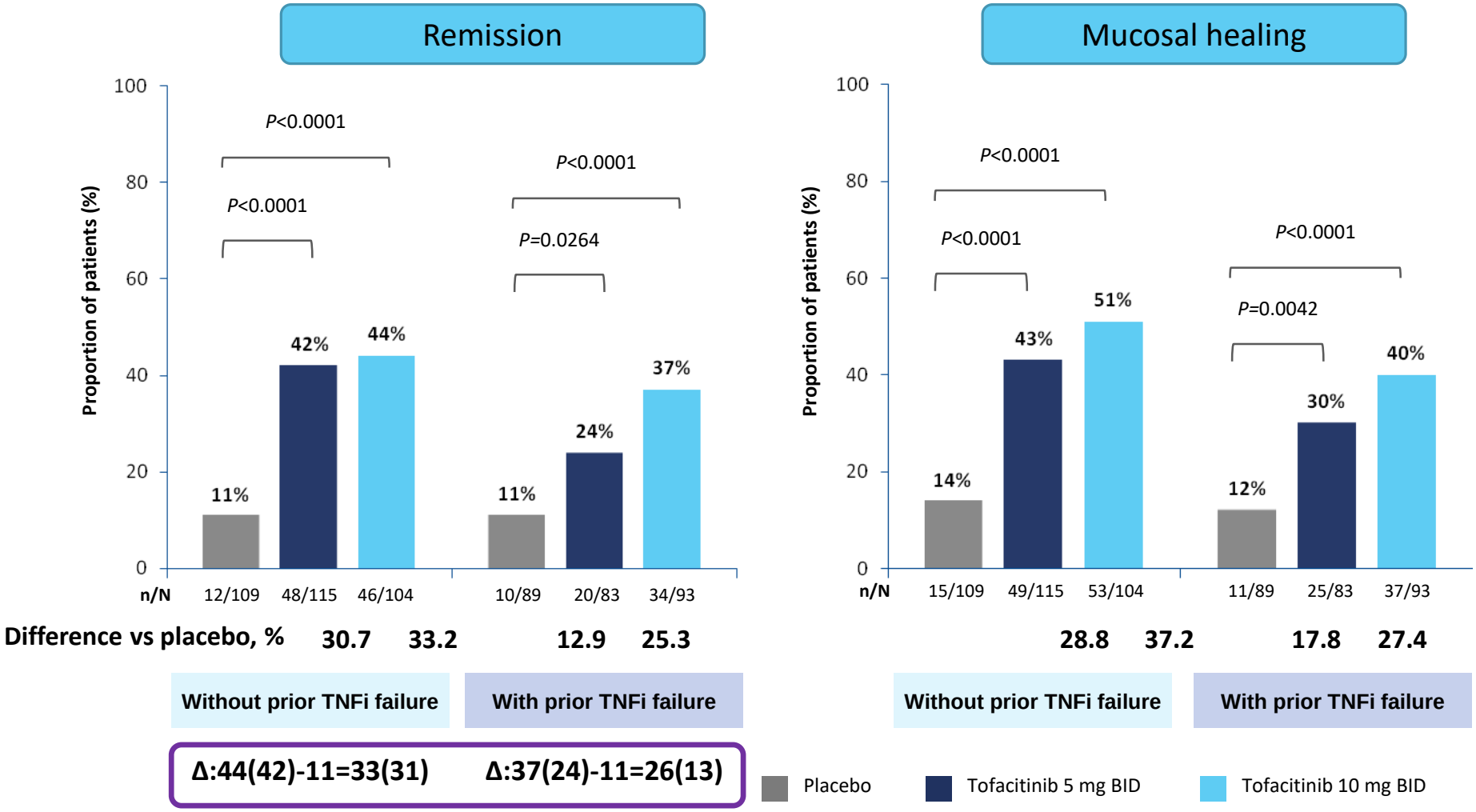
Prior anti-TNFα failure: Ύφεση και Mucosal Healing την εβδομάδα 52



Οι διαφορές (δέλτα) συγκρίσιμες, ειδικά στα 10 mg BID

1st and 2nd Line in Ulcerative Colitis Network Metanalysis

Induction of Remission-bionaive

Agent	SUCRA	%
Infliximab	0.85	30.9%
Adalimumab	0.31	16.1%
Golimumab	0.58	23.0%
Vedolizumab	0.82	31.6%
Tofacitinib	0.43	18.9%

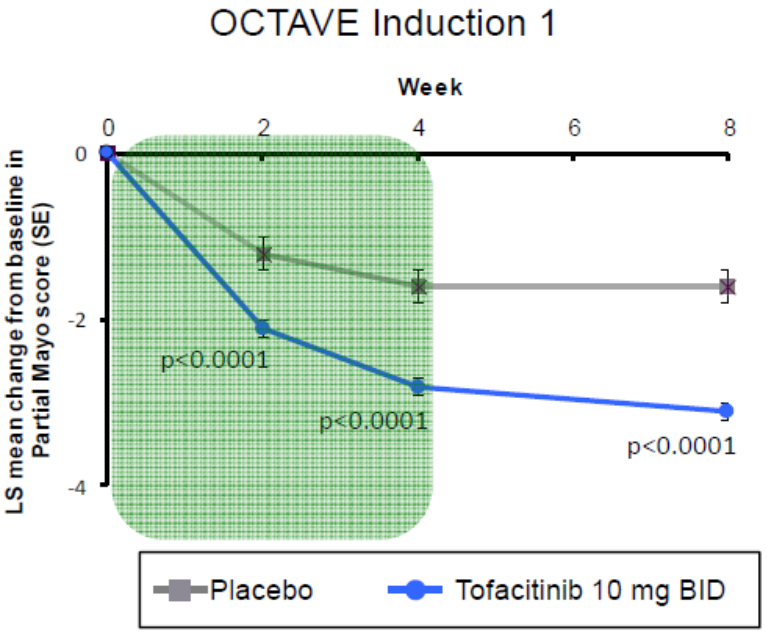
Induction of Remission-prior anti-TNF

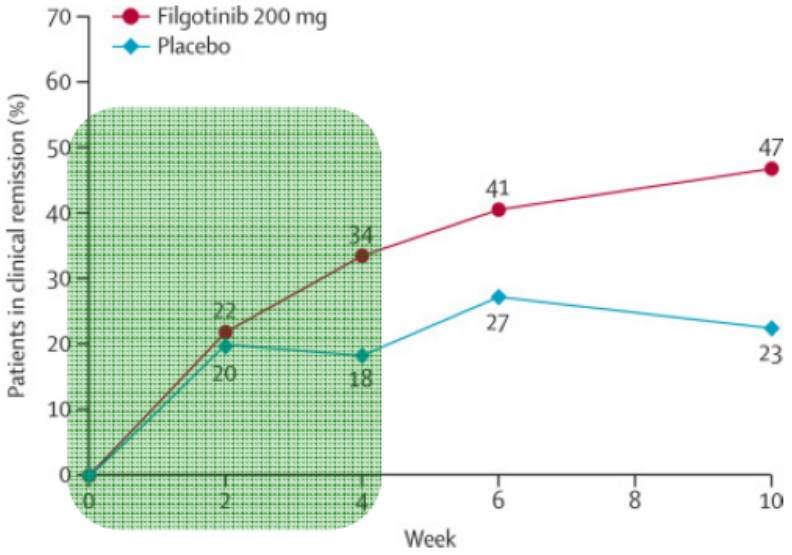
Agent	SUCRA	%
Adalimumab	0.31	4.4%
Vedolizumab	0.62	10.1%
Tofacitinib	0.96	28.8%
Infliximab	-	-
Golimumab	-	-

