Preporuke za lečenje blagog do umereno teškog ulceroznog kolitisa

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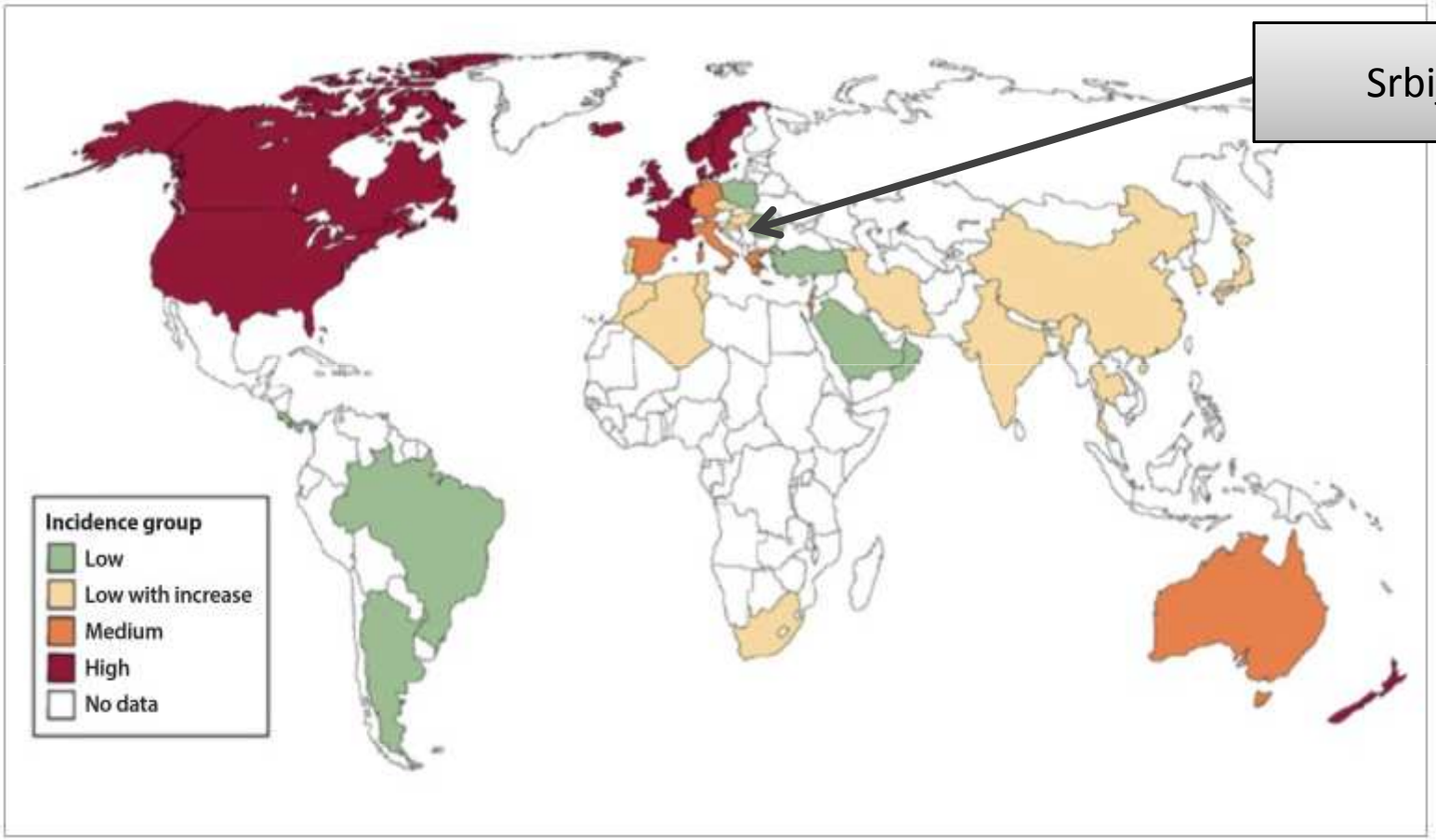
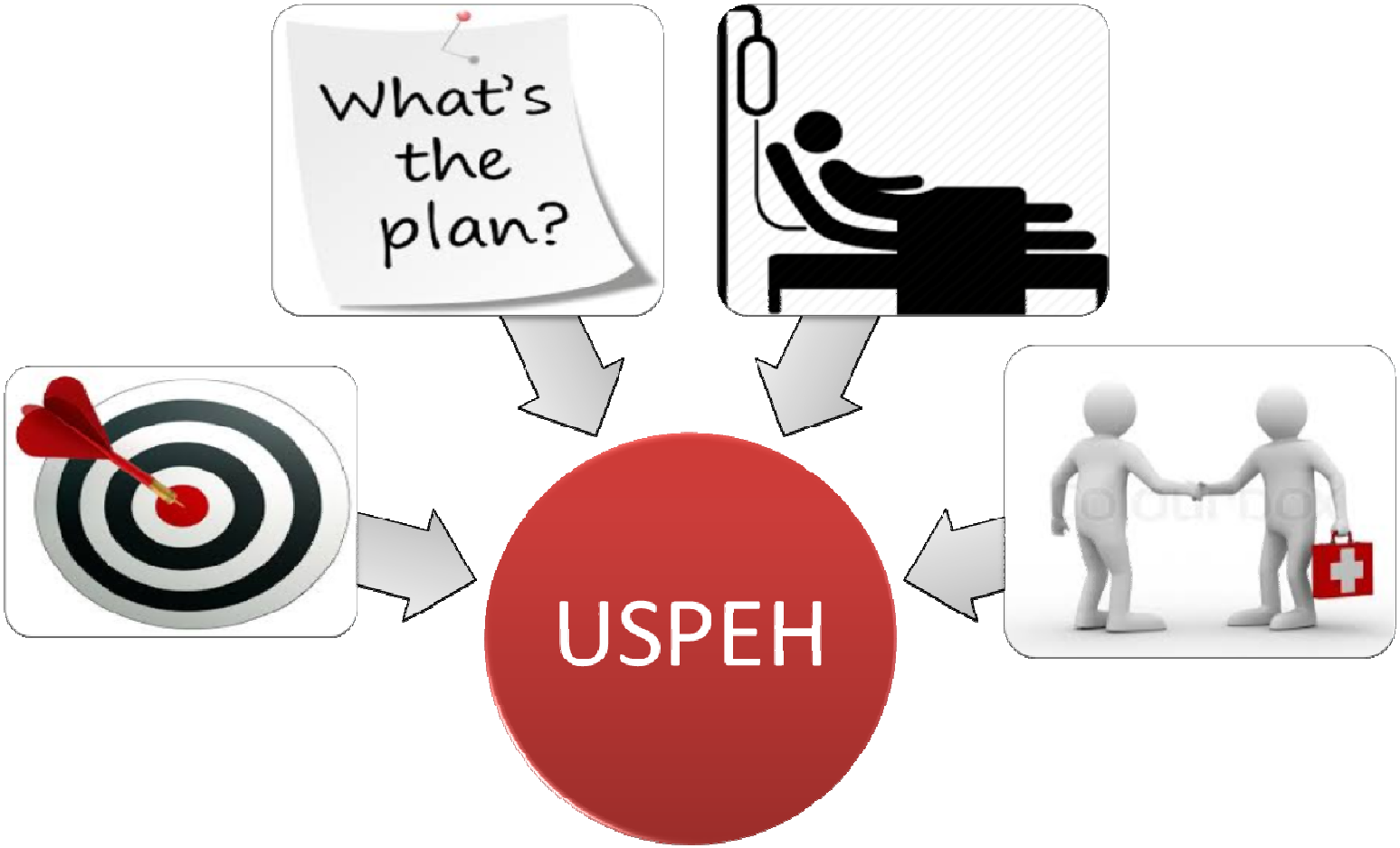
I dalje ne znamo koliko ljudi boluje od IBC



Blagi do umereno teški UK

KARAKTERISTIKA	BLAG	UMEREN	TEŽAK
Broj stolica	< 4	4 ili više ako	≥ 6 i
Puls	< 90 /min	≤ 90 /min	> 90 /min ili
Temperatura	< 37.5 °C	≤ 37.8 °C	> 37.8 °C ili
Hgb	> 11.5 g/dL	≥ 10.5 g/dL	< 10.5 g/dL ili
Se	< 20 mm/h	≤ 30 mm/h	> 30 mm/h ili
Ili CRP	normalan	≤ 30 mg/L	> 30 mg/L

Šta je potrebno za uspeh lečenja



Terapijske opcije

Terapijski ciljevi

- Indukcija remisije
- Održavanje remisije bez primene kortikosteroida
- Poboljšanje kvaliteta života
- Postizanje mukoznog zaceljenja (duboke remisije)

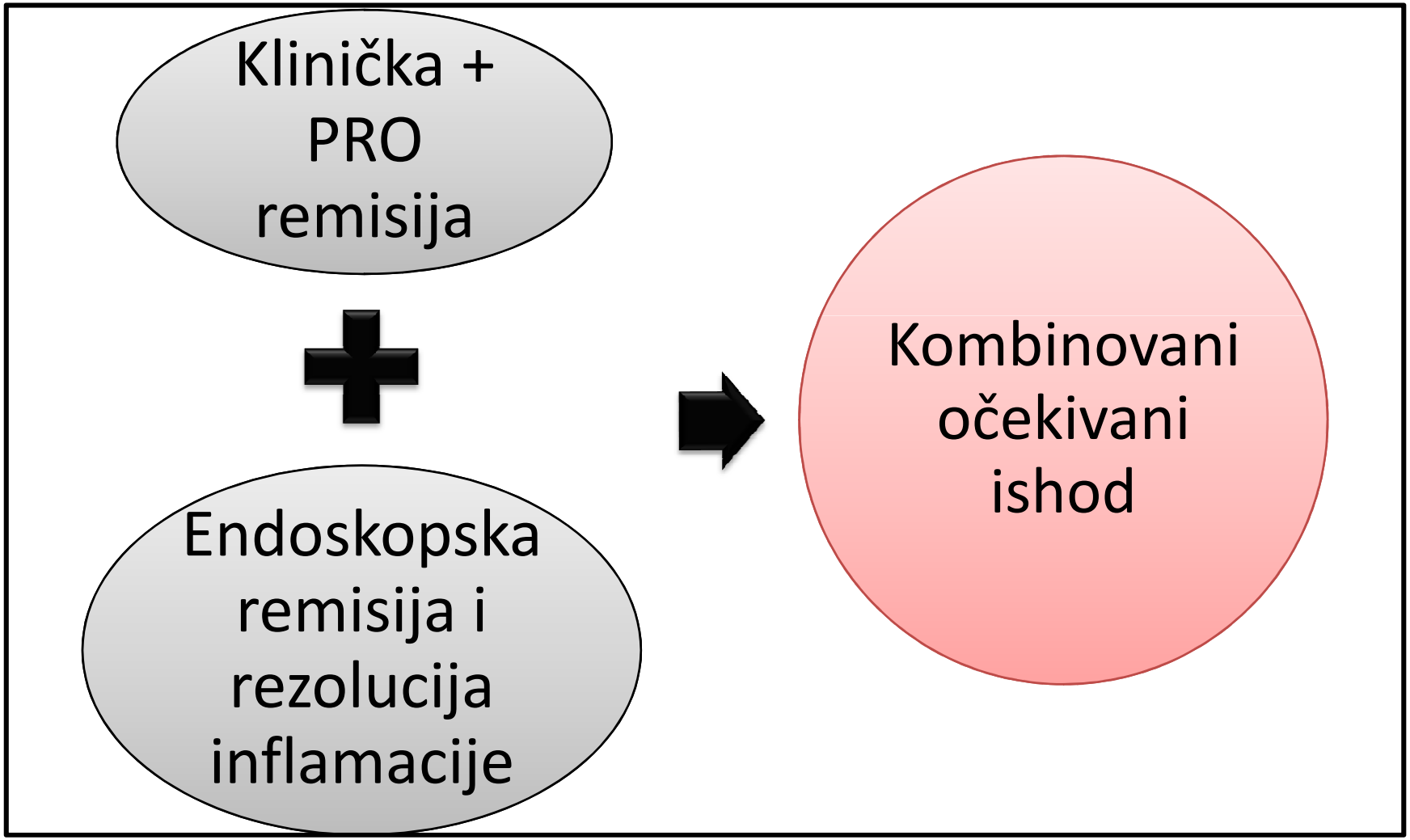
- Smanjenje potrebe za hirurgijom i hospitalizacijama
- Prevencija/lečenje komplikacija bolesti

Šta kažu pacijenti?

- **Remisija** nema simptoma
- **Blaga aktivnost** ne ograničava dnevne aktivnosti
- **Umerena aktivnost** (izostaje s posla, otkazuje obaveze)
- **Teška aktivnost** ozbiljno narušena aktivnost (vezan za kuću, toalet, hospitalizovan)

Aktivnost bolesti
(PGA-patient global assessment)

Čemu težimo….


Klinička + PRO remisija
Endoskopska remisija i rezolucija inflamacije
Kombinovani očekivani ishod

A stvaran svet oko nas…

When do you typically see the physician who primarily treats your UC?	
I schedule regular visits	161(65.2%)
Only when I'm not feeling well or have a flare-up	70(28.3%)
I try to stay away from the doctor's office and avoid it until a flare-up results in serious consequences	15(6.1%)
I never see a doctor	1(0.4%)
How involved are you in decisions about treating your UC?	
My doctor makes most decisions regarding treatment	117(48.1%)
I have an equal partnership with my doctor, where we make decisions together	81(33.3%)
My doctor advises me and helps me understand my options so I can make the best decisions on my own behalf	45(18.5%)
Patient involvement in specific treatment decisions	
I trust my doctor to make whatever treatment decisions are needed	150(61.0%)
I prefer an equal partnership with my doctor, where we make decisions together	86(35.0%)
I prefer to make most of my own treatment decisions	10(4.1%)

Kontrole

Koliko pacijent učestvuje u odluci o lečenju

Odluke o terapiji

Peyrin-Biroulet L, et al. Treatment satisfaction, preferences and perception gaps between patients and physicians in the ulcerative colitis CARES study: A real world-based study. Dig Liver Dis (2016),

How comfortable are you taking the initiative to ask your doctor about new medications and treatment options?

Very comfortable	132(53.4%)
Somewhat comfortable	86(34.8%)
Not very comfortable	24(9.7%)
Not at all comfortable	5(2.0%)

Uglavnom da 87%

Smete li da pitate doktora

How informed do you feel about the different medications available to treat UC?

Very informed	55(22.2%)
Somewhat informed	135(54.4%)
Not very informed	50(20.2%)
Not at all informed	8(3.2%)

Delimično 76%

Koliko znate o lekovima

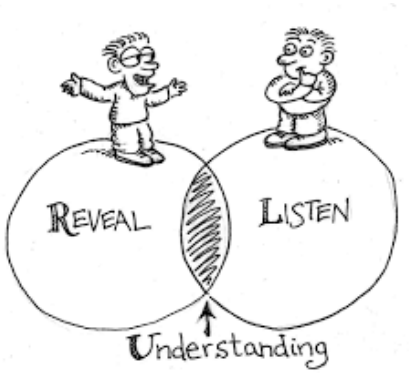
How often to you seek out information about UC and/or various treatment options that are available?

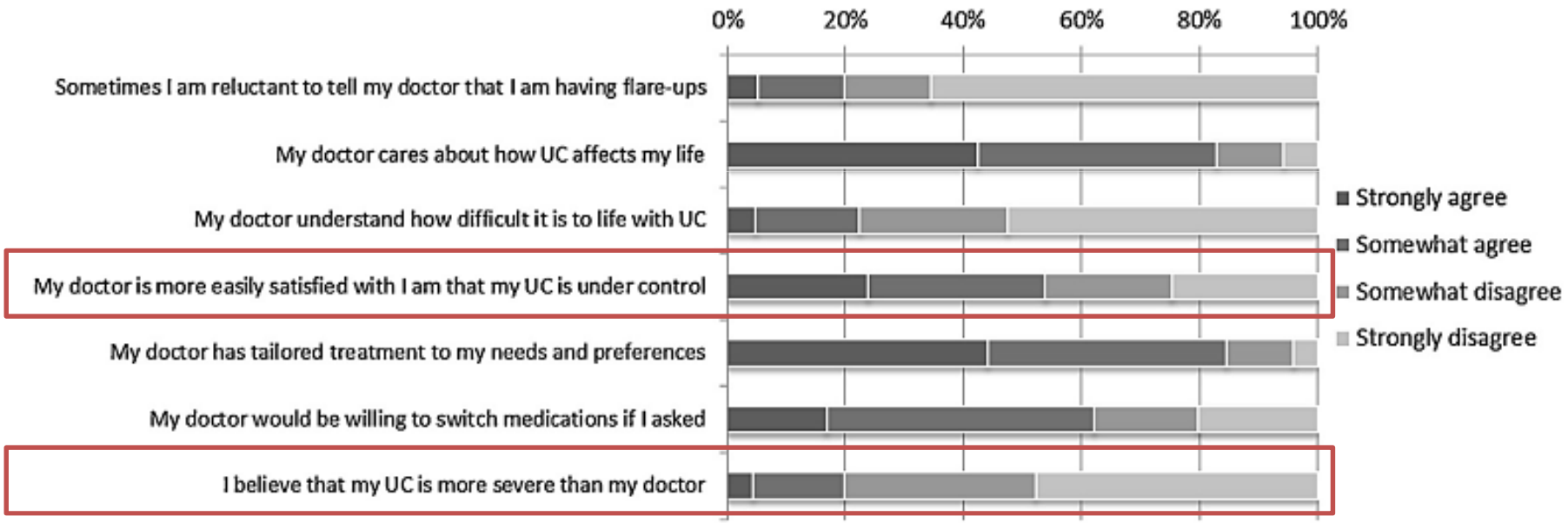
Often	48(19.4%)
Sometimes	112(45.3%)
Rarely	59(23.9%)
Never	28(11.3%)

34% retko i nikad

Koliko često tražite informacije

Šta misle pacijenti

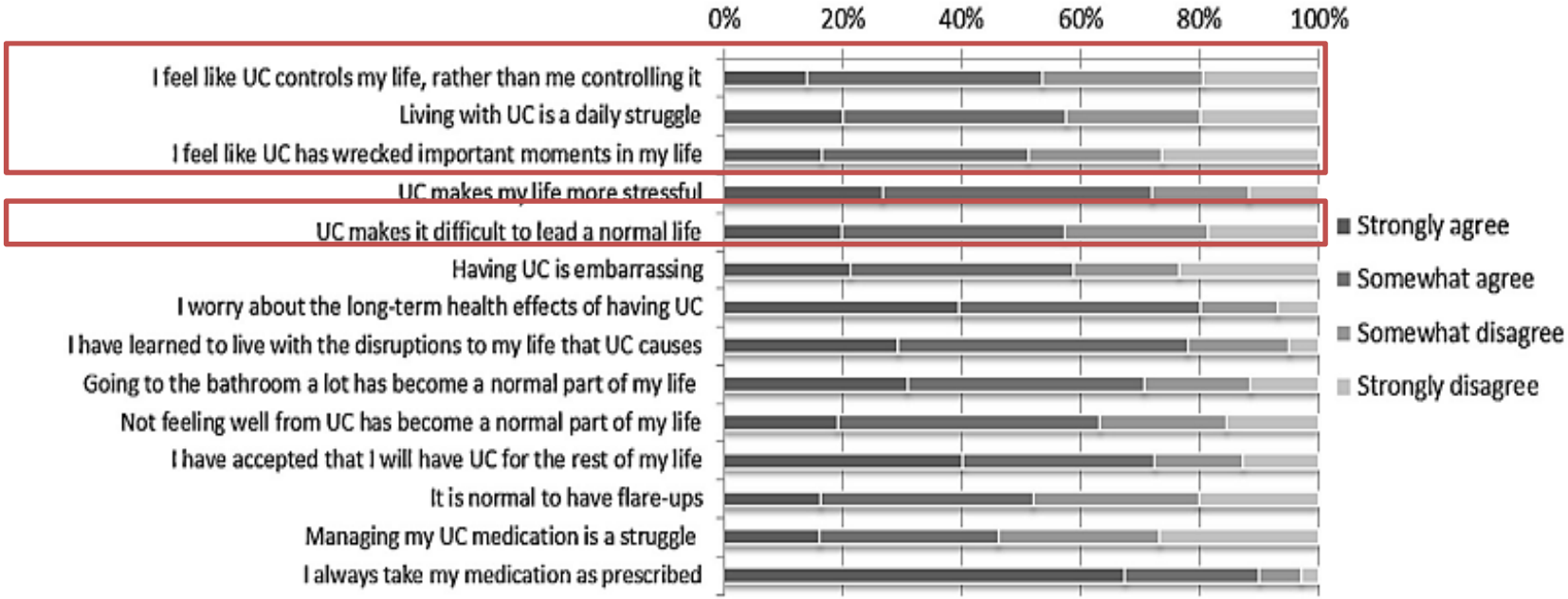




Peyrin-Biroulet L, et al. Treatment satisfaction, preferences and perception gaps between patients and physicians in the ulcerative colitis CARES study: A real world-based study. Dig Liver Dis (2016),

Šta misle pacijenti

LIFE TAKES GUTS
On A Mission To Promote Inflamatory Bowel Disease Awareness



Peyrin-Biroulet L, et al. Treatment satisfaction, preferences and perception gaps between patients and physicians in the ulcerative colitis CARES study: A real world-based study. Dig Liver Dis (2016),

Terapijske opcije

Mesalazini u UK

Lokalizacija bolesti
Formulacija leka

Proktitis-blaga i umerena aktivnost

1
- **mesalazin supp 1 g dnevno**
- mesalazin klizma (pena)

2
- **topički mesalazin + oralni mesalazin/ topički steroid**

3
- immunosupresiv i/ili biološka terapija za refraktarni proktitis

Supozitorije efikasnije nego klizma !!!

supozitorija deluje na mestu inflamacije

40% klizme u formi pene, pa se 10% tečnih klizmi nalazi u rektumu nakon 4h

Proktitis- optimalna terapija

1g topičkog mesalazina jednom dnevno

- nema povećanja efekta ukoliko se doza dalje poveća
- jedna doza je efikasna koliko i podeljene doze

Topički mesalazin efikasniji nego topički steroid

simptomatska remisija (OR 2.42)
endoskopska remisija (OR 1.89)
histološka remisija (OR 2.03).

Topički efikasniji od monoterapije oralnim preparatom

Levostrani UK blage do umerene aktivnosti

2.4 g/d indukcija remisije (blaga i umerena aktivnost)
4.8 g/d može lakše uvesti u remisiju umerenu aktivnost

1
- **kombinovano oralna i topička terapija 5ASA**
- **1g topičke+ >2g oralno**
- **JEDNOM dnevno**

2
- Sistemski KS

3
- imunosupresivi i/ili biološka terapija za refraktorni levostrani UK

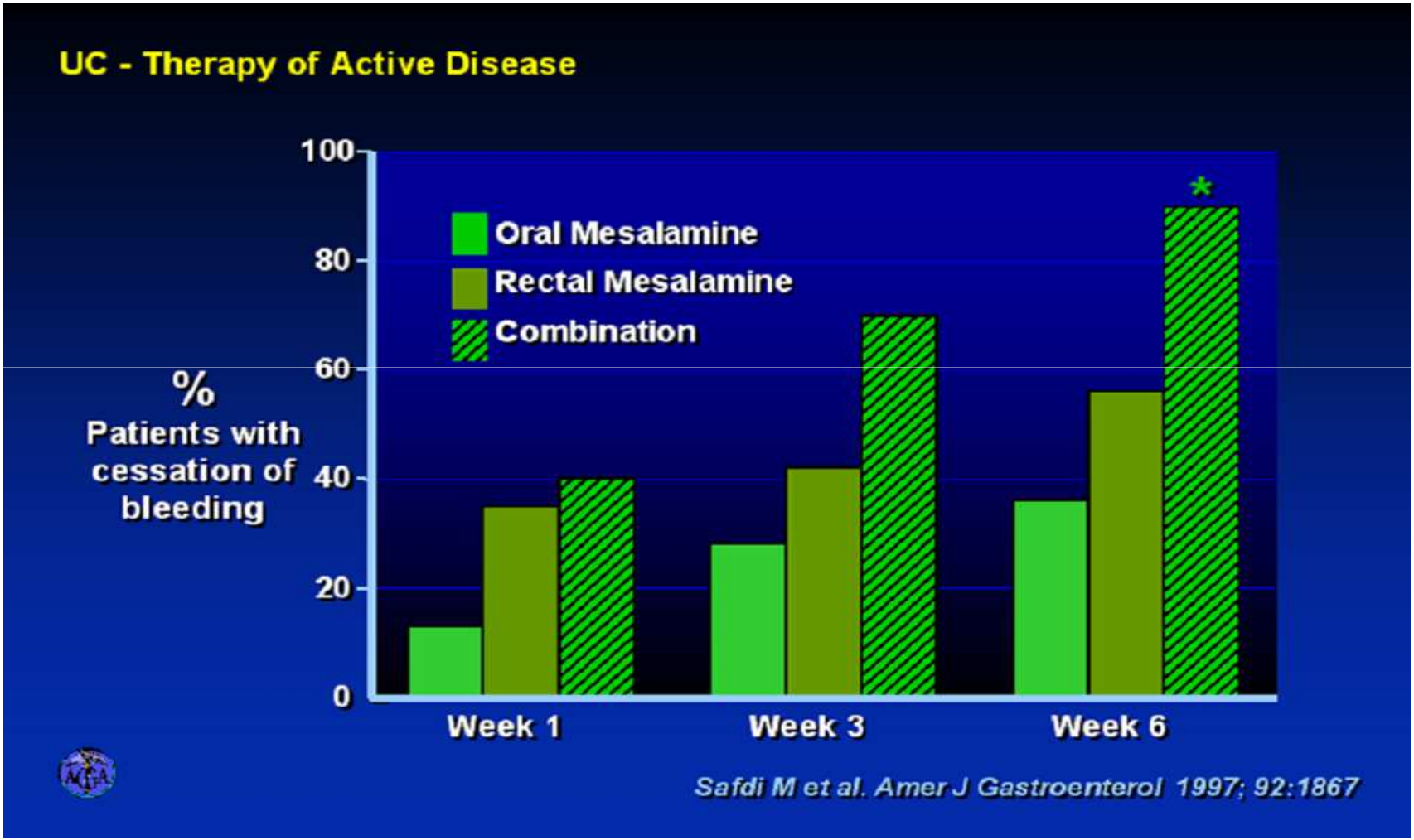
Ekstenzivni kolitis

- Doza mesalazina treba da bude **> 2.0g/dan**
- **Kombinovana terapija** (oralni+topički preparat)

  remisija 64% vs 43%
- Doziranje **jednom dnevno** (jednako efikasno kao podeljene doze)

Odsustvo odgovora na mesalazin je indikacija za započinjanje KS terapije

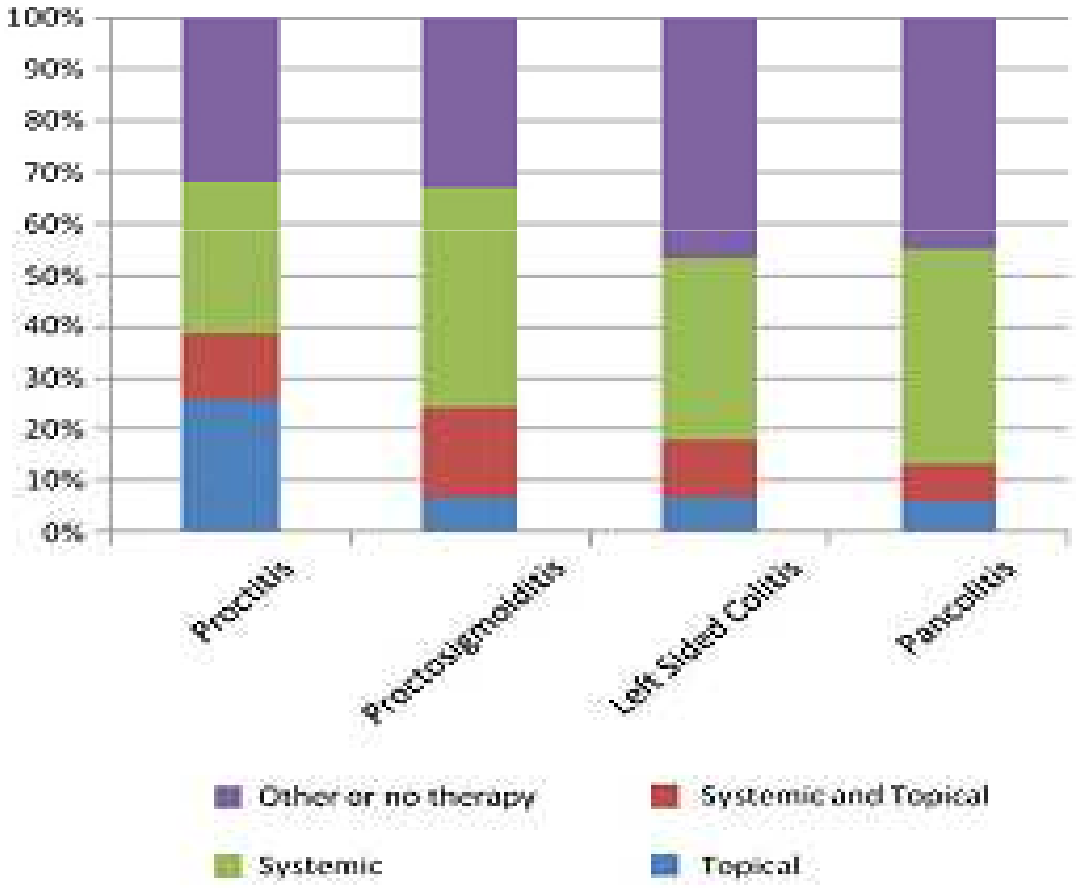
Kombinovana terapija



Safdi M et al. Am J Gastroenterol 1997;92(10):1867-71.

Kombinovana terapija je potcenjena!!!

- Švajcarska IBD kohorta 2006-2011, 790 pacijenata



Proktosigmoiditis 24% ima topičku terapiju

Pankolitis 13% ima topičku terapiju

Seibold et al, JCC 2014

Kada očekivati terapijski odgovor

Vreme potrebno za prestanak krvarenja

9 dana za 4.8 g/d

16 dana na 2.4 g/d

7 dana 4.8 g/d MMX

Kompletna remisija za 37 do 45 dana

Kombinacija oralne i topičke terapije skraćuje vreme za prestanak krvarenja

Kortikosteroidi u UK

KS u UK

- **Indukcija remisije** kod **umereno do teško aktivnih formi IBD**
- **Početi adekvatnom dozom leka** (< 15 mg neefikasne)
- **nije terapija održavanja**

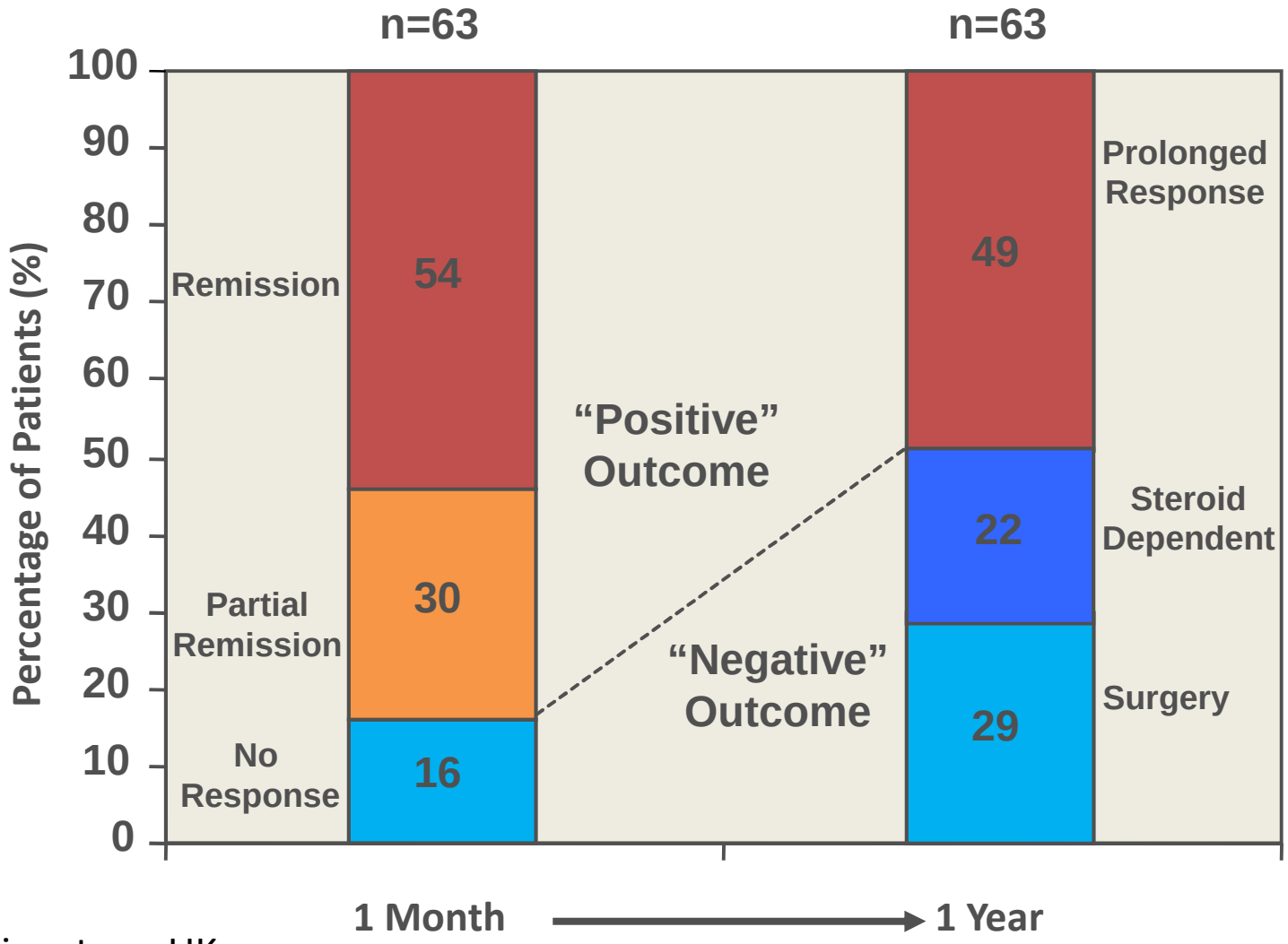
- **planirati strategiju terapije održavanja u ranoj fazi**