Tofacitinib: βέλτιστη επιλογή μετά από αποτυχία anti TNF

Singh, Aliment Pharmacol Ther 2017

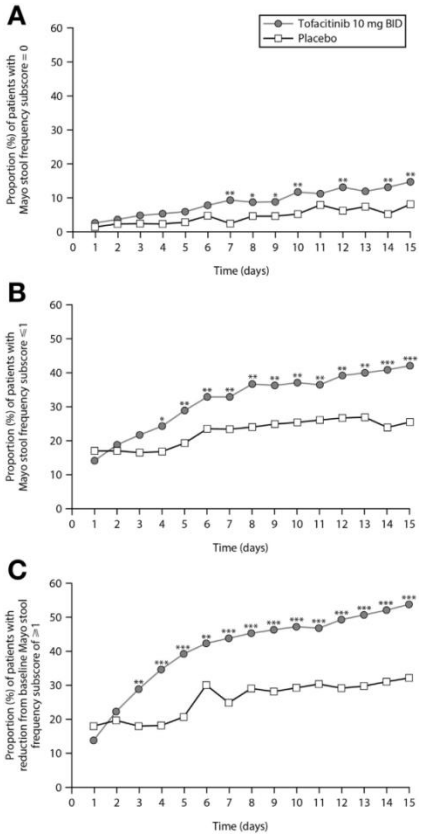
Ταχεία Δράση των JAK αναστολέων



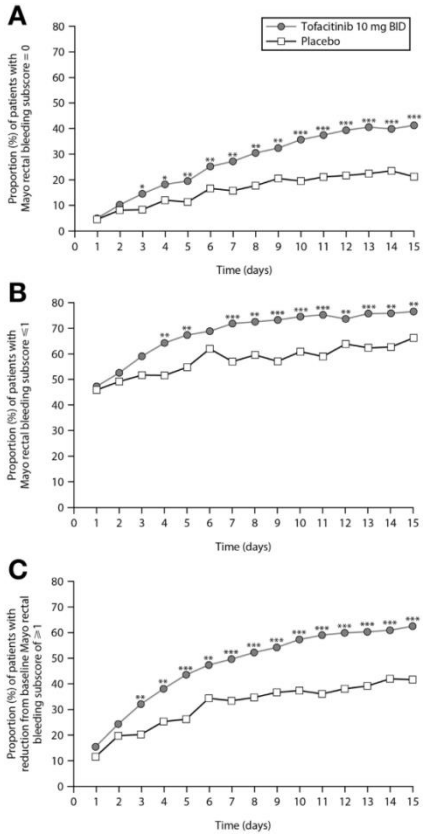


Υπερταχεία Δράση tofacitinib: 3 ημέρες

Συχνότητα Κενώσεων



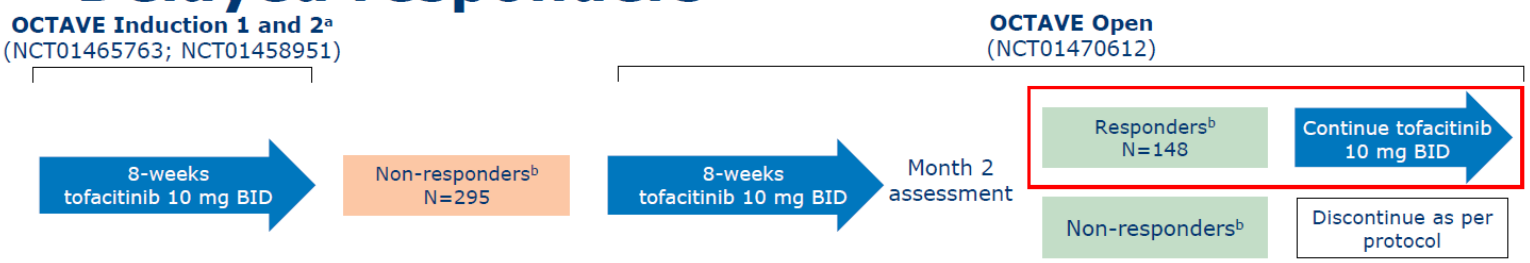
Αίμα από το Ορθό



Hanauer, Clin Gastroenterol Hepatol 2019

Late (W16) Vs Early (W8) Responders

Delayed responders



- 429 induction non-responder patients entered OCTAVE Open, of which 295 received tofacitinib 10 mg BID during induction
- At Week 8 of OCTAVE Open – ie after a total of 16 weeks induction (extended induction)
  - Patients who were still non-responders were required to discontinue, as per the protocol
  - Patients who achieved a clinical response - ie delayed responders - continued on tofacitinib 10 mg BID in OCTAVE Open (N=148)
- Efficacy was evaluated for continue tofacitinib treatment in OCTAVE Open for these delayed responders
- Safety data presented for the overall UC clinical trial program

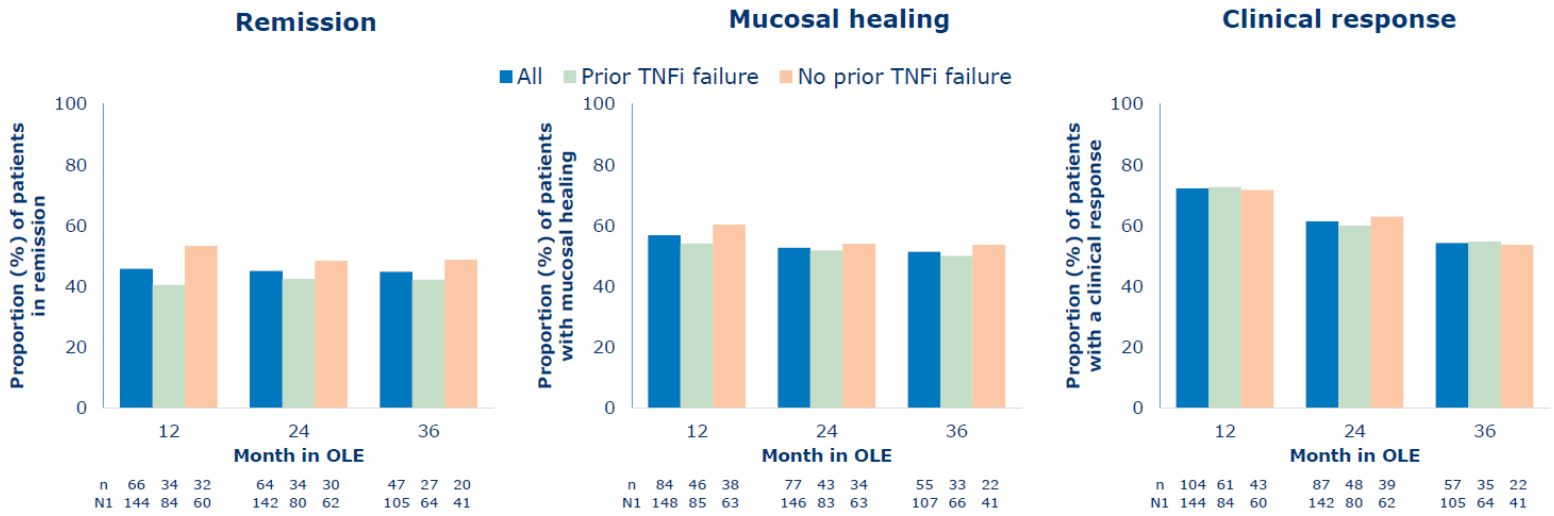
[a]Patients received either placebo (N=234) or tofacitinib 10 mg BID (N=905) during OCTAVE Induction 1 and 2. Induction responders entered OCTAVE Sustain and received placebo, tofacitinib 5 or 10 mg BID for 52 weeks; [b]Responders were defined as patients with a decrease from induction baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1 [centrally read].

BID, twice daily

Rubin, DOP 43, ECCO 2019, Copenhagen

Early versus Late Responders:
Στο έτος παρόμοια αποτελεσματικότητα

Delayed responder responses in OLE



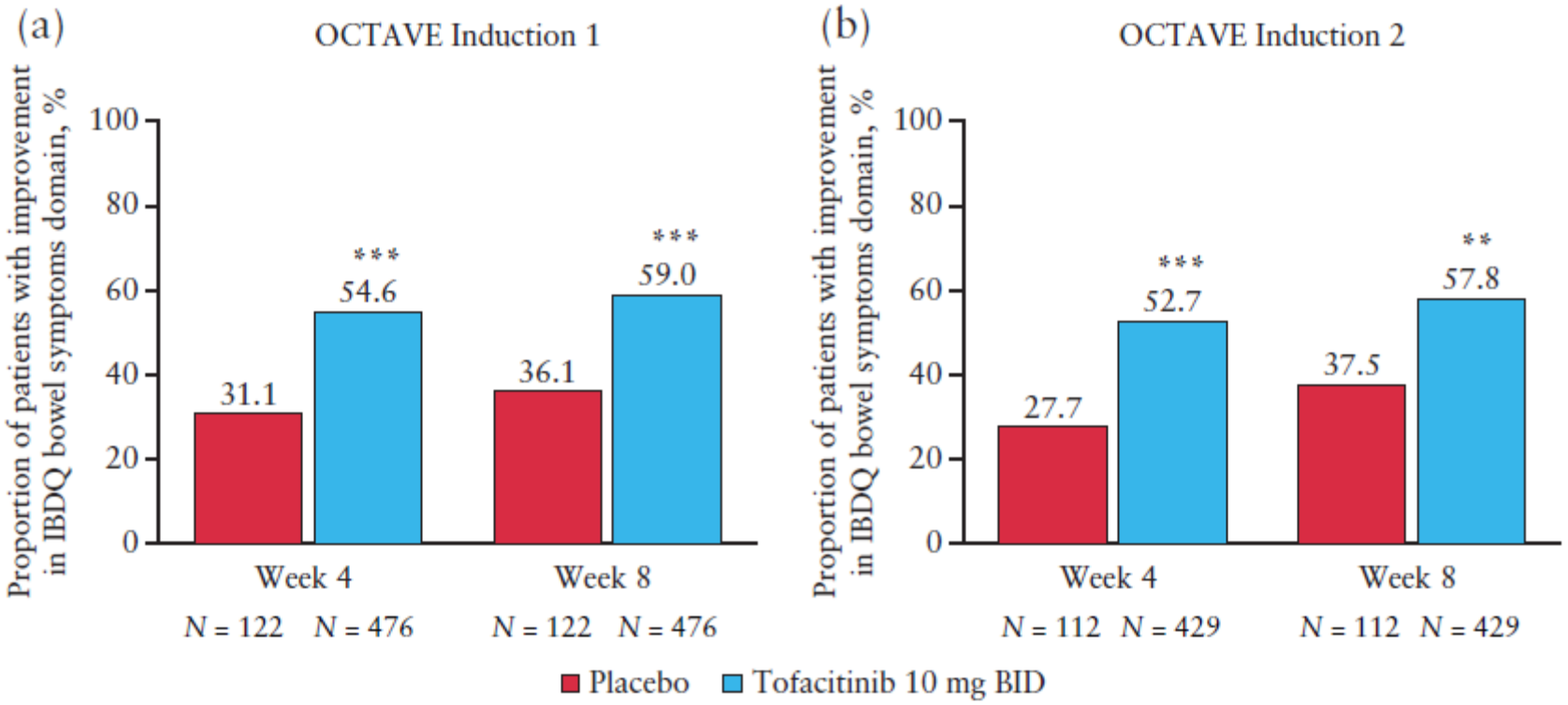
- Month 12 delayed responder patient responses were similar to Month 12 responses of 8-week induction responders who stayed on tofacitinib 10 mg BID in OCTAVE Sustain (41.0% remission; 46.2% mucosal healing; 61.8% clinical response)

Only patients who were in clinical response at Month 2 per central read of endoscopy are included in this analysis. Months 12, 24 and 36 data are based on local read endoscopy with non-responder imputation for missing data

BID, twice daily; N1, number of patients who could have reached time point (based on enrolment dates and last non-missing total Mayo score); n, number of patients with the specified response within the given category; OLE, open-label, long-term extension; TNFi, tumour necrosis factor inhibitor

Rubin, DOP 43, ECCO 2019, Copenhagen

Tofacitinib και Ποιότητα Ζωής



Panes, J Crohns Colitis 2019

Tofacitinib-UC: Αποτελεσματικό στην Επαγωγή της Ύφεσης

Table 1 Tofacitinib as induction therapy in ulcerative colitis

Phase/study	Treatment	Size	Clinical response at 8 weeks, % (*p*)	Clinical remission at 8 weeks, % (*p*)	Endoscopic response at 8 weeks, % (*p*)	Mucosal healing at 8 weeks, % (*p*)	Endoscopic remission at 8 weeks, % (*p*)
Phase II Induction	Placebo	48	42%	10%	46%	Not available	2%
Sandborn et al	0.5 mg BID	31	32% (*p*=0.39)	13% (*p*=0.76)	52% (*p*=0.64)		10% (0.14)
2012	3 mg BID	33	48% (*p*=0.55)	33% (*p*=0.01)	58% (*p*-0.30)		18% (*p*=0.01)
	10 mg BID	33	61% (*p*=10)	48% (*p*<0.001)	67% (*p*=0.07)		30% (*p*<0.001)
	15 mg BID	49	78% (*p*<0.001)	41% (*p*<0.001)	78% (*p*=0.001)		27% (*p*<0.001)
Phase III OCTAVE	Placebo	122	32.8%	8.2%	Not available	15.6%	1.6%
1 Induction	10 mg BID	476	59.9% (*p*<0.001)	18.5% (*p*=0.007)		31.3%	6.7% (*p*=0.04)
Sandborn et al	15 mg BID	16	87.5% (NA)	43.8% (NA)		(*p*<0.001)	12.5% (NA)
2017						62.5% (NA)	
Phase III OCTAVE	Placebo	112	28.6%	3.6%	Not available	11.6%	1.8%
2 Induction	10 mg BID	429	55.0% (*p*<0.001)	16.6% (*p*<0.001)		28.4%	7.0% (*p*=0.04)
Sandborn et al	15 mg BID	6	83.3% (NA)	50.0% (NA)		(*p*<0.001)	0% (NA)
2017						50.0% (NA)	

Abbreviations: BID, twice daily; NA, not applicable.