Smanjenje doze KS

- Mnoge sheme smanjivanja doza KS (zavisno od aktivnosti bolesti, ne duže od 3 meseca) :
  - **Prednizon**
    - 40 mg/d 1 nedelja → pa na 7 dana za 5mg
    - 30 mg/d 1 nedelja
    - 20 mg/d 1 mesec
    - potom smanjivati 5 mg/ 7 dana
- Treba da postoji standarni pristup da bi se na vreme prepoznala KS zavisnost- odluka o započinjanju imunomodulatorne terapije.
- **Kratka kura KS (< 3 nedelje) = rani relaps**
- **Doze < 15 mg su neefikasne za aktivnu bolest**

ECCO

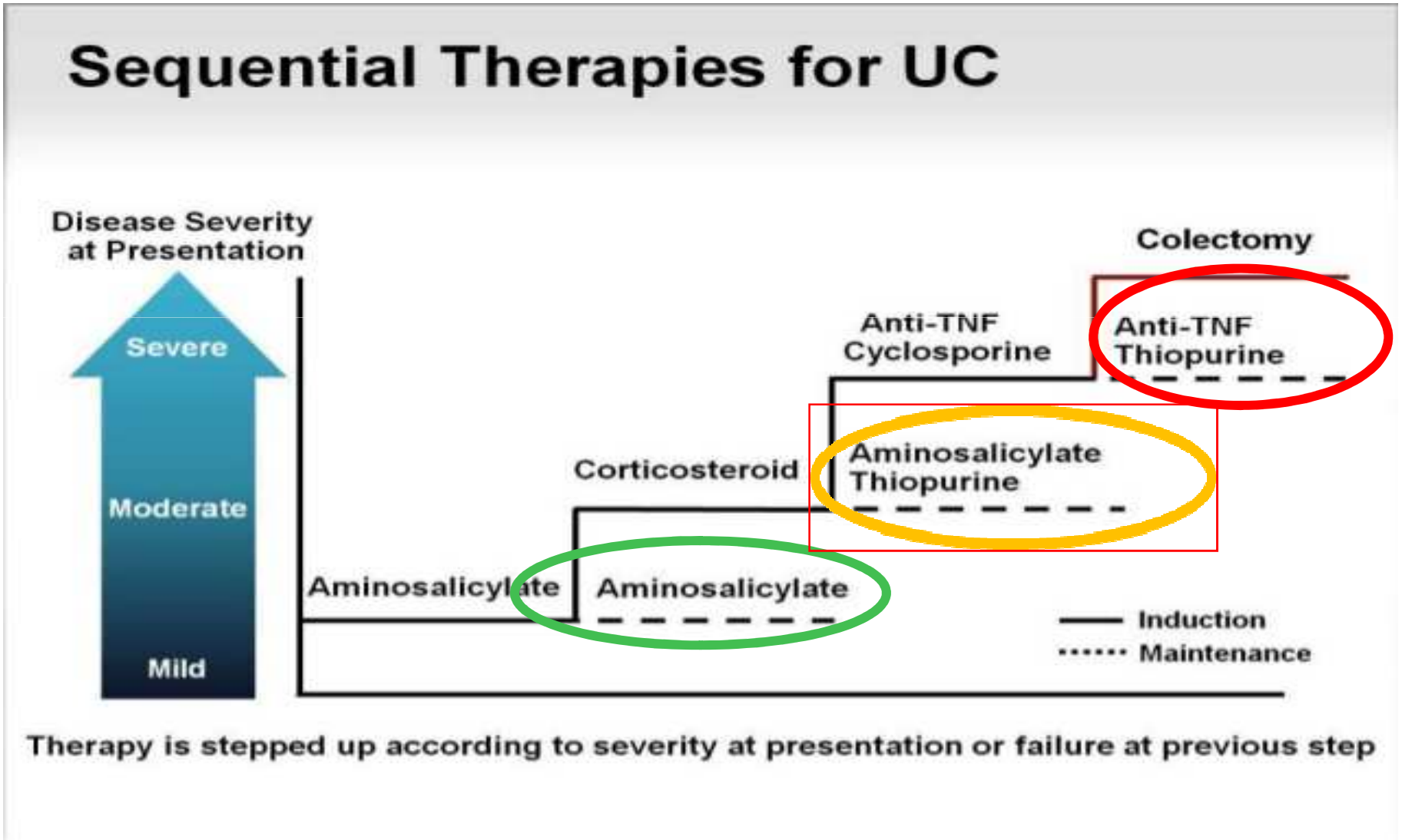
Kortikosteroidi u terapiji UK
(ishod nakon 12 meseci Faubion studija)



185 pacijenata sa UK

Faubion WA et al. Gastroenterology 2001;121:255

Lekovi u terapiji održavanja



Terapija održavanja remisije

1.

- **5 ASA** (oralni ili lokalni) **MINIMALNA EFIKASNA DOZA**
  - 1.2 g/24h PER OS
  - 3g/nedeljno rektalni

Doza koja je pacijenta uvela u remisiju.
Dozu ne menjati do prve kontrolne kolonoskopije ukoliko je pacijent u remisiji (3-6 meseci od početka remisije).

2.

- **AZA/MP**
  - česti relapsi na terapiji ASA u optimalnim dozama
  - intolerancija na ASA
  - kortikozavisan oblik bolesti
  - prediktori lošeg toka bolesti
  - nastaviti ASA zbog redukcije rizika za razvoj CRC

Imunorefrakterni oblik UC: aktivna bolest ili relaps na terapiji AZA (2-2,5mg/kgTM bez leukopenije) u trajanju minimum tri meseca
Terapija: anti- TNF

Terapija održavanja

- >50% imaju relaps u toku godinu dana nakon pogoršanja
- Kliničko pogoršanje na placebu

  29% -43% u prvih 6 meseci

  38% -76% u toku 12 meseci

ECCO Statement 6B

Preporučena za sve pacijente

Intermitentna samo u **ograničenom broju** pacijenata sa manjom ekstenzivnošću bolesti

Lečenje relapsa

- lekovi koji su u toku predhodnog relapsa bili efikasni, uz optimizaciju terapije održavanja

Relaps	Terapija
retki (≤1/godišnje)	dosadašnja
česti (≥2 /godišnje)	ASA→ AZA AZA→ IFX
kontinuirano aktivna bolest	ASA→ AZA AZA→ IFX
Rani –relaps unutar 3 meseca od postignute remisije	ASA→ KS+AZA AZA→ IFX

AZATIOPRIN

Azatioprin 2-2,5mg/kg

Indikacije

- Kortikozavisna/refraktarna i hronično aktivna bolest
- Rano kod prisustva loših prognostičkih faktora

Kortikorefrakterni oblik UK: aktivnost bolesti uprkos primeni Prednilozona u dozi do 0,75mg/kgTM tokom 4 nedelje

Kortikozavisni oblik UK:

Ne postoji mogućnost smanjenja KS<10mg/dan unutar 3 meseca od započinjanja terapije, a da ne dođe do relapsa.

Ili ukoliko dođe do relapsa unutar 3 meseca od isključenja KS

Neželjena dejstva

- pre započinjanja TPMT i EBV IgG
- Mijelosupresija
  - Lkc
    - I mesec: 1x nedeljno
    - II mesec: 2x mesečno
    - zatim 1x mesečno
- hepatotoksičnost
- infekcije
- pankreatitis
- limfoproliferativne bolesti (mladi muškarci

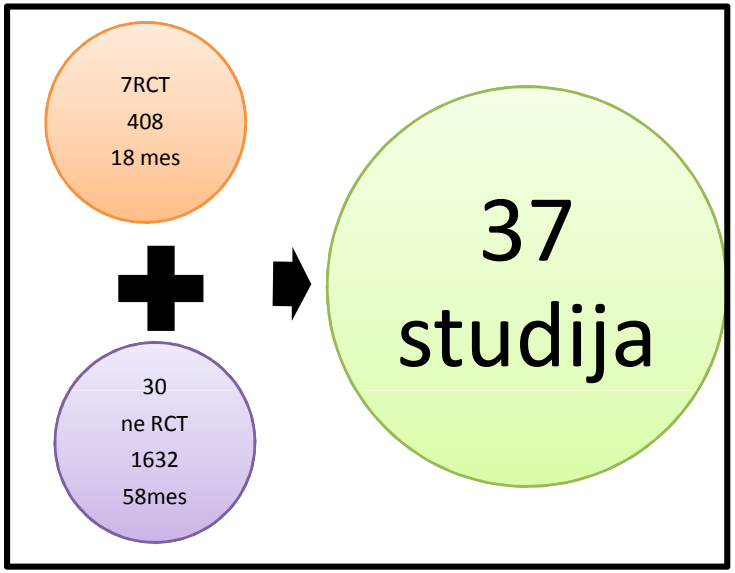
Šta može AZA

- **<u>Kontrolisane studije</u>**

- AZA vs placebo OR 2.59
- Smanjenje rizika 23%
- NNT da se spreci jedan relaps je 5
- Heterogene studije u poredjenju AZA sa ASA
- Za indukciju remisije OR 1.59, 95% CI 0.59 to 4.29
- U kvalitetnim studijama i manje OR 1.21, 95% CI 0.6 to 2.41
- Za održavanje remisije OR 2.44, 95% CI 1.42 to 4.17

- **<u>Ostale studije</u>**

- Efikasnost 65% (95% CI 62% to 67%; 30 studies)
- Za kortikorezistentne 66% (95% CI 59% to 73%)
- Efikasnost u indukciji 65% (95% CI 55% to
- Efikasnost u održavanju 76% (95% CI 71% to 81%).

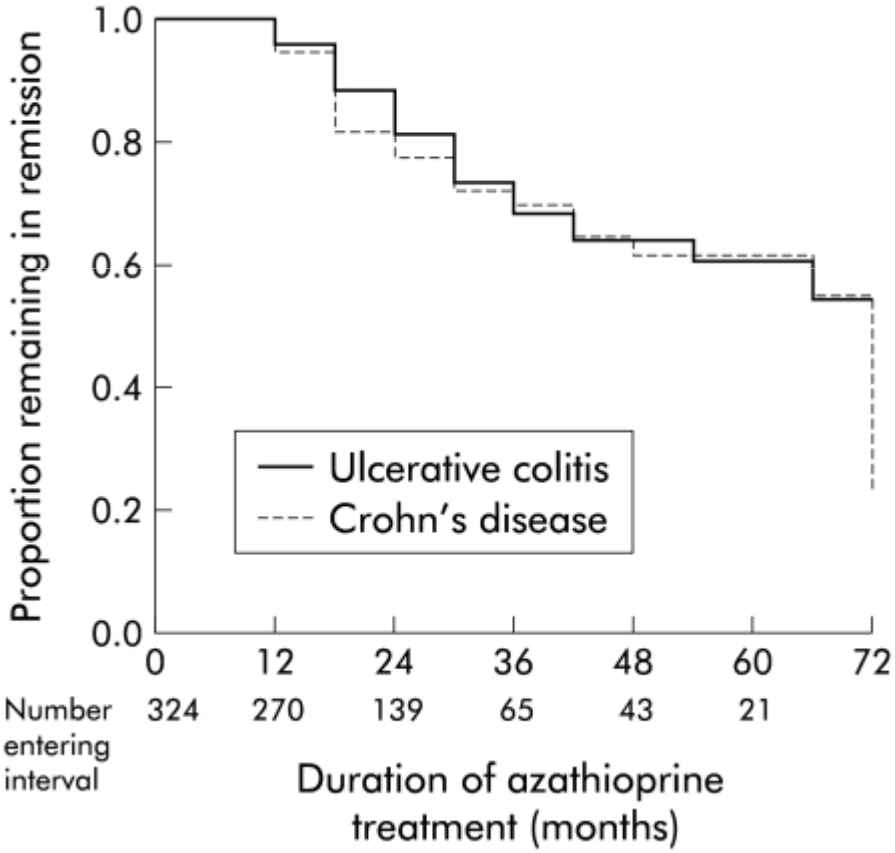


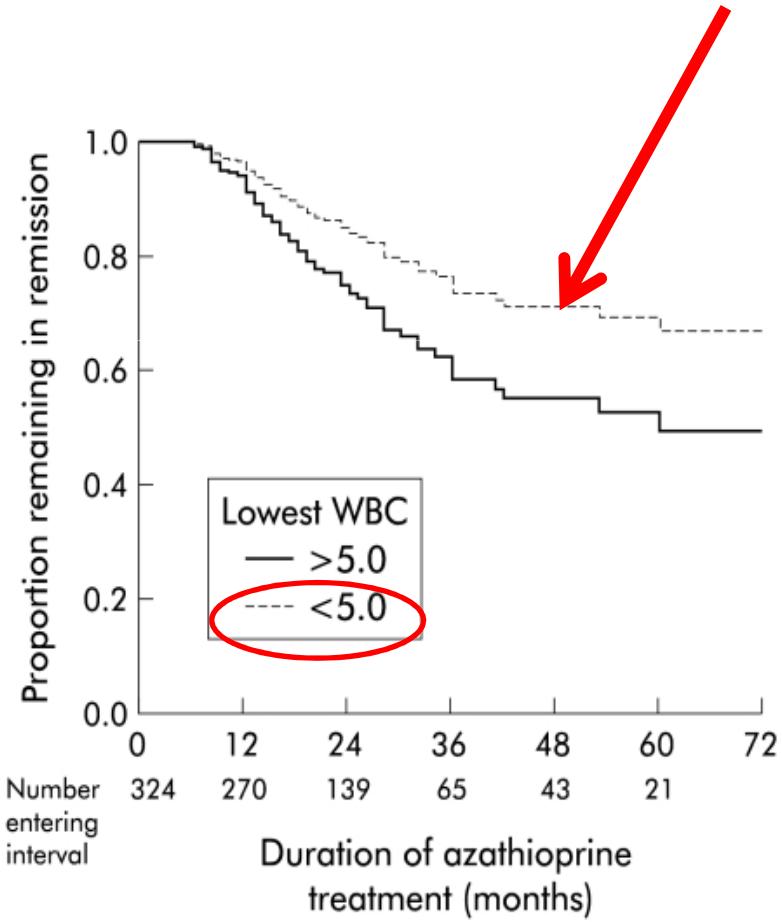
Alimentary Pharmacology & Therapeutics

Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis

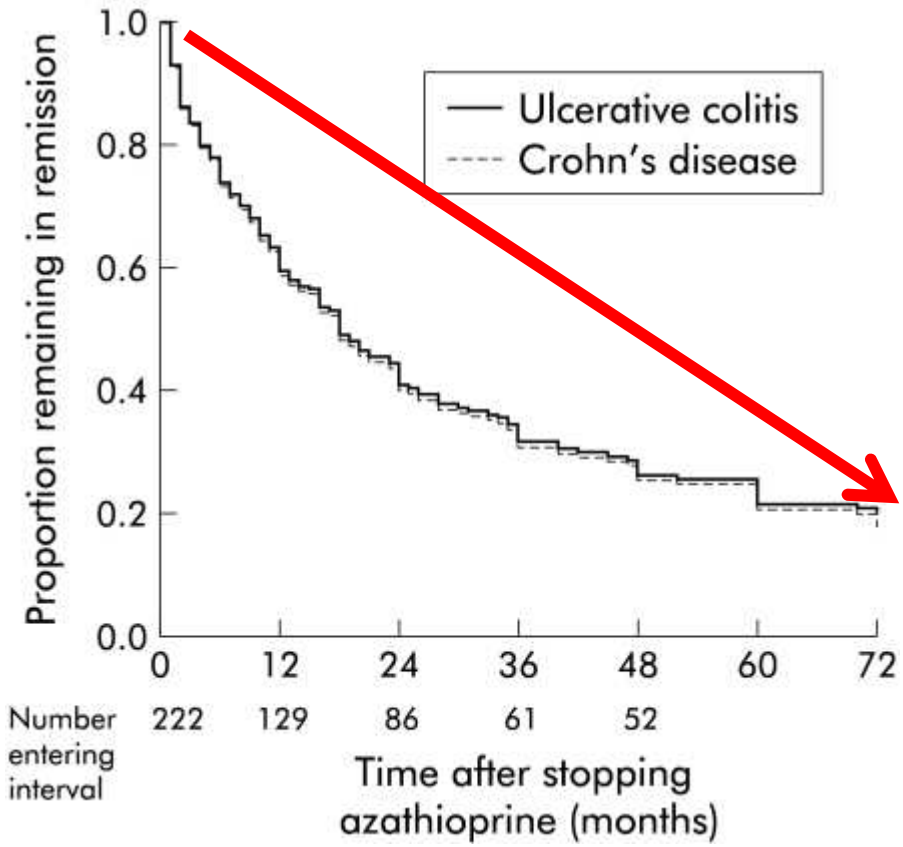
J. P. GISBERT*,†, P. M. LINARES*,†, A. G. MCNICHOLL*,†, J. MATÉ*,† & F. GOMOLLÓN†,‡