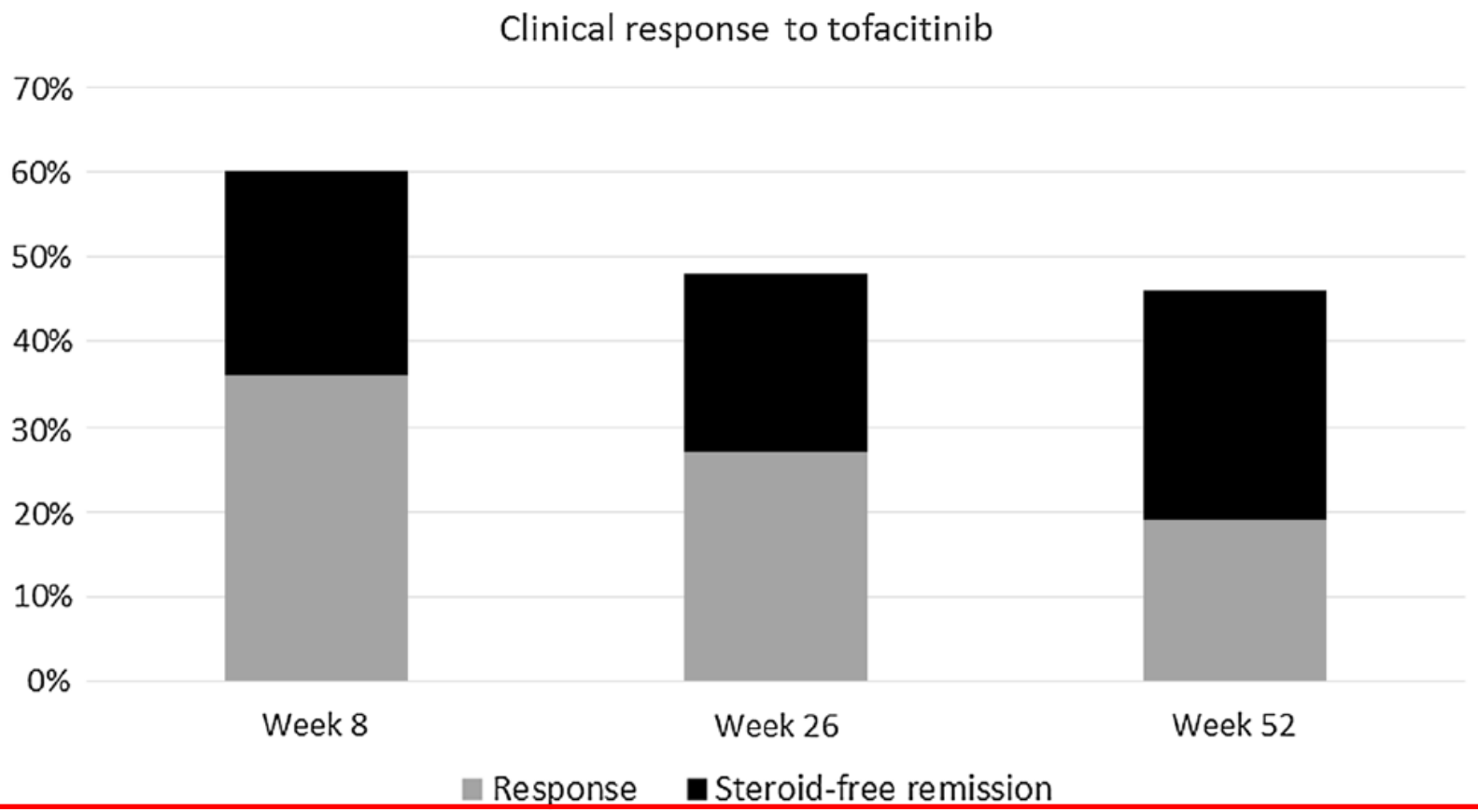
Tofacitinib-UC:
Αποτελεσματικό στην Συντήρηση της Ύφεσης

Table 2 Tofacitinib as maintenance therapy in ulcerative colitis

Phase/study	Treatment	Size	Clinical remission	healing at 52 weeks	Sustained and glucocorticoid-free remission	Sustained mucosal healing among patients with mucosal healing at baseline
Phase III OCTAVE Sustain Sandborn et al 2017	Placebo	198	11.1%	13.1%	5.1%	8.9%
	5 mg BID	198	34.3% ($p<0.001$)	37.4% ($p<0.001$)	35.4% ($p<0.001$)	33.3% ($p<0.001$)
	10 mg BID	197	40.6% ($p<0.001$)	45.7% ($p<0.001$)	47.3% ($p<0.001$)	49.4% ($p<0.001$)

Abbreviation: BID, Twice daily.

Real Life, Single Center,Chicago IBD Center: 58 UC pts, 93% prior anti TNF, 81% prior vedolizumab



33% **Remission**, 42% **12 month Steroid Free Remission**, 20% **Infections**

Weisshof, Dig Dis Sci 2019

Real Life, Retrospective, Multicenter Study, U.S.A.

- U.S.A, 6 centers, 123 UC patients
- 10 mg BID
- 40,7% anti-TNF and vedolizumab exposed
- 28.5% bionaive
- Clinical Response : W8 60.8%, W16 55.4%
- Clinical Remission : W8 13.5%, W16 48.6%
- Endoscopic healing : 64.9%
- **"The good"** : bio-naïve (aOR 5.50), high albumin
- **"The bad"** : +steroids (aHR 0.25), male (aHR 0.25), pancolitis, MES 3
- **"The ugly"**;

Ungaro, P344, ECCO 2019, Copenhagen

Real Life, Retrospective, Multicenter, France

- 37 patients, refractory UC, tofacitinib 10 mg BID
- anti-TNF-exposed: 100%
- >1 anti TNF: 70%
- Vedolizumab: 97%
- Pancolitis: 62%
- Median Mayo Score: 9(4-11)
- Week 24 Results:

-**Survival without colectomy:** 77%

-Survival without treatment interruption: 62,6%

-Clinical Response: 41%

-Steroid Free Remission: 32%

-SAEs: 13,5%

-3 cases Herpes Zoster

Lair-Mehiri, P715, ECCO 2019, Copenhagen

Safety of tofacitinib for treatment of Ulcerative Colitis Based on 4.4 Years of Data from Global Clinical Trials

Table 4. IRs of Adverse Events of Special Interest in the Maintenance and Overall Cohorts

	Maintenance cohort			Overall cohort (induction + maintenance + OLE)
	Placebo (n = 198)	Tofacitinib 5 mg BID (n = 198)	Tofacitinib 10 mg BID (n = 196)	Tofacitinib all (n = 1157)
	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)
Serious infections	2 (1.0) 1.9 (0.2–7.0)	2 (1.0) 1.4 (0.2–4.9)	1 (0.5) 0.6 (0.0–3.5)	33 (2.9) 2.0 (1.4–2.8)
HZ	1 (0.5) 1.0 (0.0–5.4)	3 (1.5) 2.1 (0.4–6.0)	10 (5.1) 6.6 (3.2–12.2)	65 (5.6) 4.1 (3.1–5.2)
OIs[a]	1 (0.5) 1.0 (0.0–5.4)	2 (1.0) 1.4 (0.2–4.9)	4 (2.0) 2.6 (0.7–6.7)	21 (1.9) 1.3 (0.8–2.0)
OIs (excluding HZ)[a]	0 (0.0) 0.0 (0.0–3.6)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	4 (0.4) 0.2 (0.1–0.6)
Malignancy (excluding NMSC)[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	11 (1.0) 0.7 (0.3–1.2)
NMSC[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	3 (1.5) 1.9 (0.4–5.6)	11 (1.0) 0.7 (0.3–1.2)
MACE[a]	0 (0.0) 0.0 (0.0–3.6)	1 (0.5) 0.7 (0.0–3.8)	1 (0.5) 0.6 (0.0–3.5)	4 (0.4) 0.2 (0.1–0.6)
GI perforations[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	3 (0.3) 0.2 (0.0–0.5)

NOTE. With the exception of malignancy (excluding NMSC), NMSC, and MACE, IRs presented in the table exclude events that occurred >28 days after the last dose of study drug.

BID, twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate, patients with ≥1 event per 100 patient-years; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; OIs, opportunistic infections; OLE, open-label extension study.

[a]Adjudicated data do not include data from Study A3921063.

Sandborn, Clin Gastroenterol and Hepatol 2019

Up to 5.4 years of safety From Global Clinical trials

- 1157 patients
- 83% 10 mg BID
- IR (Incidence Rates, unique patients with events per 100 patient years)

Death:	0.2
Serious Infections:	1.9
Herpes Zoster:	3.8
Opportunistic Infections:	1.2
Malignancy:	0.6
Non Melanoma Skin Cancer:	0.8
MACE:	0.3
Gastrointestinal Perforation:	0.1

Sandborn, P466, ECCO 2019, Copenhagen

Real Life Safety

- U.S.A., 6 centers
- 140 patients (120 UC)
- **95% 10 mg bid**
- Median follow up: 75.5 months (IQR 49.8-124.5)
- 19 Adverse Events
- 8 Serious Adverse Events (therapy discontinuation)
- 5 **Herpes Zoster**
- 2 Leucopenias
- 9 Abnormal Lipids (4 statin)

Yarur, P407, ECCO 2019, Copenhagen

Herpes Zoster Risk in IBD: Medications

TABLE 2: Treatment Type and HZ Risk from Meta-Analysis and Nested Case-Control Studies

Treatment Type	Indication(s)	HZ Risk, OR (95% CI)
TNFi biologics[a]	IBD (Crohn's disease and UC)/PsO/RA	1.28 (0.69–2.40)[b]
	IBD (Crohn's disease and UC)	1.81 (1.48–2.21)[e]
Non-TNF biologics[a,b]	Crohn's disease/PsO/RA/SLE	2.19 (1.20–4.02)
All biologics[a,c] (TNFi and non-TNF)	IBD (Crohn's disease and UC)/PsO/RA/SLE	1.71 (1.11–2.64)[b]
	IBD/PsO/RA	1.58 (1.39–1.81)[f]
All nonbiologic DMARDs[d]	PsO/RA/SLE	1.61 (0.84–3.10)[b]
	IBD/PsA/PsO/RA/AS	1.21 (1.15–1.28)[f]
Tofacitinib[b] (5 and 10 mg BID)	Pso/RA	2.16 (0.84–5.58)
5 mg BID	PsO/RA	2.10 (0.83–5.34)
10 mg BID	PsO/RA	3.01 (1.15–7.87)
MTX[b]	RA	0.89 (0.24–3.29)
Thiopurines	SLE	1.35 (0.33–5.61)[b]
	IBD (Crohn's disease and UC)	1.85 (1.61–2.13)[e]
	IBD (Crohn's disease and UC)	3.1 (1.7–5.6)[e]
Corticosteroids[e]	IBD (Crohn's disease and UC)	1.5 (1.1–2.2)
	IBD (Crohn's disease and UC)	1.73 (1.51–1.99)
Biologic and thiopurine combination therapy[e]	IBD (Crohn's disease and UC)	3.29 (2.33–4.65)

Colombel, Inflamm Bowel Dis 2018

Συστάσεις Εμβολιασμού για Έρπητα Ζωστήρα National Psoriasis Foundation

Table II. Herpes zoster risk and vaccination recommendations by treatment modality

Systemic treatment	Disease	Herpes zoster risk compared with no systemic therapy	Grade of conclusion	Quality of evidence	RZV vaccination
Tumor necrosis factor α inhibitors	PsO, PsA	=	Weak, 2A	A and B	+
Ustekinumab	PsO	Between = and ⇑	Weak, 2A	B	+
Interleukin 17 inhibitors*	PsO, PsA	=	Weak, 2A	B	+
Interleukin 23 inhibitors†	PsO	=	Weak, 2A	B	+
Tofacitinib	PsO, PsA	⇑	Strong, 1	A and B	++
Apremilast	PsO, PsA	=	Weak, 2A	B	+
Conventional synthetic DMARDs	PsO, PsA	=	Weak, 2A	B and C	+
Corticosteroid	PsO, PsA	⇑	Weak, 2A	B and C	++
Combination therapy‡	PsO, PsA	⇑	Weak, 2A	A and B	++

DMARD, Disease-modifying antirheumatic drug; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *RZV*, recombinant zoster vaccine; +, recommended; ++, strongly recommended.

*Ixekizumab, secukinumab, and brodalumab.

†Guselkumab, tildrakizumab, and risankizumab.

‡Conventional synthetic and biologic DMARDs.

Baumrin, J Am Akad Dermatol 2019

Διαχείριση Έρπητα Ζωστήρα και ΙΦΝΕ

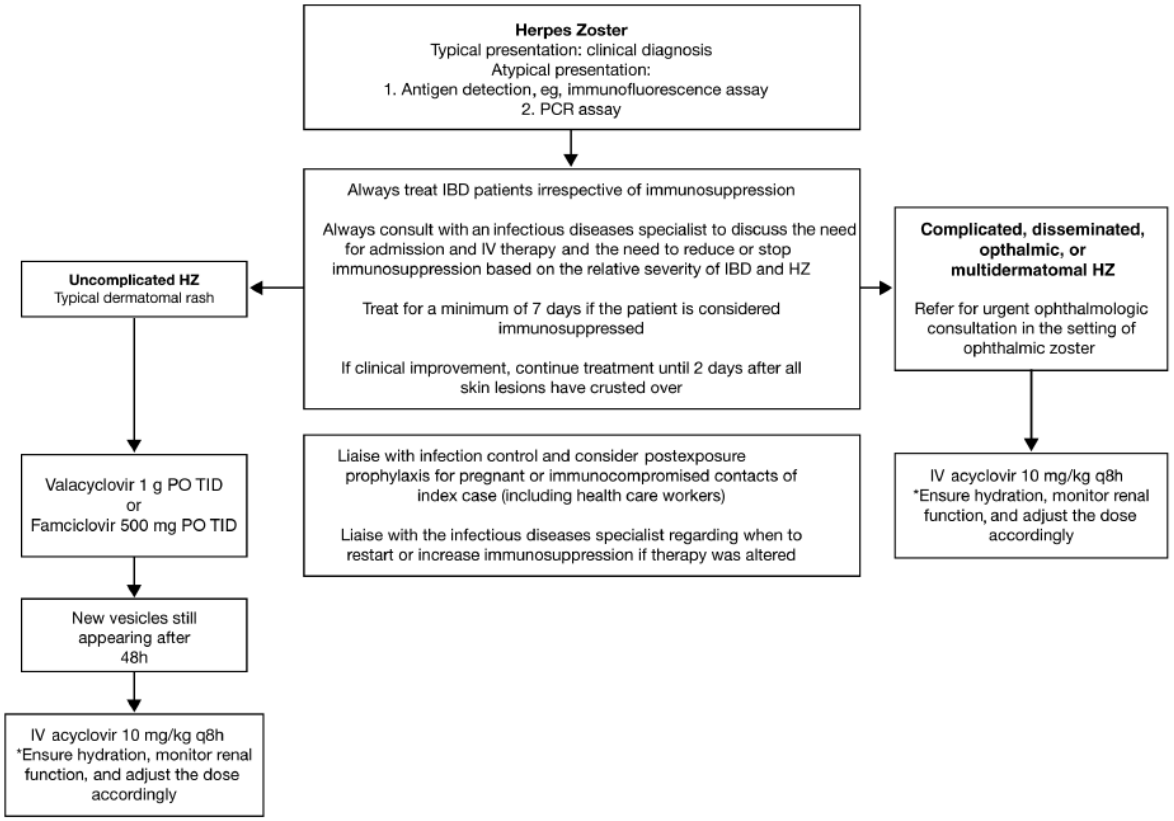
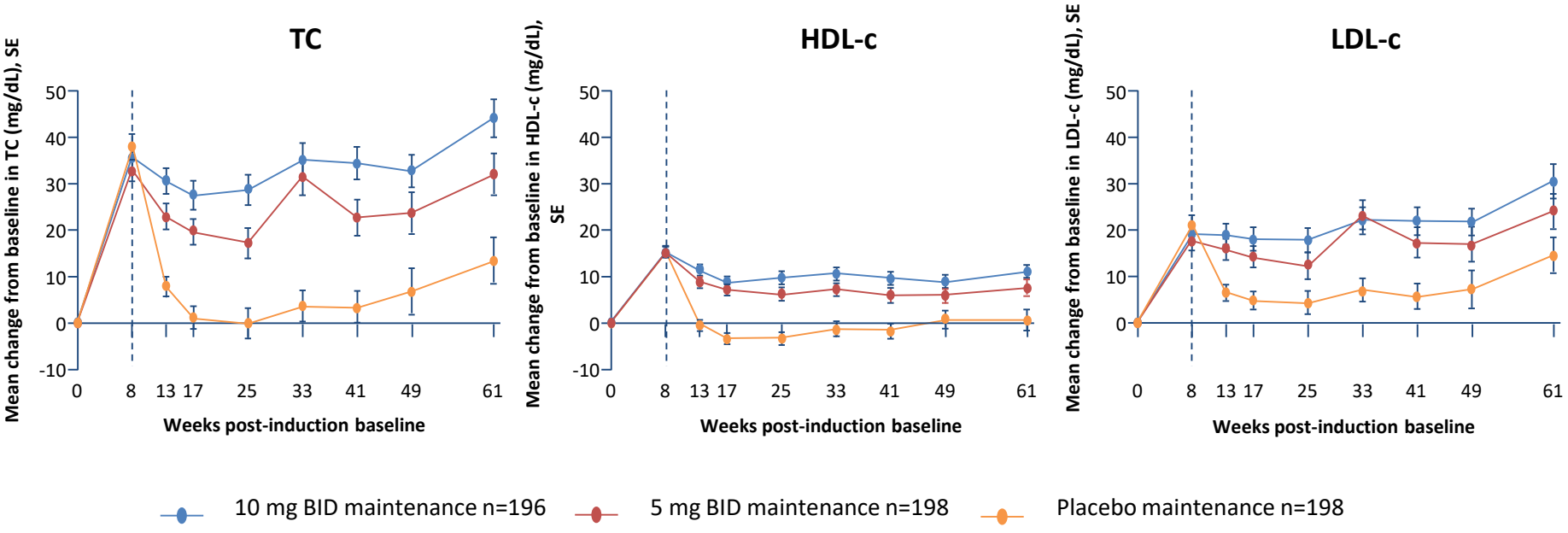