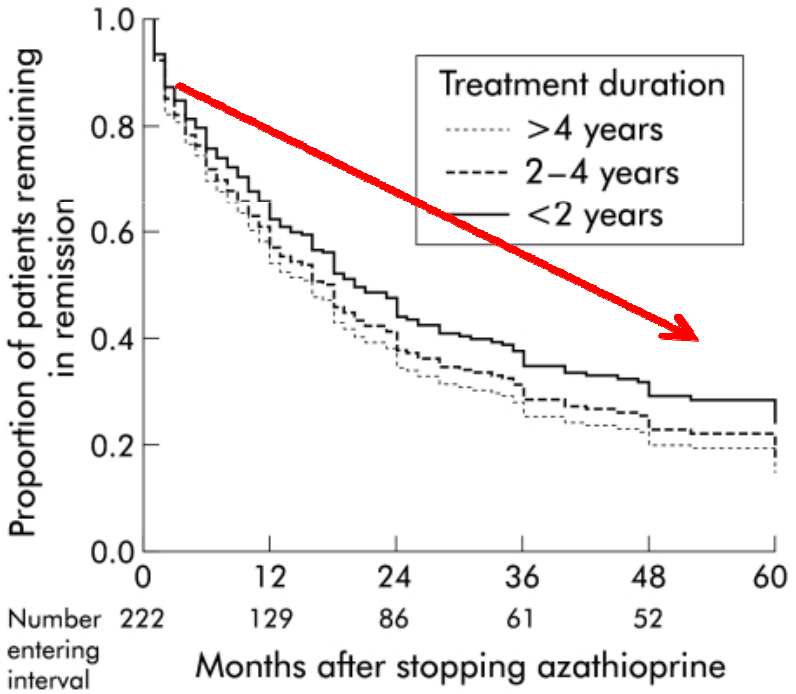
Terapija održavanja





Terapija održavanja





AZA u terapiji održavanja

- 286 pacijenata

AZA VS PLACEBO

relaps

- 44% AZA
- 65% placebo

RR 0.68

AZA vs Placebo

Neželjena dejstva

- 8% AZA
- 0% placebo

RR 5.43

Timmer et al. Cochrane Database syst Rev 2012

Azatioprin 2-2,5mg/kg

Indikacije

- Kortikozavisna/refraktarna i hronično aktivna bolest
- Rano kod prisustva loših prognostičkih faktora

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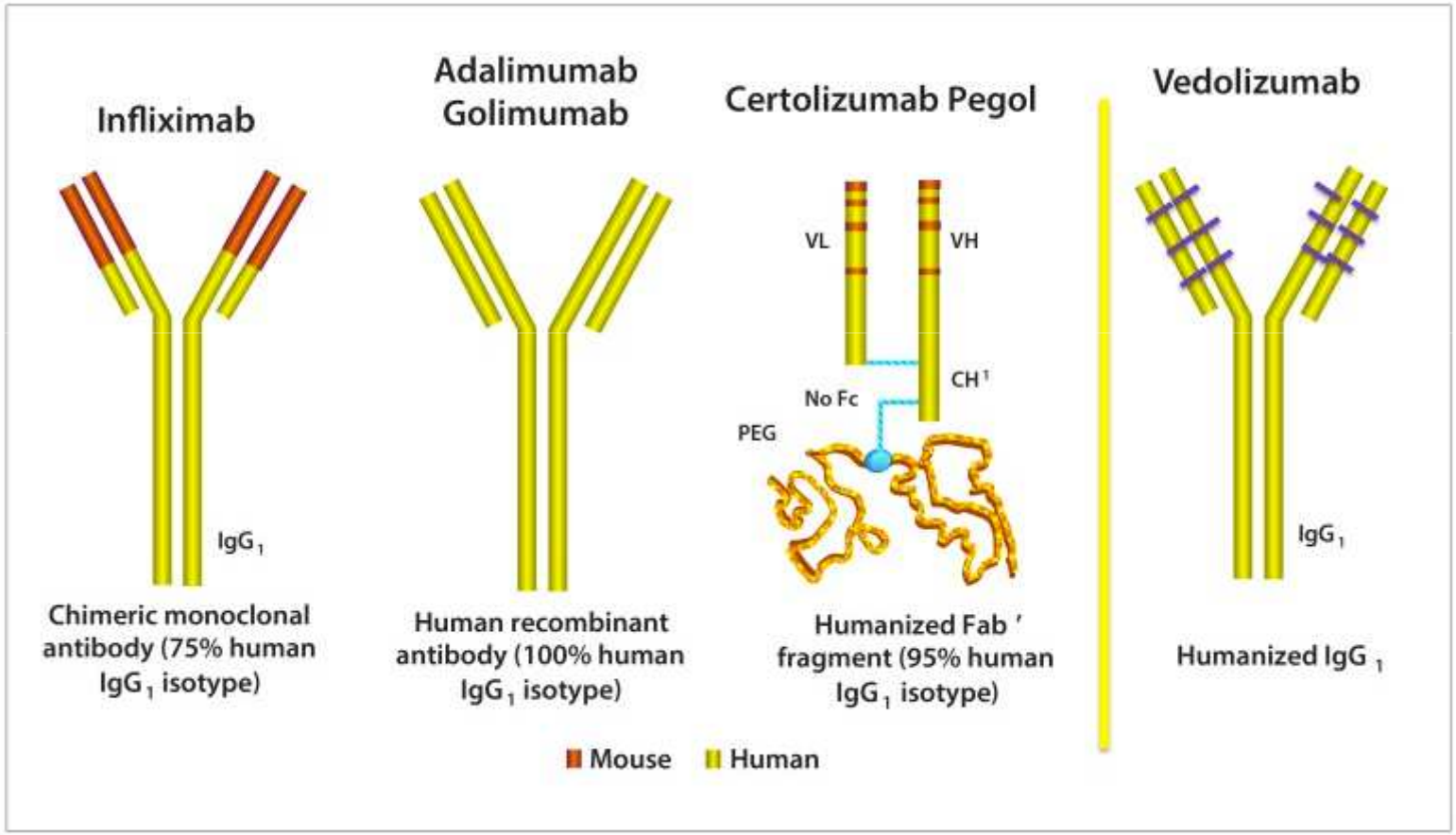
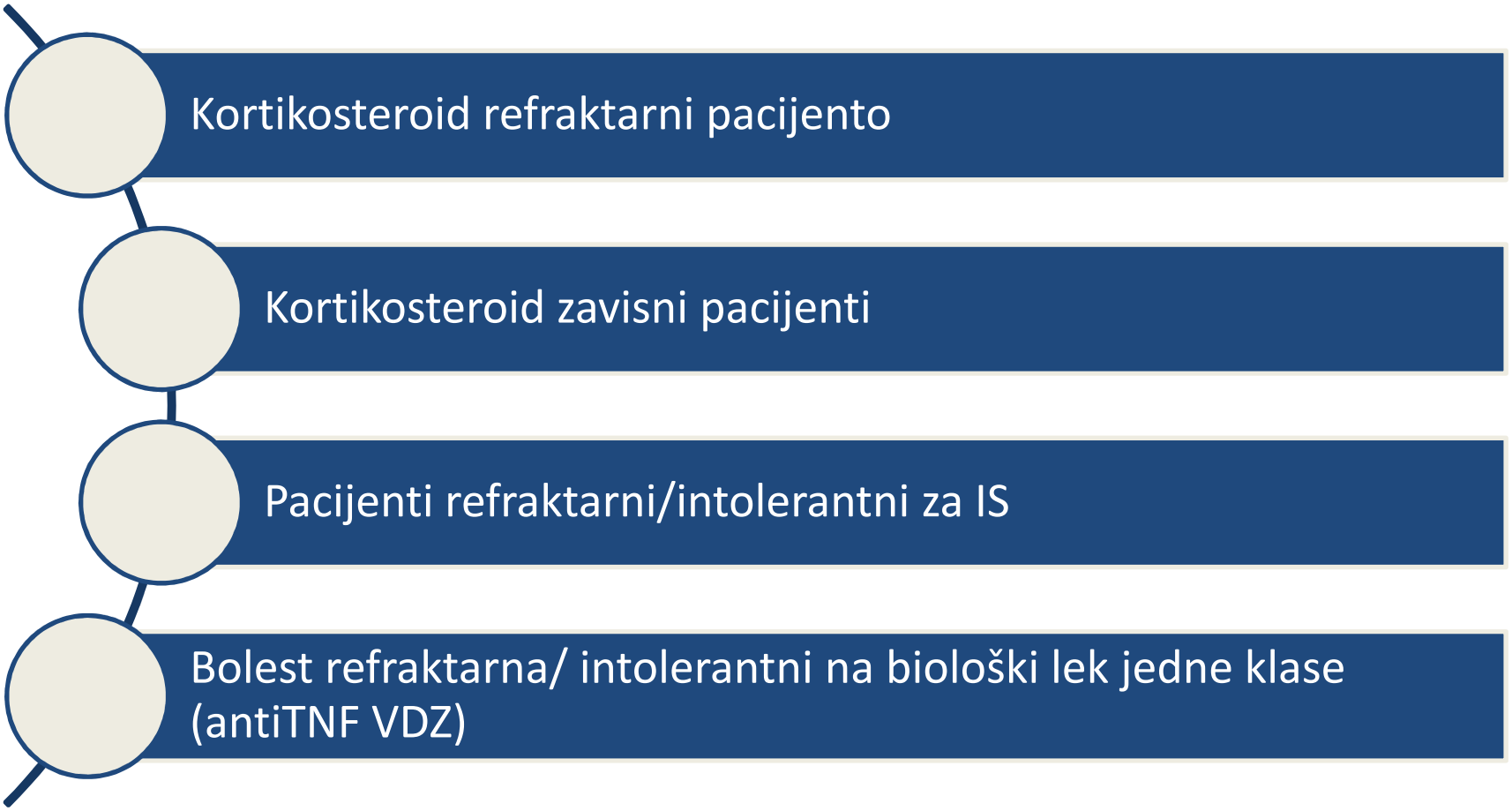
Biološki lekovi u UK blage do umerene aktvinosti



Indikacije za biološku terapiju



Koji su uslovi

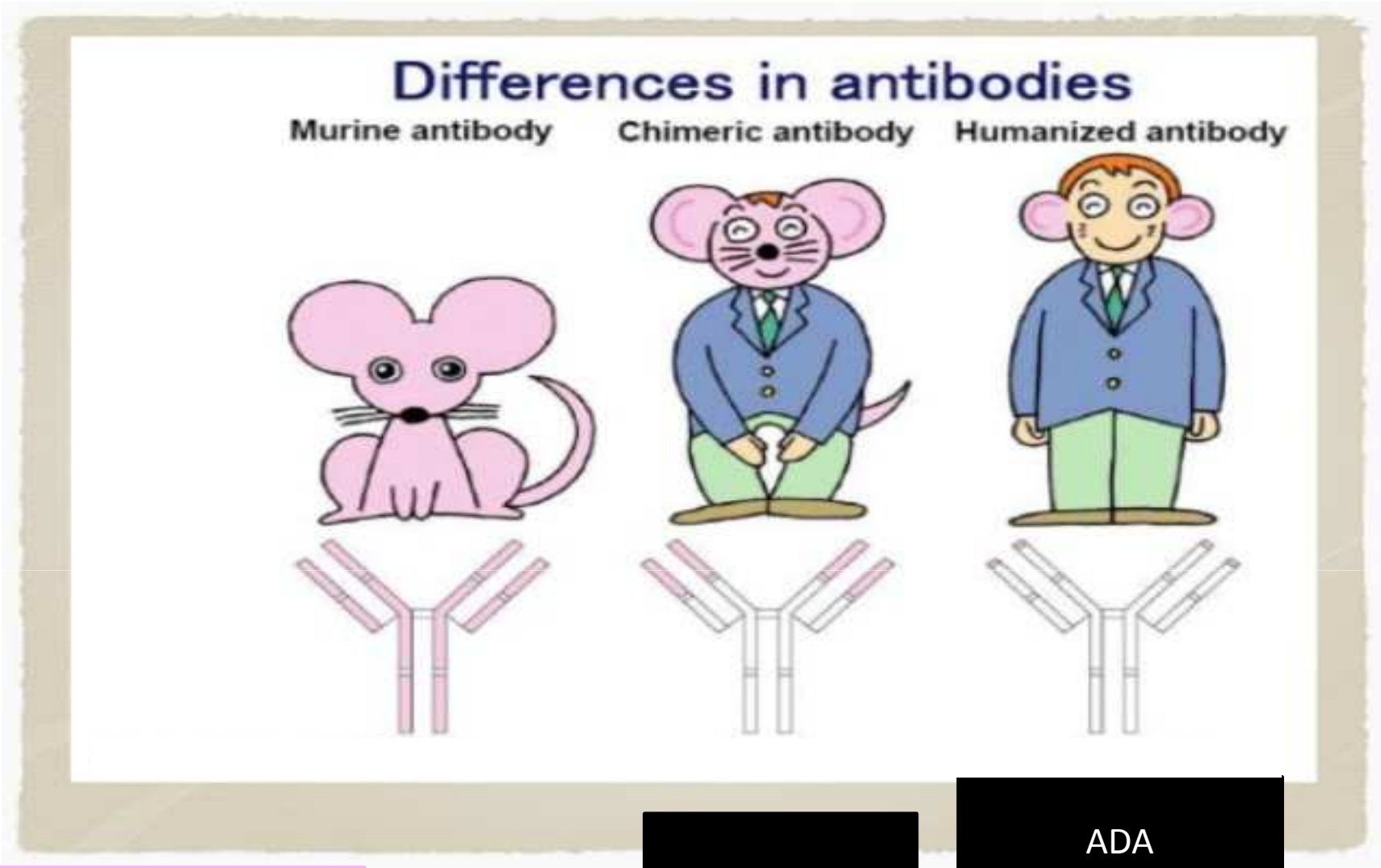
- Pravi pacijent

- Pravo vreme

INFLAMACIJA
FIBROZA

- Pravi lek
- Prava doza
- Pravi način aplikacije

Kako izabrati lek

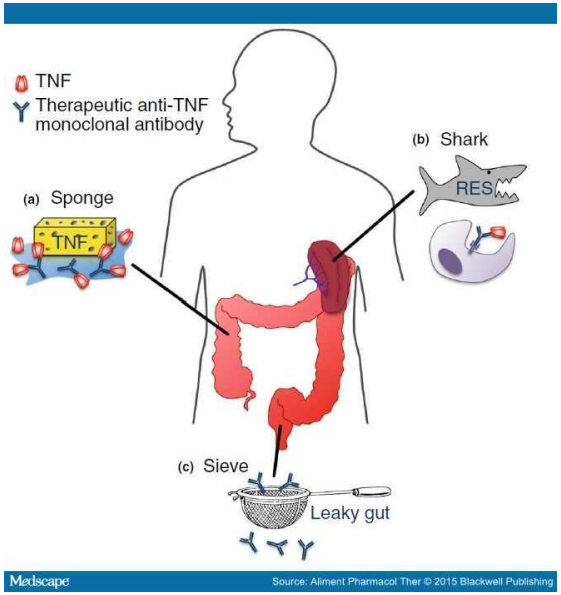


Imunogenost

IFX
75% humano

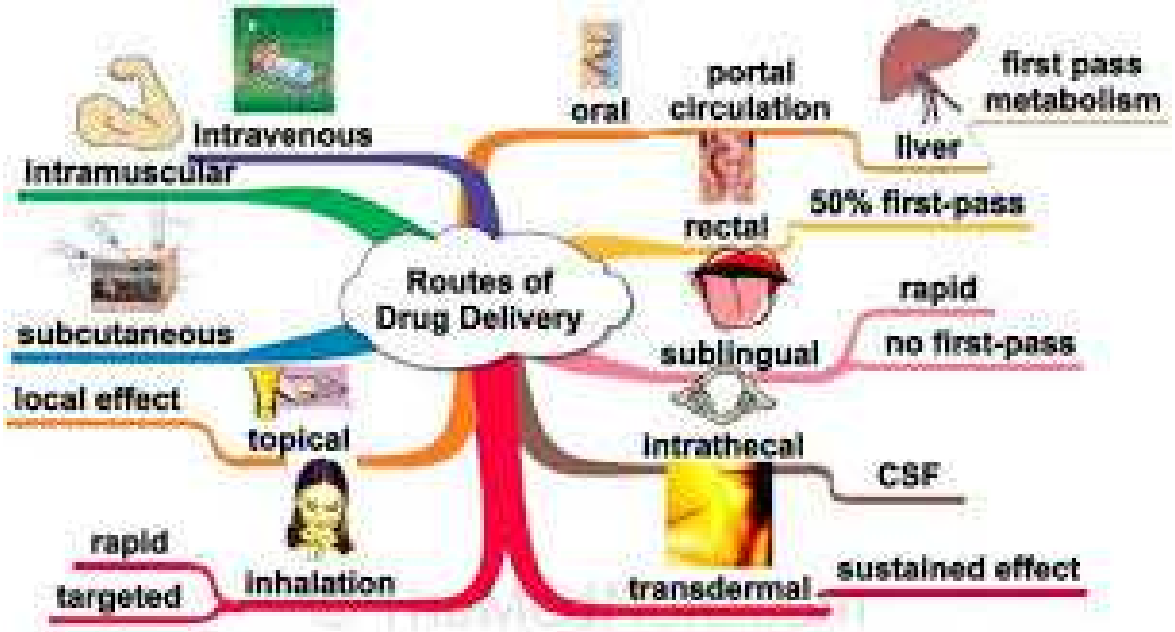
ADA
Golimumab
VDZ

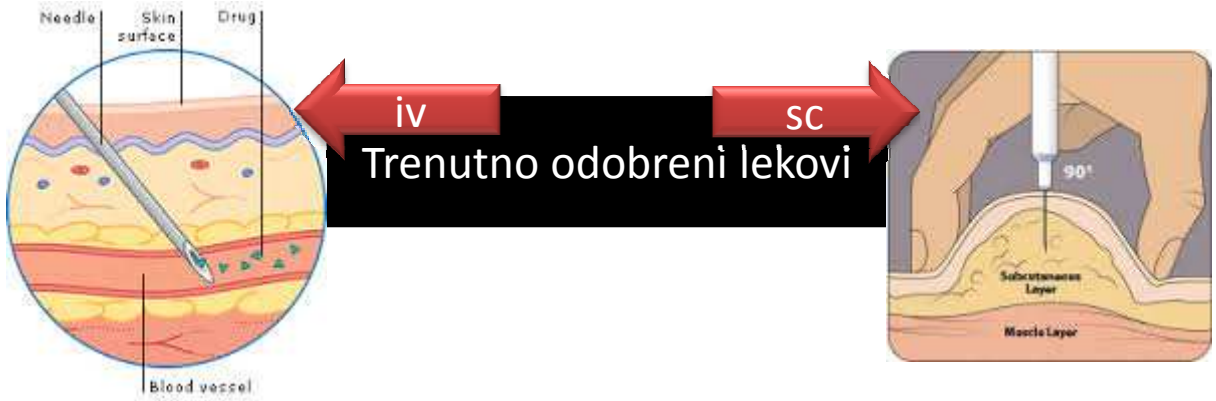
Prava doza



Standardni protokol
Optimizacija
Nivo leka i antitela u krvi?