FIGURE 2. Management of herpes zoster in patients with IBD receiving immunosuppressant treatment. Abbreviations: PCR, polymerase chain reaction; PO, orally; q8h, every 8 hours; TID, 3 times a day.

Colombel, Inflamm Bowel Dis 2018

Tofacitinib και Λιπίδια
Πρόγραμμα Κλινικών Μελετών OCTAVE



Sands, Clin Gastroenterol Hepatol 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 May 2019
EMA/267216/2019 Rev.1[1]

Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs

EMA's safety committee (PRAC) is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at high risk of blood clots in the lungs. These include patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients who take combined hormonal contraceptives, are receiving hormone replacement therapy or are undergoing major surgery.

In addition, doctors should consider other factors that may increase the risk of blood clots in the lungs including age, obesity, smoking or immobilisation.

Xeljanz is currently authorised for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis.

The PRAC's recommendation follows results from an ongoing study (study A3921133) in patients with rheumatoid arthritis. This study showed an increased risk of blood clots in the lungs and death when the 10 mg twice daily dose was used, which is double the recommended dose for rheumatoid arthritis.

The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any condition must be switched to alternative treatments.

Patients should not stop or change their dose of Xeljanz without talking to their doctor. They should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood, which could indicate the presence of a blood clot in the lungs.

The new recommendations are temporary and follow previous PRAC advice not to exceed the recommended 5 mg twice daily dose when treating rheumatoid arthritis. The PRAC will now carry out a review of all available evidence, and updated guidance will be provided to patients and healthcare professionals once the review is concluded.

EMA, 17.05.2019

ΕΟΦ, Φαρμακοεπαγρύπνηση tofacitinib 21.05.2019

Πνευμονική εμβολή

Η πνευμονική εμβολή έχει παρατηρηθεί σε ασθενείς που λαμβάνουν τοφασιτινίμπη σε κλινικές δοκιμές και σε αναφορές μετά την κυκλοφορία του προϊόντος στην αγορά. Η τοφασιτινίμπη 10 mg δύο φορές ημερησίως αντενδείκνυται σε ασθενείς που διατρέχουν υψηλό κίνδυνο πνευμονικής εμβολής (βλ. επίσης παράγραφο 4.3). Επιπρόσθετοι παράγοντες κινδύνου που θα πρέπει να λαμβάνονται υπόψιν κατά την αξιολόγηση κινδύνου του ασθενούς για πνευμονική εμβολή, είναι η ηλικία, η παχυσαρκία, το κάπνισμα και η ακινητοποίηση.

Pulmonary Embolism in Tofacitinib UC Development Program: OKTAVE OPEN: 4 cases, late, risk factors present

1. 68-year-old white male from United States (Tofacitinib 10mg BID)
Died on Day 384 due to pulmonary embolism, which started on Day 383, reported as a complication of cholangiocarcinoma with metastases to peritoneum; the event occurred within 2 days of endoscopic retrograde cholangiopancreatography (ERCP).

2. 56-year-old white male from Slovakia (Tofacitinib 10mg BID)
Occurred on Day 174, subject was hospitalized. Discharged in good condition on Day 188. Medical history of hypertension, hypercholesterolemia, hepatic steatosis, autoimmune thyroid disease, stroke, phlebothrombosis in left arm and in right leg as separate incidents.

3. 24-year-old black male from United States (Tofacitinib 10mg BID)
Occurred on Day 153, subject was hospitalized. Discharged on day 157. Medical history of DVT and PE.

4. 19-year-old white female from United states (tofacitinib 10mg BID)
Occurred on Day 569, subject was hospitalized on the next day. The subject recovered from the event on Day 574. Started oral contraceptives for dysfunctional uterine bleeding 4 months prior to the event.

FDA: 7-26-2019

"The U.S. Food and Drug Administration has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent ***Boxed Warning****, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.*

The 10 mg twice daily dose of tofacitinib *is not approved for RA or psoriatic arthritis (PsA). This dose is* ***only approved for ulcerative colitis*** *for initial treatment and for long-term use in limited situations. While the increased risks of blood clots and of death were seen in patients taking this dose for RA, these risks may also apply to those taking tofacitinib for ulcerative colitis"*

FDA Health Care Professionals

*-For the treatment of ulcerative colitis, reserve tofacitinib as **second-line** therapy for use in patients who have failed or cannot tolerate TNF blockers.*

***-**For ulcerative colitis, use tofacitinib **at the lowest effective dose and for the shortest duration needed** to achieve/maintain therapeutic response.*

*-The **induction dose is 10 mg twice daily for 8 weeks**. Evaluate patients and transition to maintenance therapy depending on therapeutic response**. If needed, continue 10 mg twice daily for an additional 8 weeks or a maximum of 16 weeks.** Discontinue 10 mg twice daily after 16 weeks if adequate therapeutic response is not achieved.*

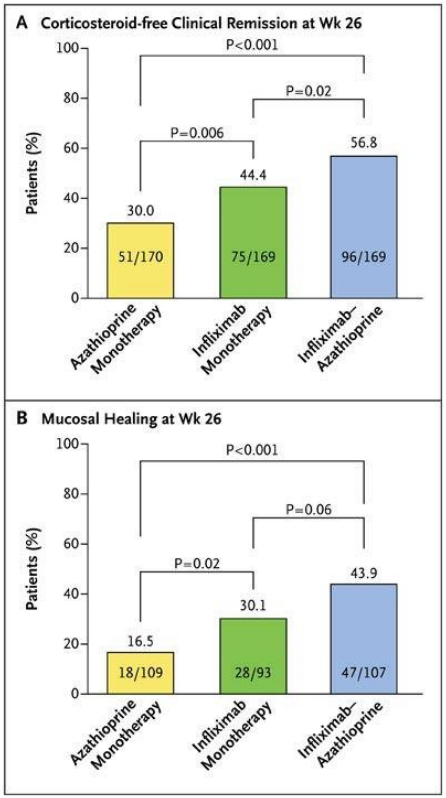
*-**The maintenance dose is 5 mg twice daily**. Use of **10 mg twice daily** beyond induction should be limited to those with **loss of response** and used **for the shortest duration**, with careful **consideration of the benefits and risks** for the individual patient. Use the lowest effective dose needed to maintain response.*

*-**Discontinue** tofacitinib and promptly evaluate patients with **symptoms of thrombosis.***

*-**Avoid** tofacitinib in patients who may be at **increased risk of thrombosis**.*

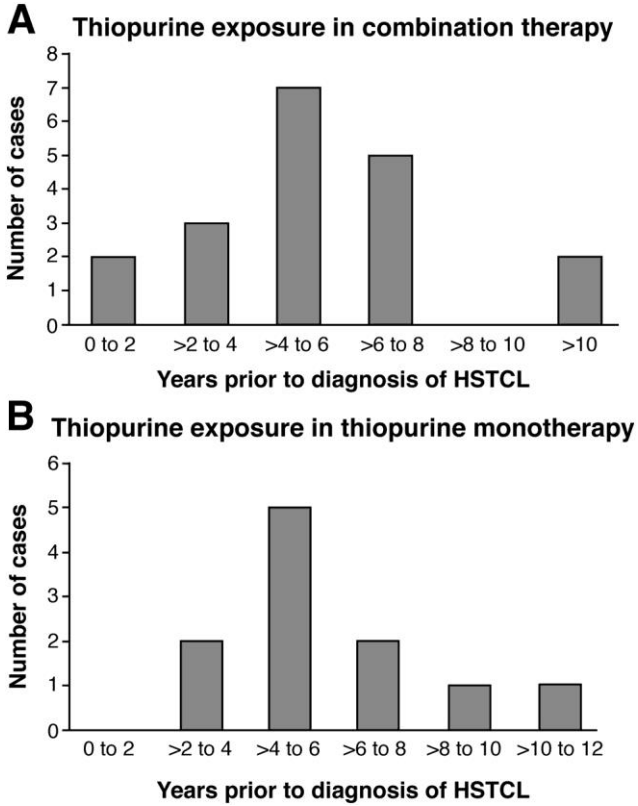
Anti-TNF παράγοντες και Ηπατοσπληνικό Λέμφωμα

Combination Therapy IFX+AZA:



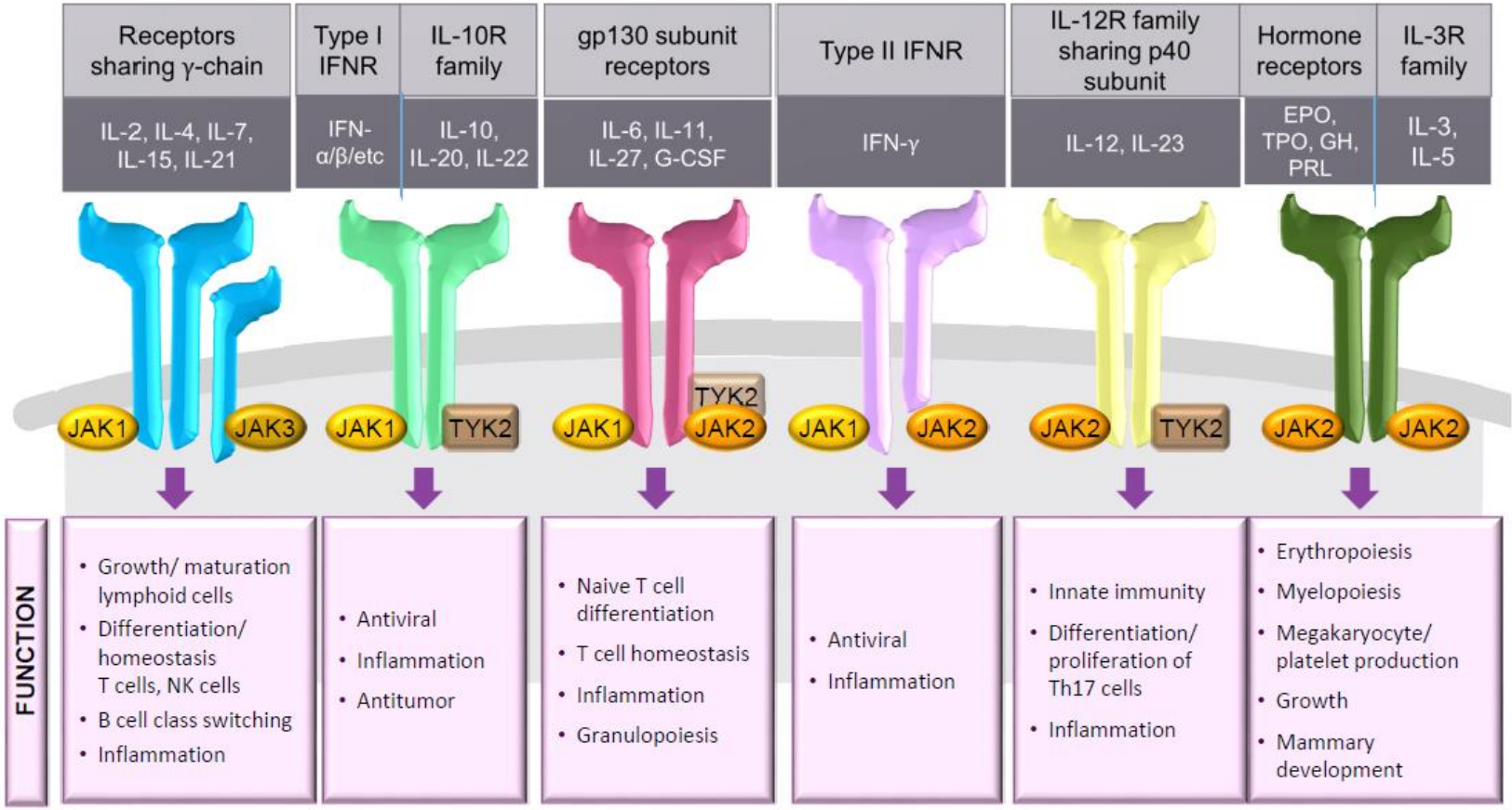
Colombel, N Eng J Med 2010

Hepatosplenic T-Cell Lymphoma



Kotlyar, Clin Gastroenterol Hepatol 2011

JAK Selectivity?



JAK Εκλεκτικότητα και Εργαστηριακές Παράμετροι

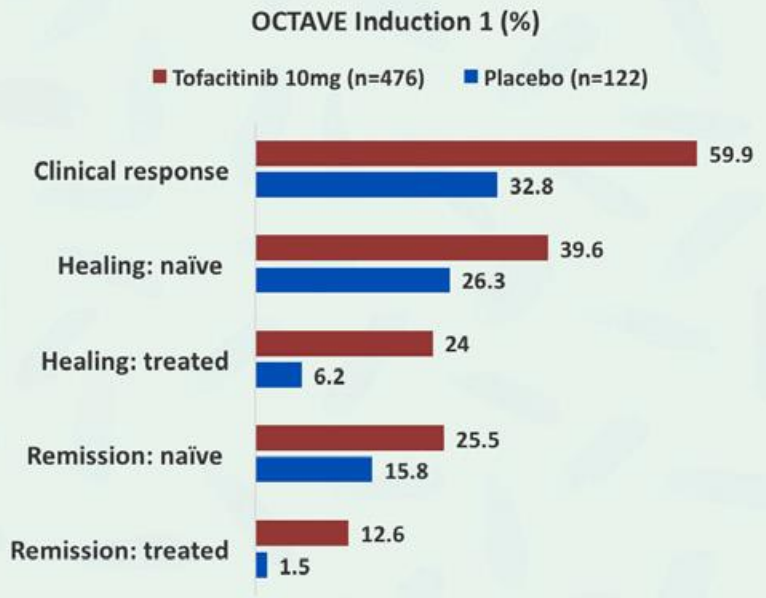
Table 1 JAK selectivity and changes in laboratory parameters