Način aplikacije leka





- Pravi pacijent
- Pravi lek
- Prava doza
- Pravi put
- Pravo vreme

Biološka terapija u IBC

- Infliximab — ACT1 i ACT2
- Adalimumab — ULTRA 1,ULTRA2 (ULTRA3)
- Golimumab — PURSUIT

- Vedolizumab — GEMINI

Mehanizam dejstva

selektivni

neselektivni

Outcomes	ACT 1[6]			ACT 2[6]		
	IFX 5 mg/kg (n=121) n (%) *P*[a]	IFX 10 mg/kg (n=122) n (%) *P*[a]	Placebo (n=121) n (%)	IFX 5 mg/kg (n=121) n (%) *P*[a]	IFX 10 mg/kg (n=120) n (%) *P*[a]	Placebo (n=123) n (%)
Clinical response at week 8	84 (64.9) <0.001	76 (61.5) <0.001	45 (37.2)	78 (64.5) <0.001	83 (69.2) <0.001	36 (29.3)
Clinical response at week 30	63 (52.1) <0.001	62 (50.8) 0.002	36 (29.8)	57 (47.1) <0.001	72 (60) <0.001	32 (26)
Clinical remission week 30	41 (33.9) 0.001	45 (36.9) <0.001	19 (15.7)	31 (25.6) 0.003	43 (35.8) <0.001	13 (10.6)
Clinical remission week 54	42 (34.7) 0.001	42 (34.4) 0.001	20 (16.5)	/	/	/

	ULTRA 1[11]			ULTRA 2[12]	
	ADA 160/80 mg (n=130) n (%) *P*[a]	ADA 80/40 mg (n=130) n (%) *P*[a]	Placebo (n=130) n (%)	ADA 160/80 mg (n=248) n (%) *P*[a]	Placebo (n=246) n (%)
Clinical remission at week 8	24 (18.5) 0.031	13 (10) 0.833	12 (9.2)	41 (16.5) 0.019	23 (9.3)
Clinical remission at week 52	/	/	/	43 (17.3) 0.004	21 (8.5)
Clinical response at week 8	71 (54.6)	67 (51.5)	58 (44.6)	125 (50.4) 0.001	85 (34.6)
Clinical response at week 52	/	/	/	75 (30.2) 0.002	45 (18.3)

PURSUIT-SC[17]	Golimumab 200/100 mg, n (%) (n=253)	Golimumab 400/200 mg, n (%) (n=257)	Placebo, n (%) (n=251)	*P*
Clinical response[a]	129 (51)	141 (54.9)	76 (30.3)	<0.0001[b]
Clinical remission[a]	45 (17.8)	46 (17.9)	16 (6.4)	<0.0001[b]
Mucosal healing[a]	107 (42.3)	116 (45.1)	72 (28.7)	0.0014[c] <0.0001[d]
PURSUIT-M[19]	**Golimumab 100 mg, n (%) (n=151)**	**Golimumab 50 mg, n (%) (n=151)**	**Placebo n (%) (n=154)**	***P***
CCR	75 (49.7)	71 (47)	48 (31.2)	<0.001[e] 0.010[f]
Clinical remission at both week 30 and 54	42 (27.8)	35 (23.2)	24 (15.6)	0.004[e] 0.122[f]
Mucosal healing at both week 30 and 54	64 (42.4)	62 (41.7)	41 (26.6)	0.002[e] 0.011[f]

Vedolizumab

Table 2 Proportion of patients meeting efficacy endpoints at week 52

Outcome	Placebo (n=126)	Vedolizumab every 8 weeks (n=122)	Vedolizumab every 4 weeks (n=125)	*P*-value
Clinical remission at week 52	20 (15.9%)	51 (41.8%)	56 (44.8%)	<0.001
Durable clinical response*	30 (23.8%)	69 (56.6%)	65 (52.0%)	<0.001
Durable clinic remission#	11 (8.7%)	25 (20.5%)	30 (24.0%)	0.008
Mucosal healing at week 52‡	25 (19.8%)	63 (51.6%)	70 (56.0%)	<0.001
Glucocorticoid-free remission‡‡	10 (13.9%)	22 (31.4%)	33 (17.6%)	0.01

Notes: Patients must have achieved clinical response at week 6 to continue into UC trial II. This group includes patients who were not in clinical remission at week 6. *Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point at weeks 6 and 52. #Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point at weeks 6 and 52. ‡Improvement in endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability). ‡‡Corticosteroid-free clinical remission: assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at week 6 (n=72 for placebo and n=70 for vedolizumab every 8 weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup who discontinued corticosteroids by week 52 and the proportion of patients in clinical remission at week 52.

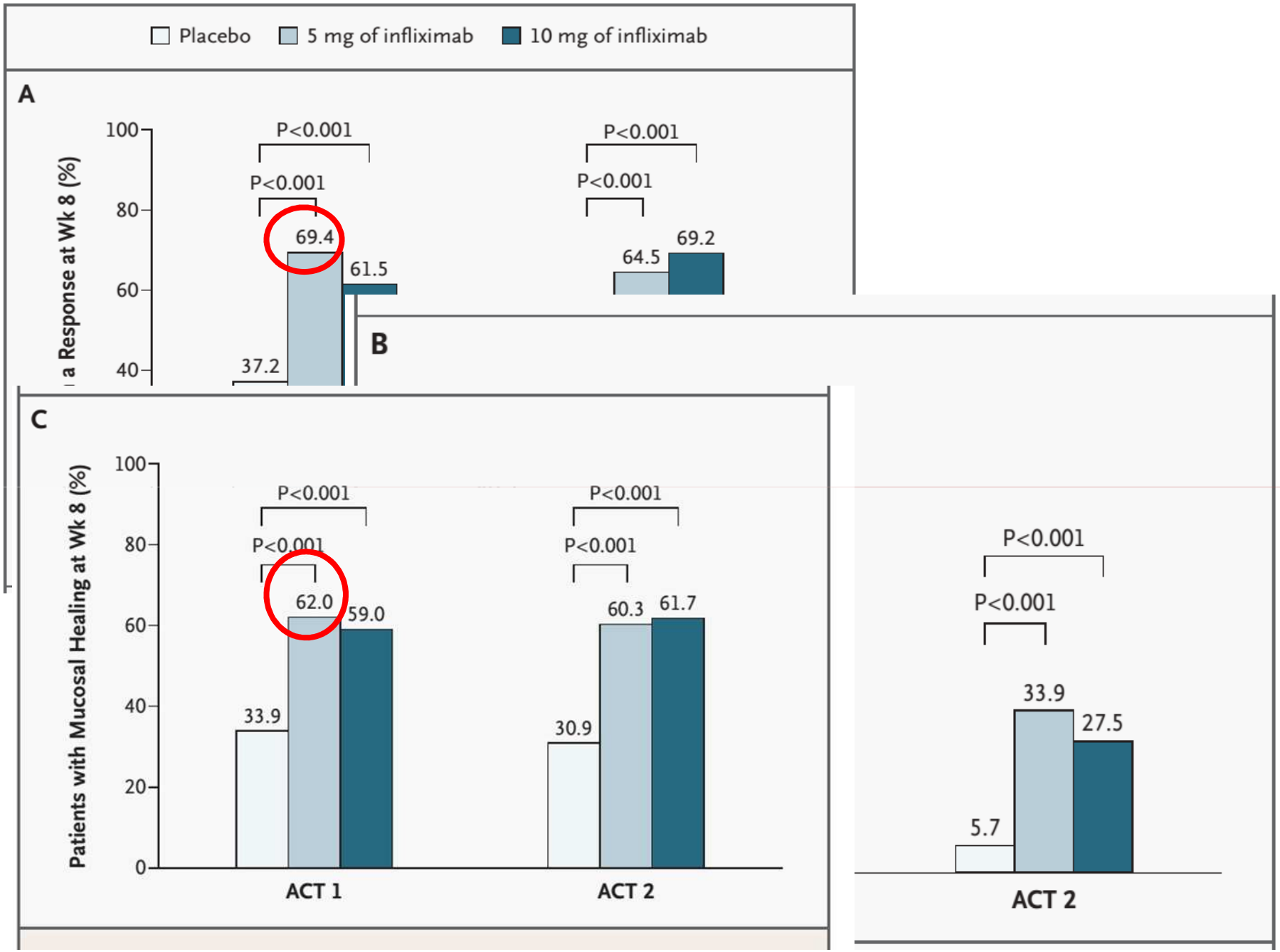
Infliximab ACT rezultati

- Klinički odgovor na terapiju (Clinical response) smanjenje vrednosti Mayo skora za ≥ 3 ili za 30% uz smanjenje subskora rektalnog kravrenja za 1 ili skor za rektalno krvarenje 0 ili 1.

- Klinička remisija (Clinical remission) Mayo skor 2 ili manje i nijedan subskor preko 1

- Mukozno zaceljenje (Mucosal healing) endoskopski subskor 0 ili 1

U studiji aktivni UC naivni na antiTNF, Mayo skor 6-12



Rutgeerts, et al. *N Engl J Med* 2005;353:2462-76

Infliximab

- Nakon 8 nedelja i indukcione terapije

ACT 1

remisija

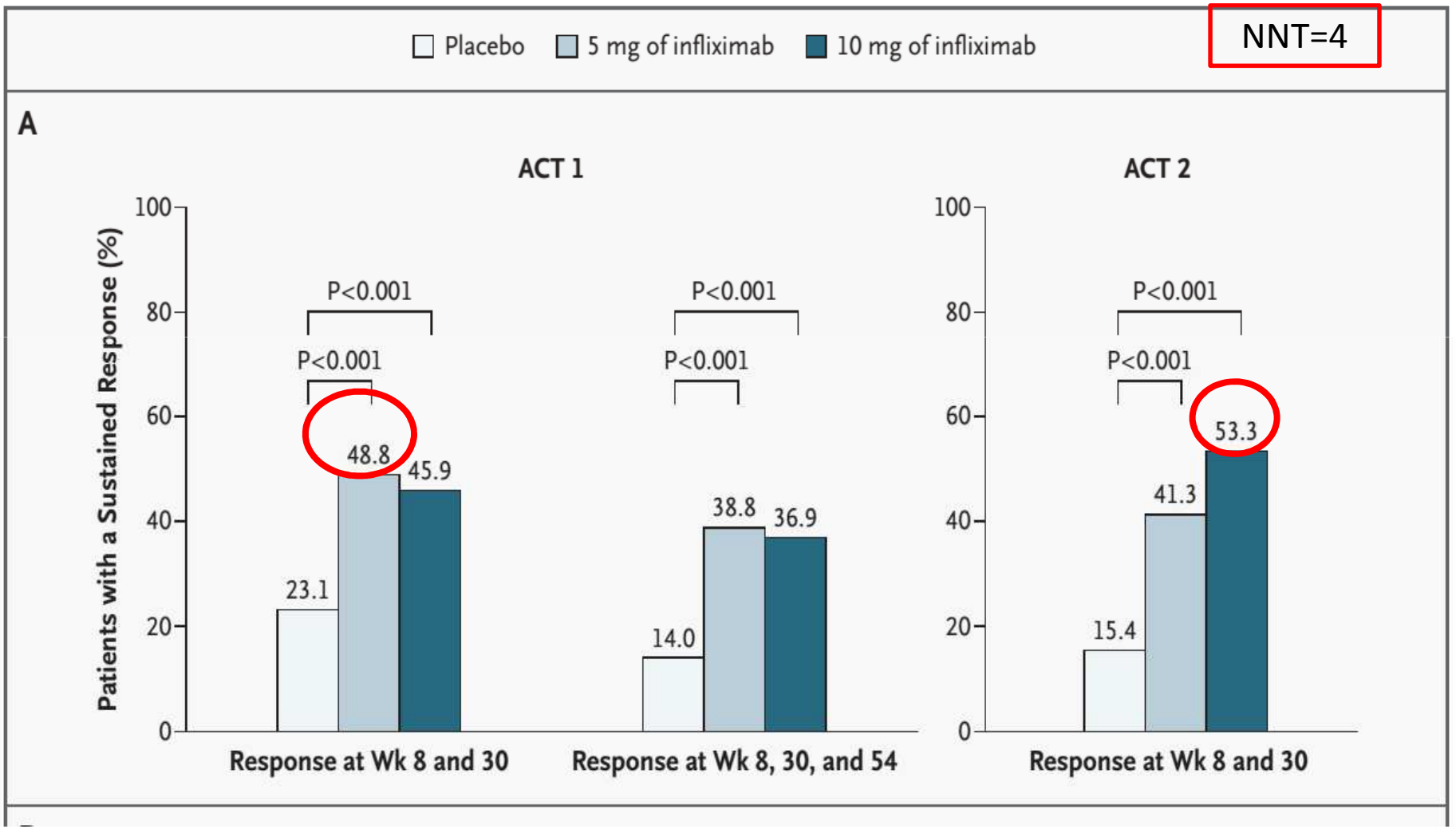
- 39% 5 mg/kg IFX
- 32% 10mg/kg IFX
- 15% placebo

ACT 2

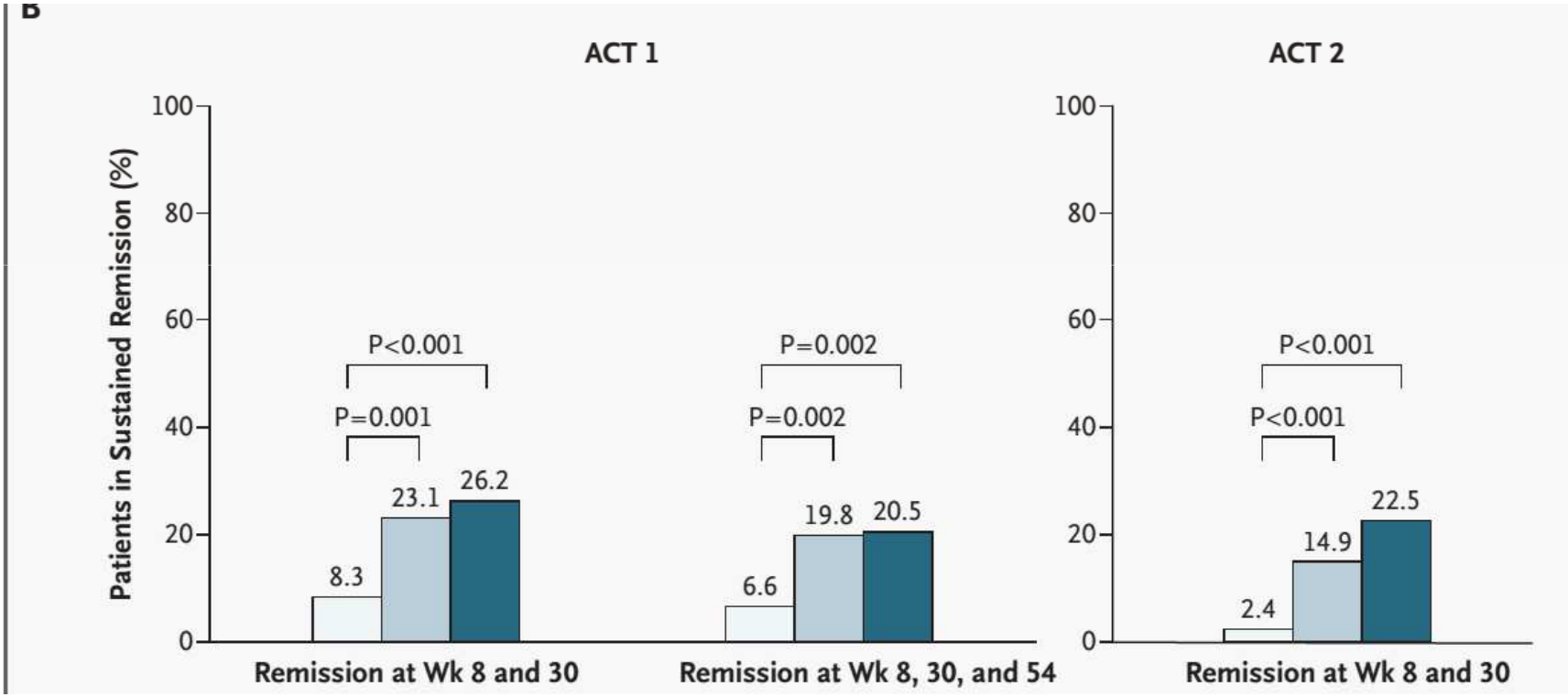
remisija

- 34% 5 mg/kg IFX
- 28% 10mg/kg IFX
- 5% placebo

Produženi terapijski odgovor

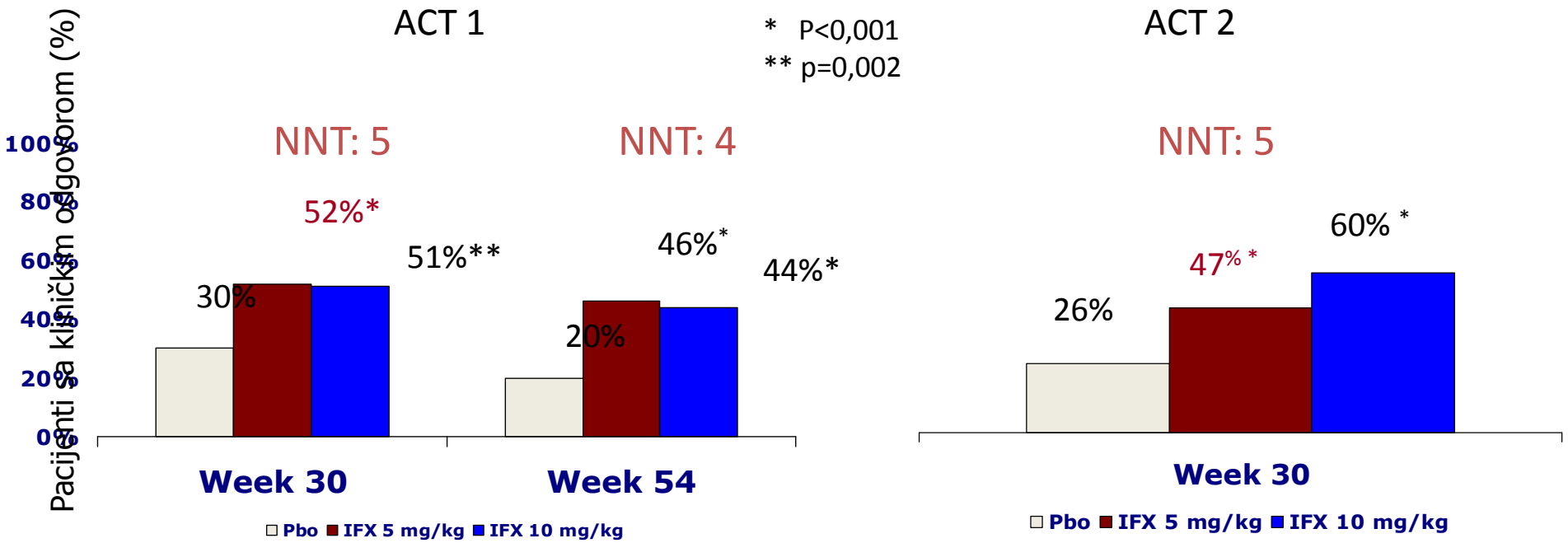


Remisija


B
ACT 1
ACT 2
Patients in Sustained Remission (%)
100
80
60
40
20
0
P<0.001
P=0.001
P=0.002
P=0.002
P<0.001
P<0.001
8.3
23.1
26.2
6.6
19.8
20.5
2.4
14.9
22.5
Remission at Wk 8 and 30
Remission at Wk 8, 30, and 54
Remission at Wk 8 and 30

Infliximab ODRŽAVANJE : ACT rezultati

Klinički odgovor* 30 i 54 nedelja



*Klinički odgovor: Smanjenje Mayo skora za ≥30% i ≥3 I smanjenje skora rektalnog krvarenja ≥1 ili subskor za rektalno krvarenje 0ili 1

Rutgeerts, et al. *N Engl J Med* 2005;353:2462-76

Variable	ACT 1			ACT 2		
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)
Clinical response						
Week 8 — no. (%)	45 (37.2)	84 (69.4)	75 (61.5)	36 (29.3)	78 (64.5)	83 (69.2)
P value		<0.001	<0.001		<0.001	<0.001
Week 30 — no. (%)	36 (29.8)	63 (52.1)	62 (50.8)	32 (26.0)	57 (47.1)	72 (60.0)
P value		<0.001	0.002		<0.001	<0.001
Week 54 — no. (%)	24 (19.8)	55 (45.5)	54 (44.3)	—	—	—
Clinical remission — no. (%)						
Week 8	18 (14.9)	47 (38.8)	39 (32.0)	7 (5.7)	41 (33.9)	33 (27.5)
P value		<0.001	0.002		<0.001	<0.001
Week 30	19 (15.7)	41 (33.9)	45 (36.9)	13 (10.6)	31 (25.6)	43 (35.8)
P value		0.001	<0.001		0.003	<0.001
Week 54	20 (16.5)	42 (34.7)	42 (34.4)	—	—	—
P value		0.001	0.001			

Infliximab

- Na završetku studije

ACT 1

remisija 54 nedelja

- 35% 5 mg/kg IFX
- 34% 10mg/kg IFX
- 17% placebo

ACT 2

remisija 30 nedelja

- 26% 5 mg/kg IFX
- 36% 10mg/kg IFX
- 11% placebo

Infliximab

- U svakom trenutku u remisiji

ACT 1

remisija

- 20% 5 mg/kg IFX
- 7%placebo

ACT 2

remisija

- 15% 5 mg/kg IFX
- 2% placebo

Infliximab ACT extension

- Grupa sa placebom nije praćena
- **229/484 pacijenta**
- 181 praćeni godinu dana
- 92 praćeni 2 godine
- Minimalna aktivnost bolesti u 56 ned 92%, u 104 nedelji 97%
- Remisija bez kortikosteroida 75% i 98%
- 30.6% isključeni sa terapije
- 76.5 % Remisija ili blaga bolest

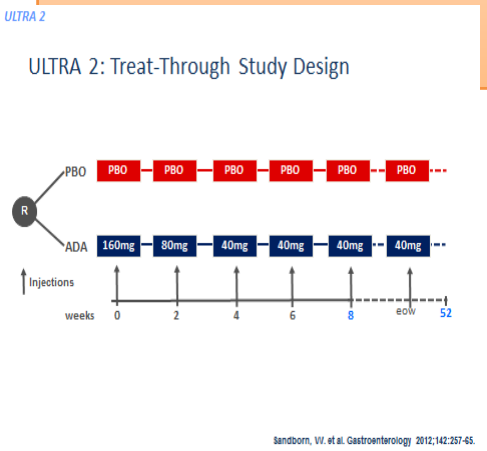
  90.0% ostalo u remisiji

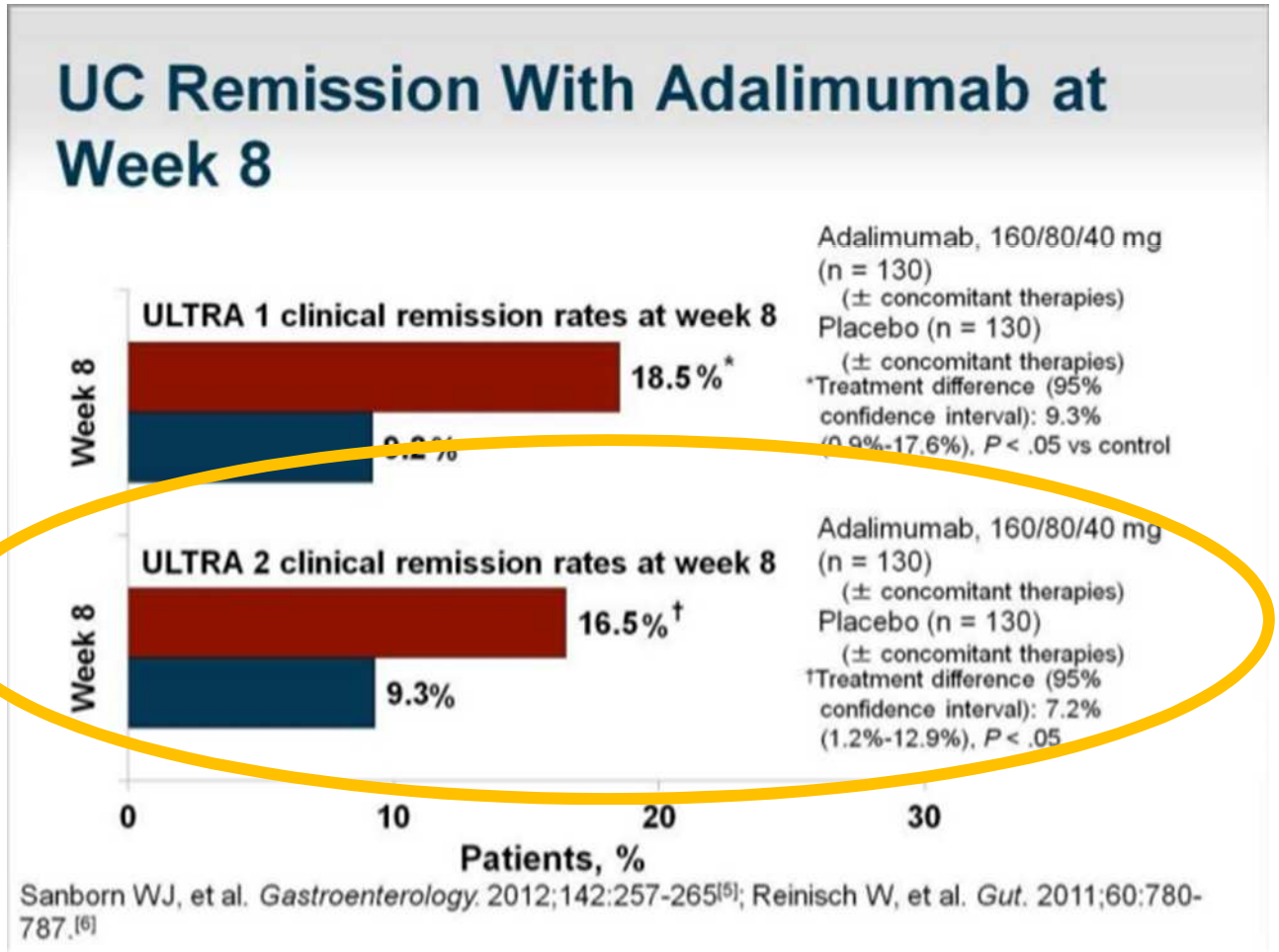
  94.3% blaga bolest

Adalimumab

- ULTRA 2 studija

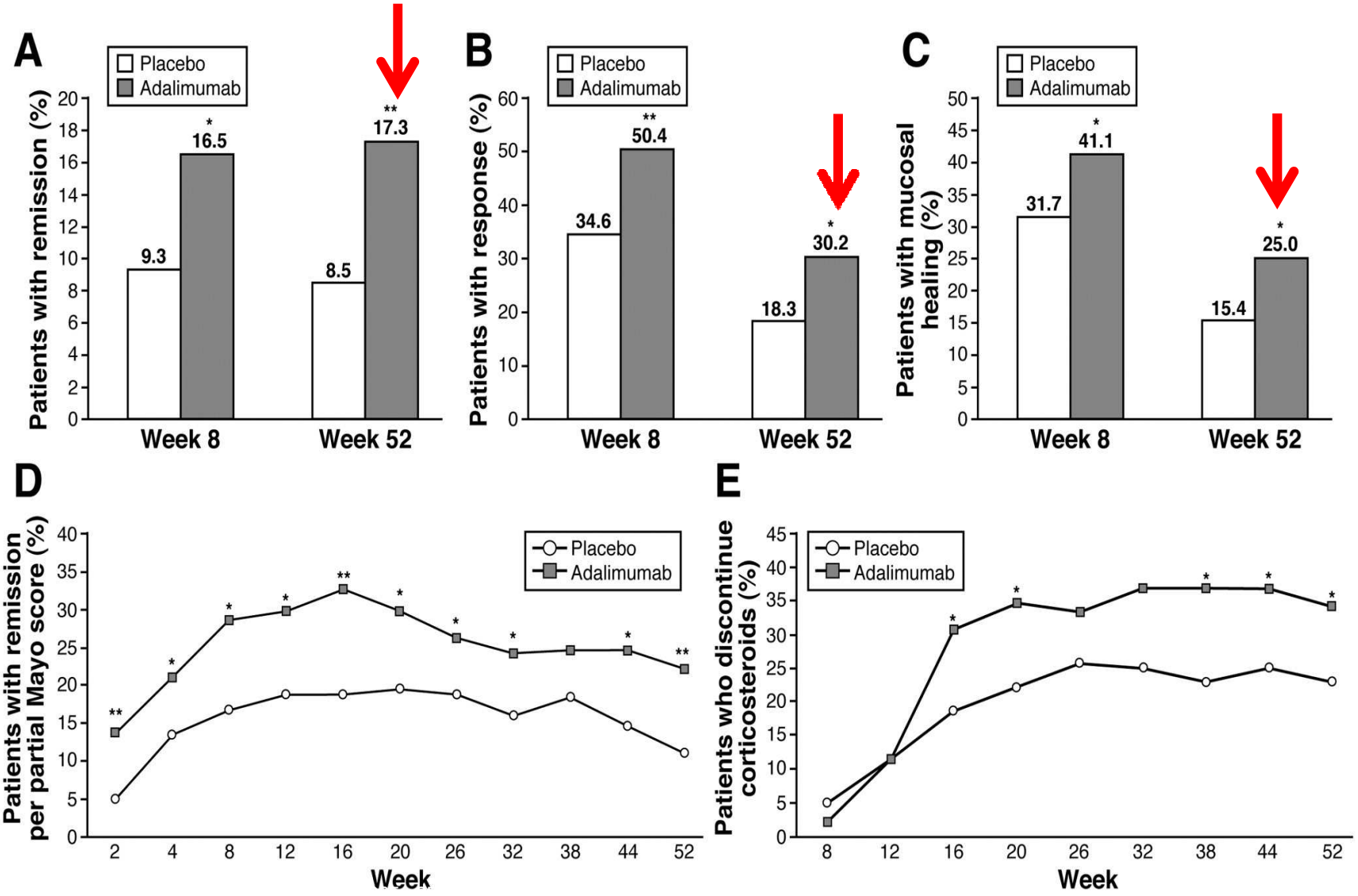
Treat trough study design





Sanborn WJ, et al. *Gastroenterology*. 2012;142:257-265[5]; Reinisch W, et al. *Gut*. 2011;60:780-787.[6]

Adalimumab


A
Placebo
Adalimumab
Patients with remission (%)
9.3
16.5
8.5
17.3
Week 8
Week 52
B
Placebo
Adalimumab
Patients with response (%)
34.6
50.4
18.3
30.2
Week 8
Week 52
C
Placebo
Adalimumab
Patients with mucosal healing (%)
31.7
41.1
15.4
25.0
Week 8
Week 52
D
Placebo
Adalimumab
Patients with remission per partial Mayo score (%)
Week
E
Placebo
Adalimumab
Patients who discontinue corticosteroids (%)
Week

Adalimumab ULTRA 2

anti-TNF naivni

klinička remisija 52 nedelja

ADA 22%

Placebo 12.4%

(*P* 0 .029)

NNT=11 za remisiju

NNT= 8 za klinički odgovor

Prethodno primali anti TNF

klinička remisija 52 nedelja

ADA 10,2%

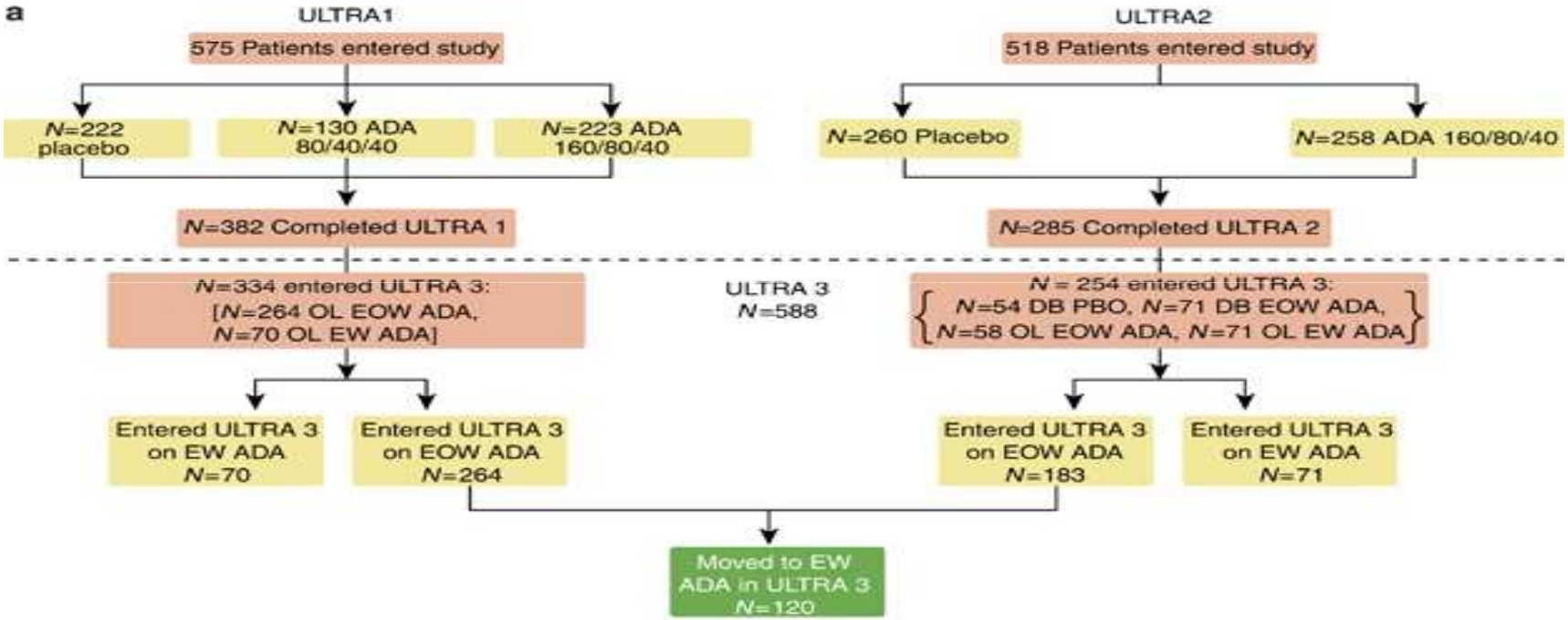
Placebo 3%

(*P* 0 .039)