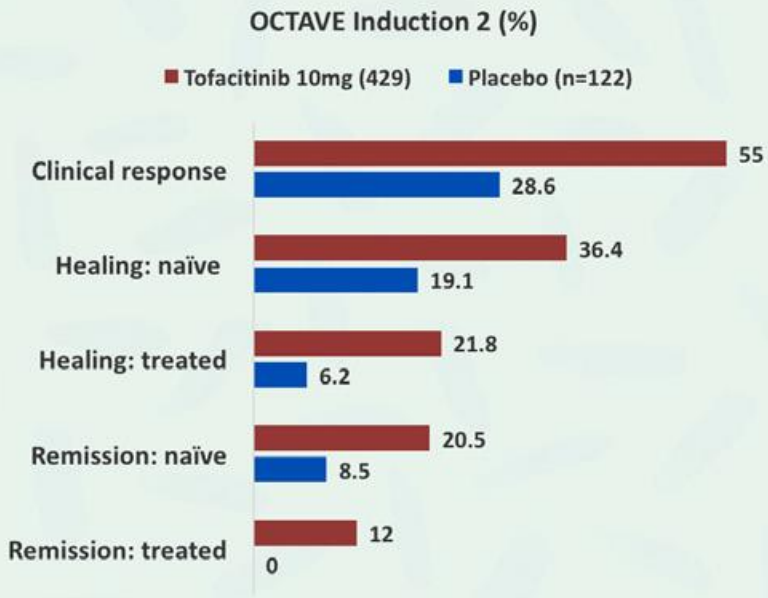
Compound	Tofacitinib	Filgotinib	Upadacitinib	TD-1473
Indication in IBD, stage of development	UC, approved by the FDA and EMA	CD, phase III UC, phase III	CD, phase III UC, phase III	CD, phase III UC, phase III
Target	JAK1, JAK2, JAK3	JAK1	JAK1	JAK1, JAK2, JAK3, TYK2
Gut selectivity	–	–	–	+
Haemoglobin level	↑	↑	↓	No change*
Lymphocyte no	↓	No change	↓	No change*
Neutrophil no	↓	↓	↓	No change*
Platelet count	↓	↓	No data	No change*
NK cell no	↓	No change	↓	No change*
HDL level	↑	↑	↑	No change*
LDL level	↑	No change	↑	No change*
Liver transaminase level	↑	No change	↑	No change*
Creatinine level	↑	↑	↑	No change*
Creatine phosphokinase level	↑	No data	↑	No change*

Danese, Gut 2019

FUTURE JAKis (tofacitinib) Positioning in IBD?

Tofacitinib Efficacy in UC





Treated, tumor necrosis factor-alpha inhibitor treated; Healing, mucosal healing.

Sandborn WJ, et al. Abstract 767. Presented at Digestive Disease Week May 21-24, 2016; San Diego, California.

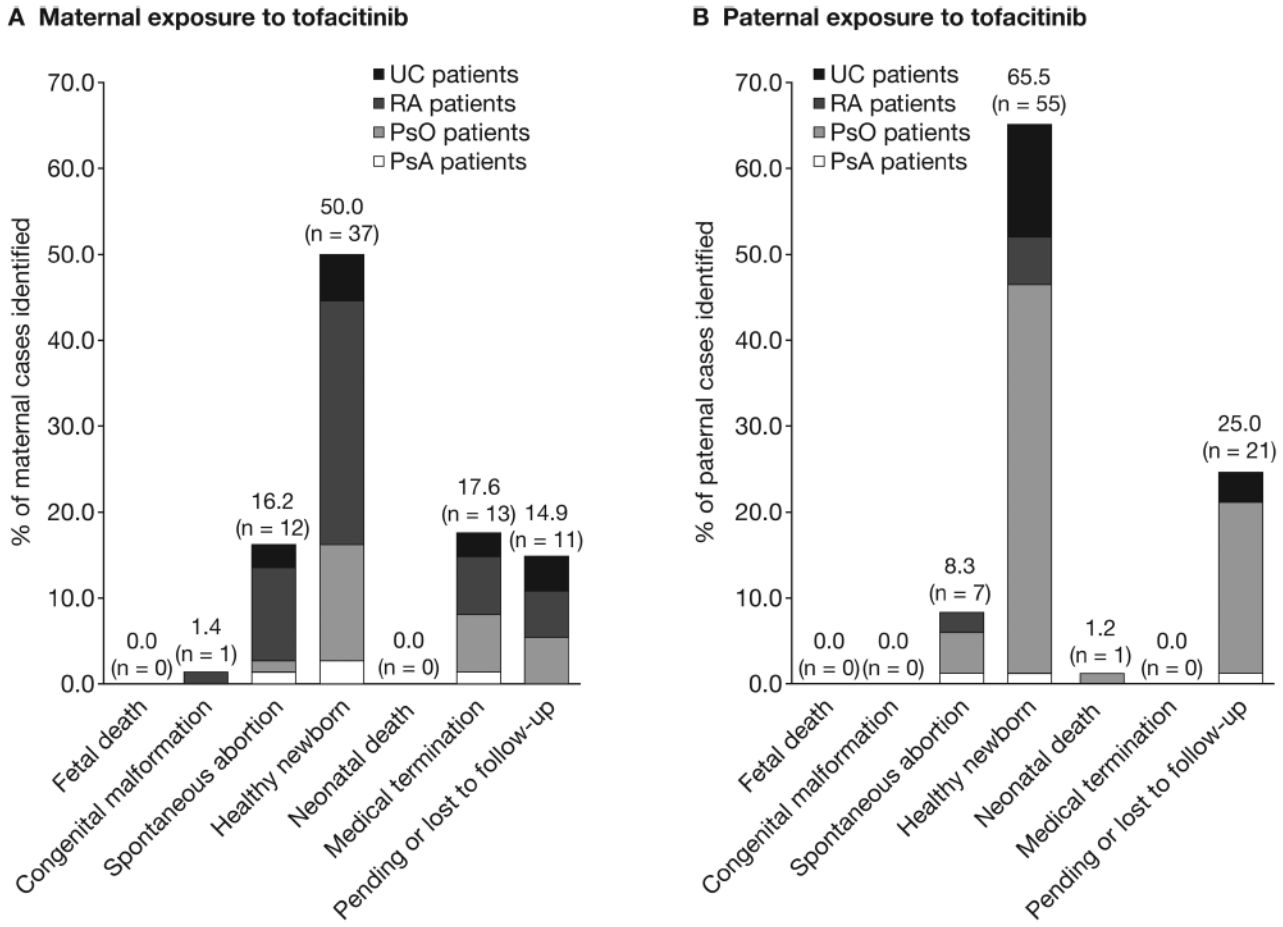
Tofacitinib: Προσαρμογές Δόσεων

Table 3. Tofacitinib dose adjustments in special conditions.

Condition	Value	Recommendation
Low absolute lymphocyte count (ALC)	ALC ⩾ 750 ALC 500–750 ALC < 500	Maintain Reduce to 5 mg twice daily Discontinue
Low absolute neutrophil count (ANC)	ANC ⩾ 1000 ANC 500–1000 ANC < 500	Maintain Reduce to 5 mg twice daily Discontinue
Low hemoglobin value	Decrease ⩽ 2 g/dl and Hb ⩾ 9.0 g/dl Decrease > 2 g/dl or Hb < 8.0 g/dl	Maintain Interrupt until Hb normalizes
Hepatic impairment	Child Pugh A	No dose adjustment
	Child Pugh B	Reduce to 5 mg once daily if 5 mg twice daily is the indicated dose in the absence of hepatic impairment Reduce to 5 mg twice daily if 10 mg twice daily is the indicated dose in the absence of hepatic impairment
	Child Pugh C	Contraindicated
Renal impairment	Mild: Cr. clearance 50–80 ml/min	No dose adjustment
	Moderate: Cr. clearance 30–49 ml/min	No dose adjustment
	Severe: Cr. clearance < 30 ml/min	Reduce to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily Reduce to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily Patients with severe renal impairment should remain on a reduced dose even after hemodialysis

Hb, Hemoglobin; Cr., creatinine.

Tofacitinib στην Ελκώδη Κολίτιδα και Κύηση



Mahadevan, Inflamm Bowel Dis 2018

Συμπεράσματα

- Το Tofacitinib αποτελεσματικό στην Ελκώδη Κολίτιδα
- Χρήσιμο Θεραπευτικό Όπλο:

-anti-TNF αποτυχία

-από το στόμα

-ταχεία δράση

-μονοθεραπεία

-απουσία ανοσογονικότητας (on-off therapy;)

- Προσεκτική Επιλογή ασθενών
- Εκτίμηση σχέσης ασφάλειας και αποτελεσματικότητας ανά ασθενή

Σας Ευχαριστώ Πολύ

Μύτη, Ποσείδι, Χαλκιδική