NNT=14 za remisiju

NNT= 10 za klinički odgovor

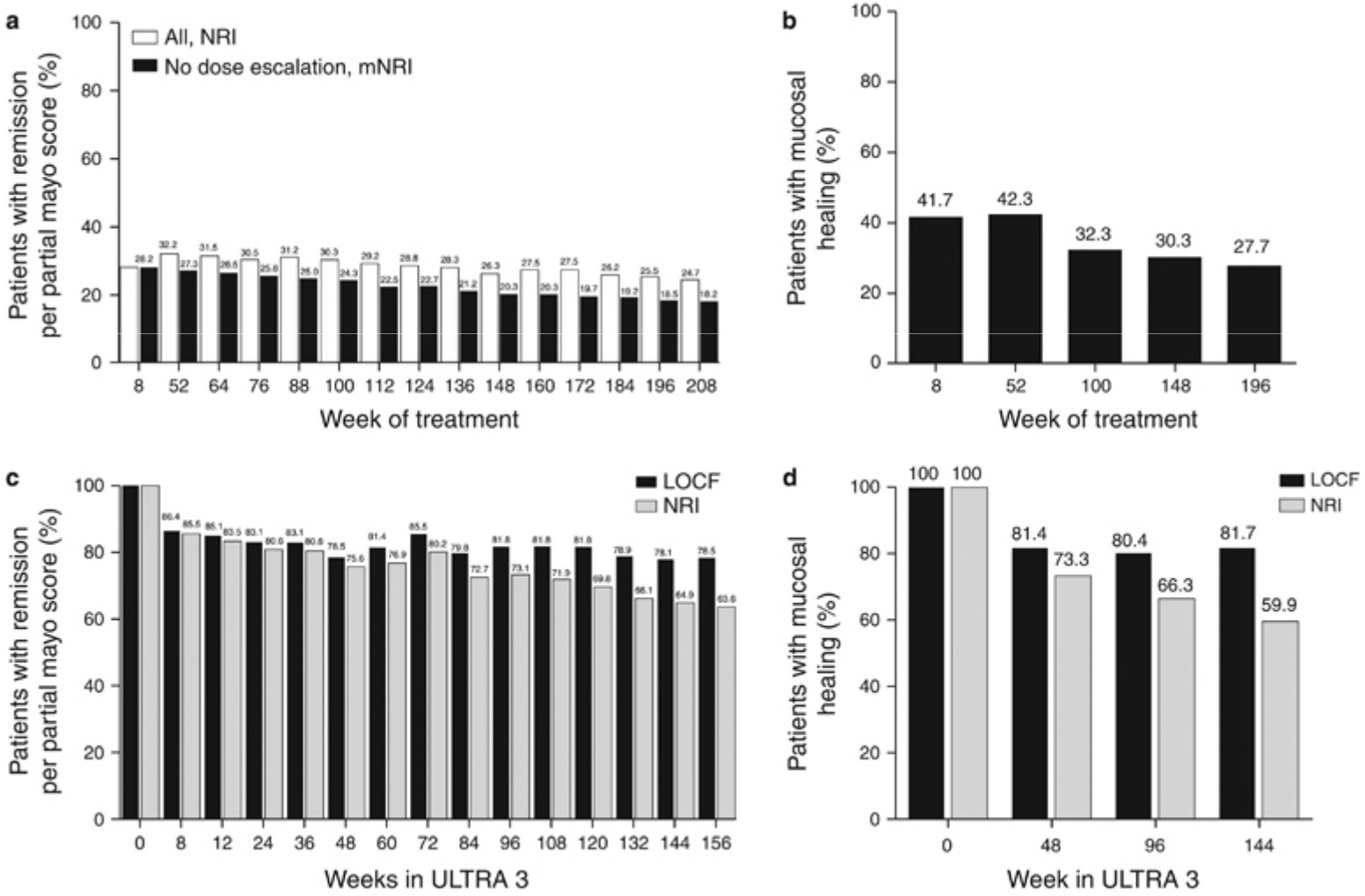
Adalimumab ULTRA 3



b Number of patients by visit

Week from lead-in study baseline	ADA Randomized set (N)	ADA Extension set (N)
0	600	N/A
52	389	588
100	292	517
160	225	418
208	199	360

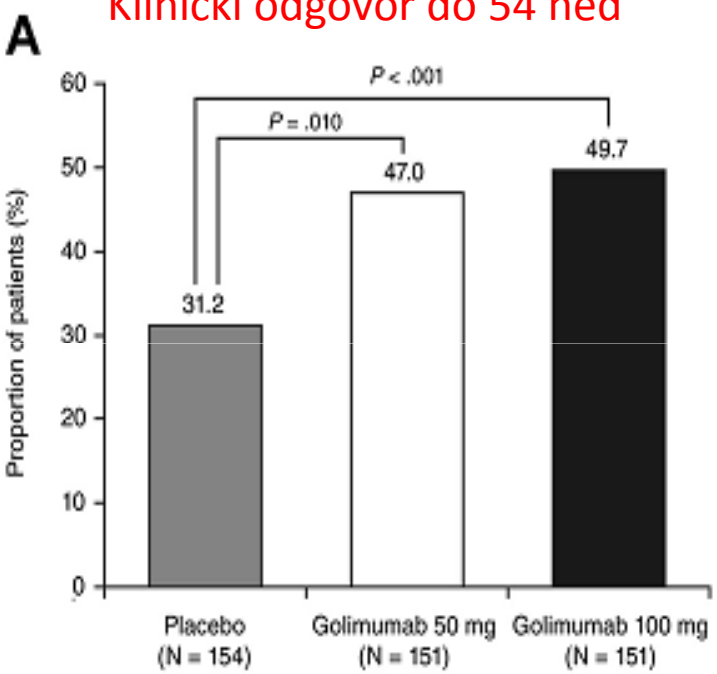
Adalimumab ULTRA 3-4 godine



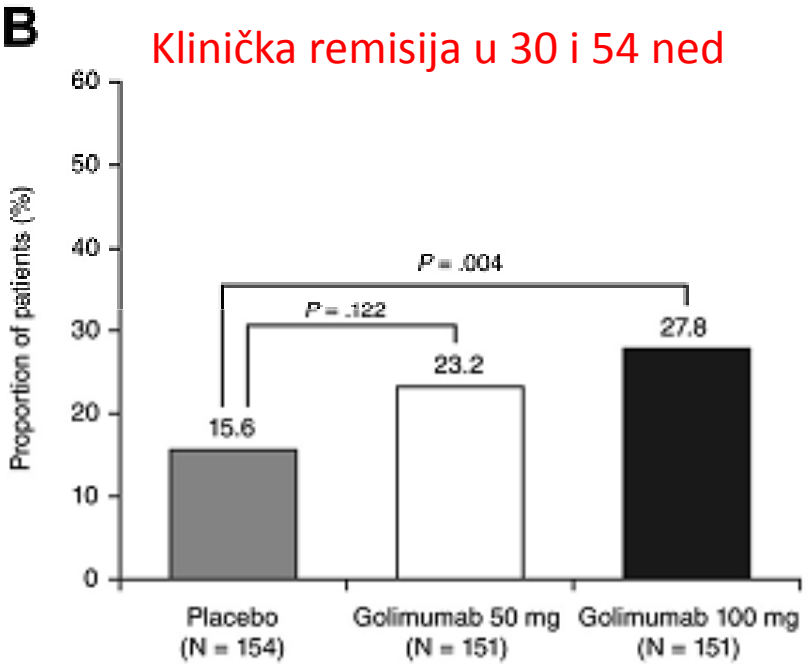
Colombel et al. Am J gastroenterol 2014

Golimumab

Klinički odgovor do 54 ned

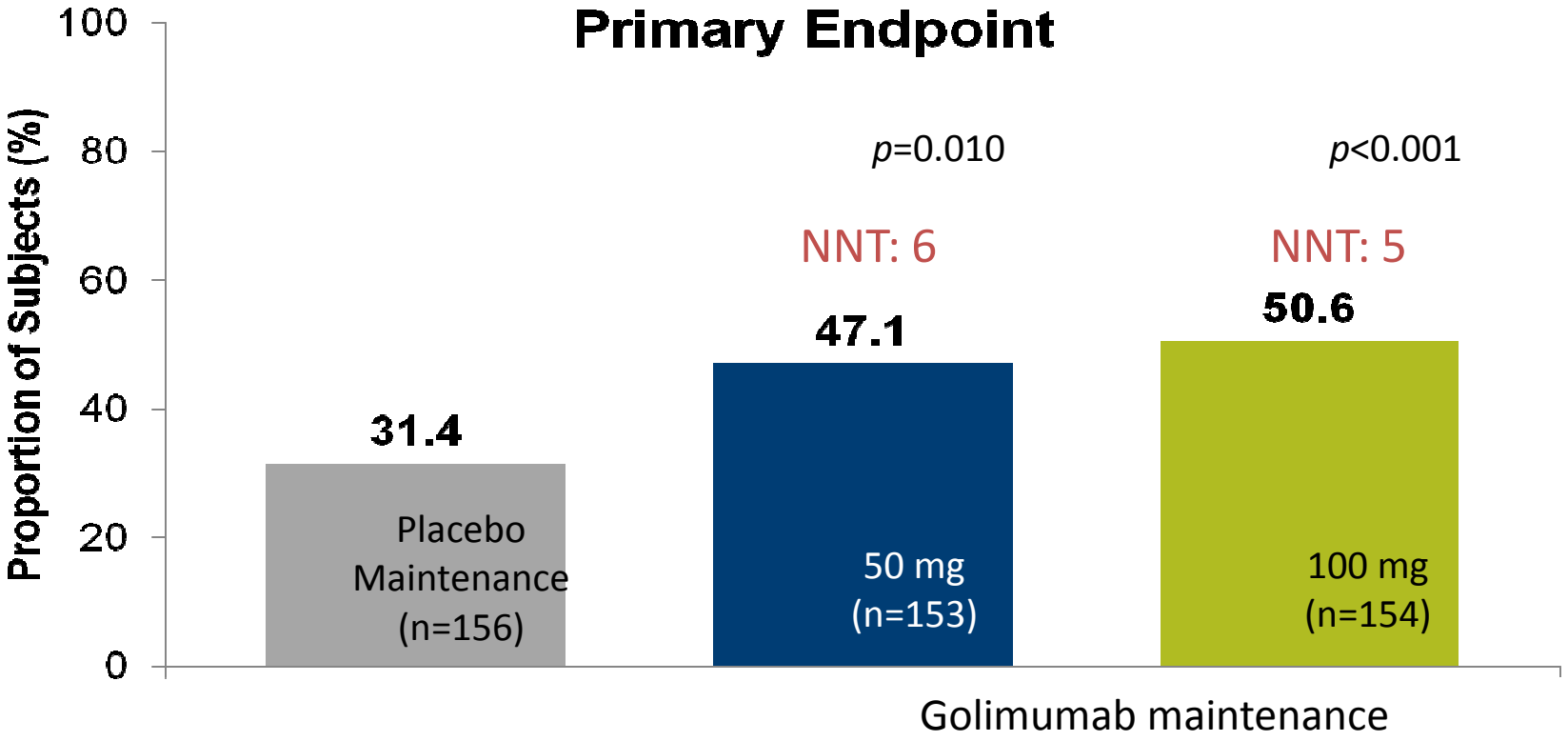


Klinička remisija u 30 i 54 ned



Simponi Maintenance : PURSUIT results

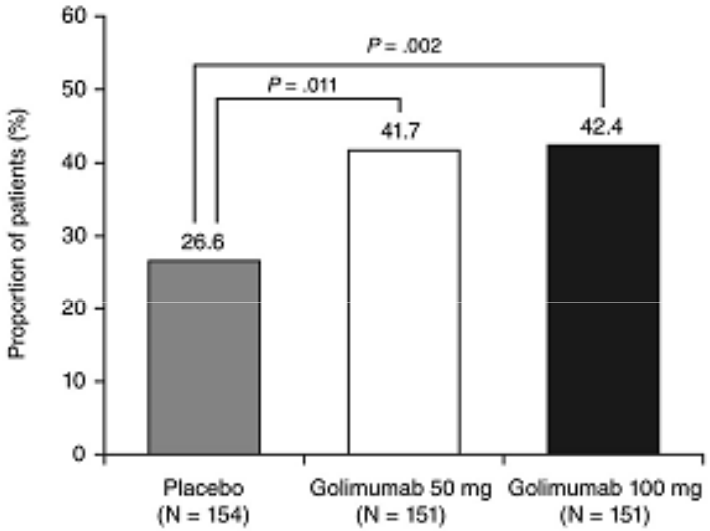
Clinical response* through Wk 54 in GLM Induction Responders: CONTINUOUS CLINICAL RESPONSE



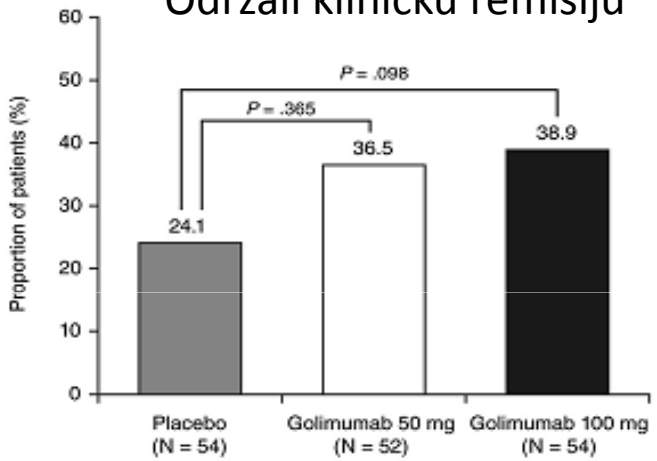
*Defined as a decrease from Week 0 of an induction study in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Golimumab

C **Mukozno zaceljenje (30 i 54)**



D Održali kliničku remisiju



E U 54 nedelji bili u remisiji

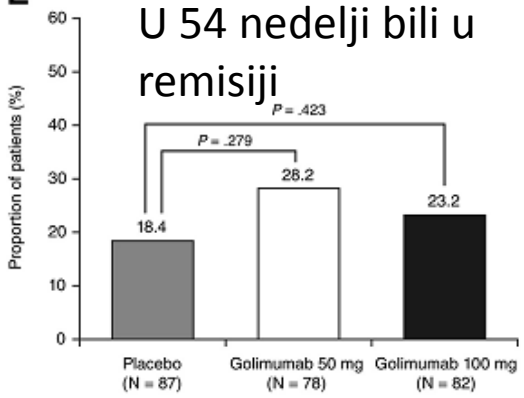


Figure 3. Proportion of golimumab-induction responders who (*A*) maintained clinical response through week 54; (*B*) achieved clinical remission at both weeks 30 and 54; (*C*) achieved mucosal healing at both weeks 30 and 54; (*D*) maintained clinical remission among those who were in clinical remission at baseline; and (*E*) achieved corticosteroid-free clinical remission at week 54 among those who were receiving corticosteroids at baseline. (*A*–*E*) Patients who had a prohibited change in UC medication, an ostomy or colectomy, a dose adjustment, or discontinued study agent because of a lack of therapeutic effect before the week 54 visit were considered not to have a clinical response, be in clinical remission, be in corticosteroid-free clinical remission, or have mucosal healing. (*A*–*D*) Patients who had all 4 Mayo subscores missing at weeks 30 or 54 were considered not to be in clinical response or clinical remission. Patients who had a missing endoscopy subscore at week 30 or week 54 were considered not to have mucosal healing. (*E*) Patients who had a missing value in corticosteroid use at a time point had their last available value carried forward to that time point. UC, ulcerative colitis.

Vedolizumab

US RWE data

- Efficacy of Vedolizumab as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort (Shelton, *Inflammatory Bowel Disease* 2015) INDUKCIONI PROTOKOL
- Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice (Vivio, *Journal of Crohn's and Colitis* 2016)

French Early-Access Program

- Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease (Amiot, *Clinical Gastroenterology and Hepatology* 2016, *epub ahead of print*)

German Registry

- Vedolizumab induction therapy for inflammatory bowel disease in clinical practice – a nationwide consecutive German cohort study (Baumgart, *Aliment Pharmacol Ther* 2016)

Multicenter US Consortium

- Vedolizumab for Moderate to Severely Active Inflammatory Bowel Disease: A Multicenter US Consortium (Dulai, 2015 ACG)

2 UK tertiary IBD centers

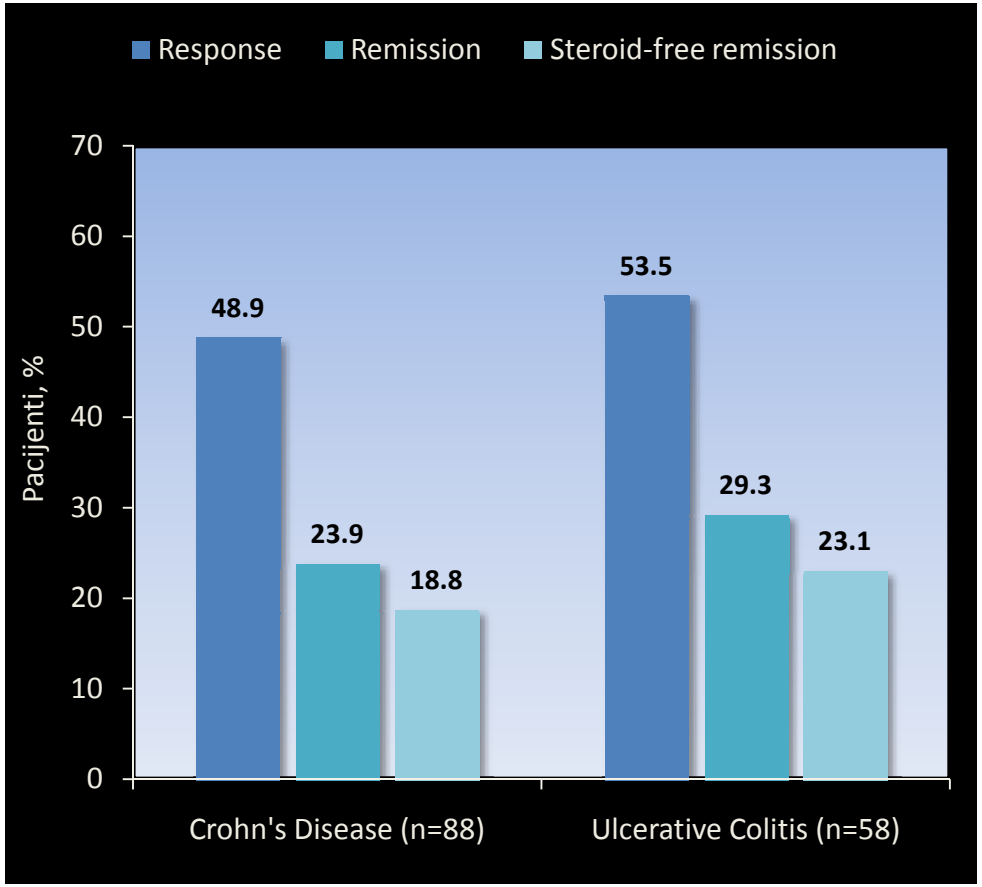
- Vedolizumab: early experience and medium term outcome from 2 UK IBD centers (Samaan MA, Frontline Gastroenterology 2016)

- Klinički odgovor i klinička remisija
- 14. nedelja
- Šta su prediktori odgovora na terapiju?
- VDZ 300 mg i.v. 0, 2, 6 i 14 nedelja
- Klinički odgovor
  - klinički odgovor smanjen HBI≥3 (CD) i simple clinical colitis activity index (SCCAI) ≥3 (UK)
  - klinička remisija HBI ≤4 (CD) i SCCAI ≤2 (UC)
  - Pad vrednosti CRP i smanjenje potrebe za kortikosteroidima
- Logistička regresija za procenu prediktora

Efikasnost vedolizumaba kao indukcione terapije u pacijenata sa refraktarnim oblikom IBC

Shelton et al. Inflamm Bowel Dis 2015

Klinički ishod 14. nedelji



Baseline Characteristics	Ulcerative Colitis		
	MGH (n=40)	BWH (n=25)	Total (n=65)
Mean age, y (SD)	40.7 (14.3)	40.3 (12.9)	40.5 (13.7)
Male, n (%)	22 (55.0)	10 (40.0)	32 (49.2)
Mean duration of disease, y (SD)	9.1 (7.1)	11.6 (6.7)	10.1 (7.0)
Current smoker, n (%)	1 (2.5)	2 (8.0)	3 (4.6)
Mean HBI score[a] (SD)	–	–	–
Mean SCCAI score[a] (SD)	6.5 (2.7)	–	–
Mean CRP, mg/L (SD)	8.8 (12.8)	11.4 (17.9)	9.8 (14.9)
Number of prior anti-TNFs, mean (SD)	2.1 (0.9)	1.7 (0.8)	1.9 (0.9)
≥2 prior anti-TNF agents, n (%)	27 (67.5)	13 (52.0)	40 (61.5)
Number of prior biologics, mean (SD)	–	–	–
Prior surgery for CD, n (%)	–	–	–
Corticosteroid at induction, n (%)	27 (67.5)	10 (41.7)	37 (57.8)
Prednisone equiv. dose, mean (SD)	17.2 (16.2)	13.8 (19.1)	15.9 (17.5)
Concomitant immunosuppressant, n (%)	10 (25.6)	7 (28.0)	17 (26.6)
Thriopurines	6 (15.4)	5 (20.0)	11 (17.2)
Methotrexate	4 (10.3)	2 (8.0)	6 (9.4)

- 48.1% CD
- 47.6% UC

Povišen CRP u ref opsegu u 14. nedelji

Shelton E et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: A multicenter cohort. *Inflamm Bowel Dis* 2015;21:2879-85.

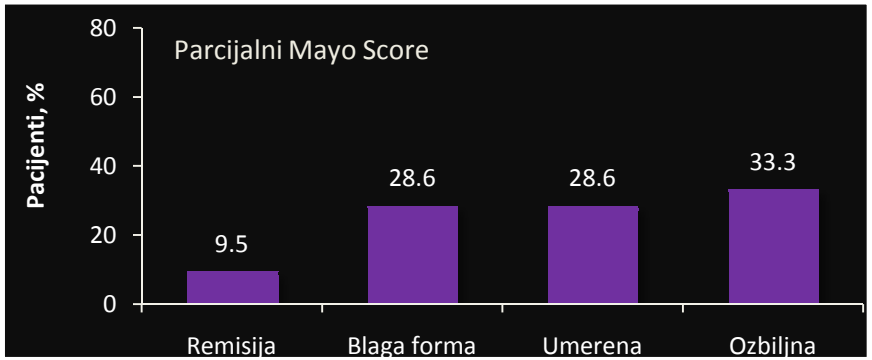
US – Washington Univ. (CD/UC)

Efikasnost i bezbednost vedolizumaba u prvoj godini lečenja pacijenata sa IBC

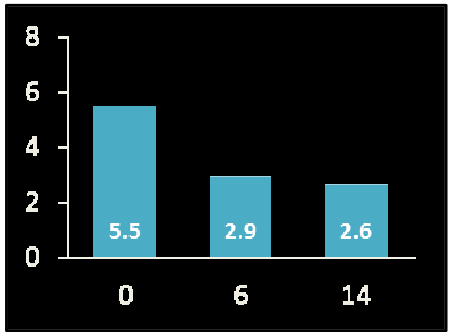
Vivio et al. JCC 2016

Characteristic	UC (n=21)
Median age, y	46.2
Male/female, %	38.1/61.9
Prior anti-TNF therapies, %	
0	23.8
1	38.0
2	33.3
3	4.8
Prior surgeries, %	
0	95.2
1	4.8
2	–
3	–
Steroid use at baseline, %	
Oral	14.3
Topical	33.3
IMM use at baseline, %	47.6
AZA and/or 6-MP	47.6
Methotrexate	–

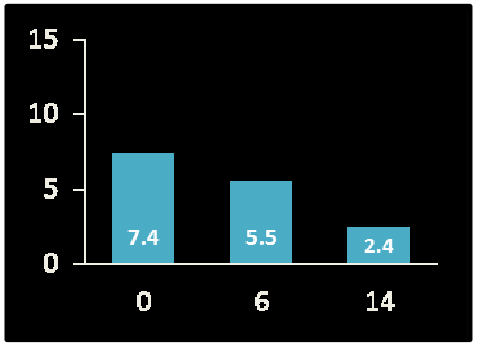
6-MP, merkaptopurin; AZA, azatioprin
IMM, imunomodulator; TNF, tumor necrosis factor



Parcijalni Mayo



CRP

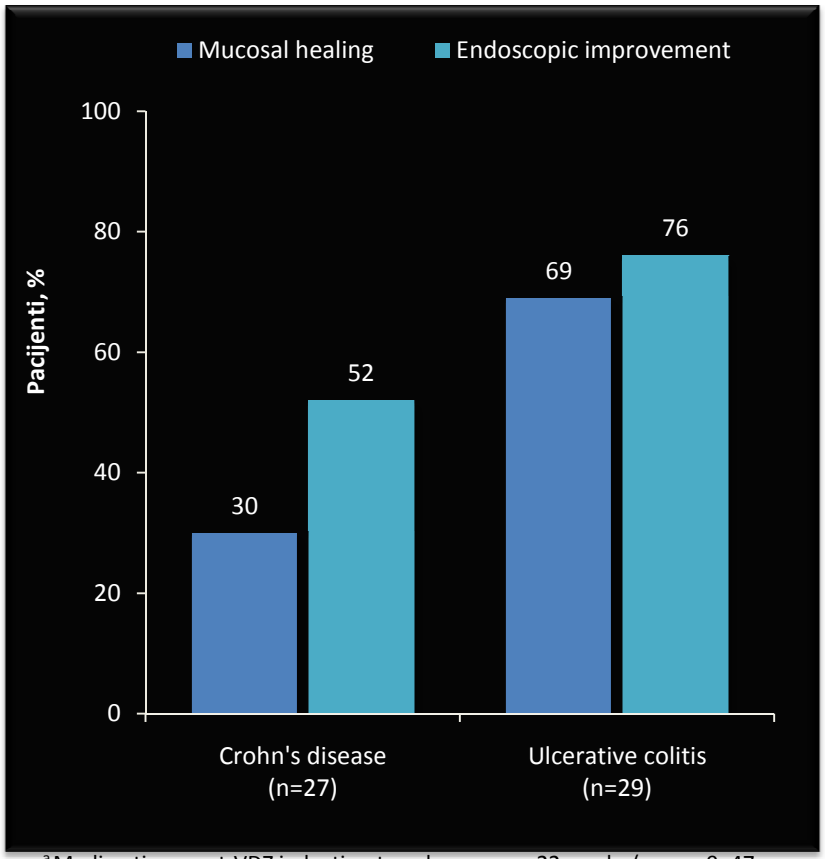


Vivio EE, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis* 2016;10:402-9.

US – Washington Univ. (CD/UC)

Mukozno zaceljenje i trajanje terapije

Mukozno zaceljenje



[a] Median time post-VDZ induction to colonoscopy, 22 weeks (range, 9–47 weeks) in CD and 22 weeks (range, 12–52 weeks) in UC

Cohort		Ulcerative Colitis (n=21)	
		Event	N
Prospective Cohort	Week 0–14	Total proctocolectomy Fever [a] Conjunctivitis	2 1 1
	After Week 14	Total proctocolectomy Diverting loop ileostomy	1 1
Retrospective Cohort	Week 0–14	Total proctocolectomy	2
	After Week 14	NR	–

Mali broj u prospektivnoj studiji (51,115)

Vivio EE, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis* 2016;10:402-9.

EU – French Early-Access Program (CD/UC)

Efikasnost i bezbednosti vedolizumaba kao indukcione terapije u pacijenata sa IBC

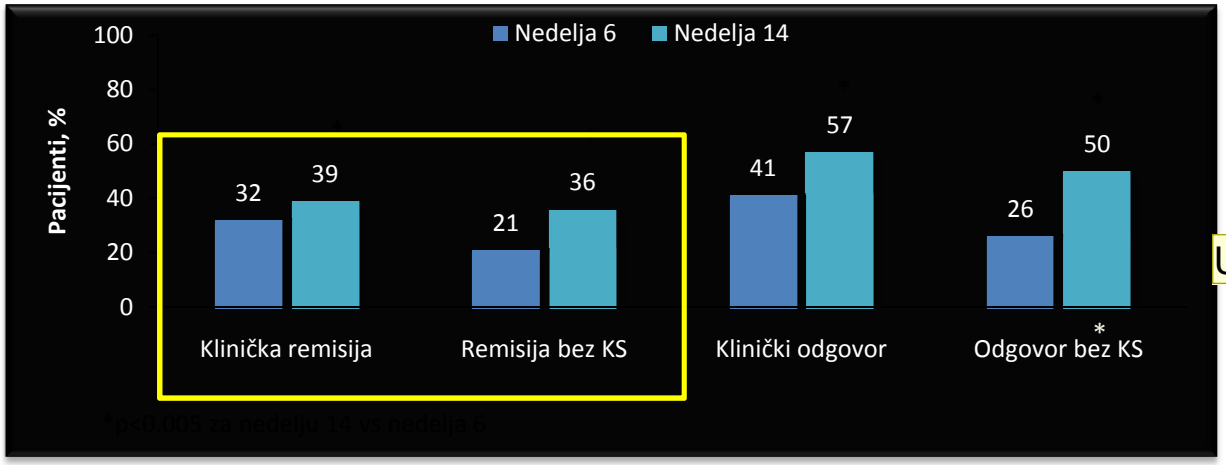
Amiot et al. Clin Gastroenterol Hepatol 2016

Patient Characteristics	UC (n=121)
Mean age, y (SD)	42.8 (16.1)
Male, n (%)	67 (55)
Mean BMI, kg/m^2 (SD)	23.3 (4.6)
Smoking history, n (%)	
Former smoker	37 (31)
Active smoker	5 (4)
Mean disease duration, y (SD)	8.8 (7.1)
Extra-intestinal disease, n (%)	18 (15)
Primary sclerosing cholangitis	8 (7)
Ankylosing spondylitis	6 (5)
Familial history of IBD	9 (9)
Mean age at diagnosis, y (SD)	24.6 (11.1)
Prior medications, n (%)	
Immunosuppressant	115 (95)
Anti-TNF agent	118 (98)
Concomitant medications, n (%)	
Glucocorticoids only	41 (34)
Immunosuppressants only	14 (12)
Both	12 (10)
Hemoglobin, g/L (SD)	11.9 (3.2)
CRP, mg/L	19.5 (21.2)

Ulcerative colitis		
Disease location, n (%)		
Proctitis	–	9 (7)
Left-sided colitis	–	29 (24)
Pancolitis	–	83 (69)

- **umereno do teškoaktivnom UK i KB koji nisu odgovorili na anti TNF**
- **Prospektivna kohortna studija 41 centar u Francuskoj**
- VDZ 300 mg i.v u 0, 2, 6 i 14 nedelji a potom svakih 8 nedelja
- Optimizacija ako nisu odgovorili na indukcionu terapiju (300 mg/ 4 nedelje)
- Ishod remisija bez steroida u 14 nedelji (HBI ≤4 CD i parcijalni Mayo skor <3)

EU – French Early-Access Program (CD/UC)



U1

HBI Skor

Response	Variable	OR (95% CI)	P-value
Less likely	CRP >20 mg/L	0.30 (0.11–0.80)	0.02
	Mayo score >9	0.21 (0.08–0.57)	0.002
More likely	Week 6 clinical response	5.3 (2.2–13.1)	<0.001

- 1/3 pacijenata koji nisu odgovorili na antiTNF će postići remisiju bez upotrebe kortikosteroida
- Bezbedan lek
- Klinički odgovor u 6 nedelji najbitniji za ishod u 14.oj nedelji

Slide 70

U1 animacija ne stoji dobro i ja bas volim okrugle shapes ali dobro promenila sam
USER; 8.9.2016

Bezbednosni profil

Event, n (%)	Patients with IBD (N=294)
Adverse event	93 (31.6)
Headache	16 (5.4)
Paresthesia	13 (4.4)
IBD exacerbation	12 (4.1)
Infusion-related reaction	2 (0.7)
Arthralgia	1 (0.3)
Vertigo	1 (0.3)
Deep venous thrombosis	1 (0.3)
Pruritus	1 (0.3)
Strokes	1 (0.3)
Liver test abnormalities	1 (0.3)
Arthralgia	1 (0.3)
Any serious adverse event*	24 (8.2)
Adverse event of infection	37 (12.6)
Rhinopharyngitis	12 (4.1)
Upper respiratory tract infection	6 (2.0)
GI infection	5 (1.7)†
Flu or flu-like infection	3 (1.0)
Sinusitis	3 (1.0)
Pharyngitis	3 (1.0)
Miscellaneous	11 (3.7)
Any serious infection‡	7 (2.4)
Any cancer§	1 (0.3)

Amiot A, et al. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients with Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology* 2016. Epub 22 February 2016.

EU – German Registry (CD/UC)

Efikasnost vedolizumaba kao indukcione terapije u pacijenata sa IBC (nacionalna studija u Nemačkoj)

Baumgart et al. Aliment Pharmacol Ther 2016

	Ulcerative Colitis n=115
Median age (95% CI), year	42 (37–46)*
Median disease duration (95% CI), year	7 (5–9)*
Gender, n (%)	
Female	49 (42.6)
Male	66 (57.4)
Current smoker, n (%)	9 (7.8)
Median CRP (95% CI), mg/dl	0.63 (0.47–0.90)†
Median Partial Mayo Score (95% CI)	6 (6–7)
Median HBI Score (95% CI)	
Number of previous anti-TNF therapies, n (%)	
0	28 (24.3)
1	30 (26.1)
2	30 (26.1)
3	27 (23.5)
Concomitant Medications, n (%)	
Steroids	96 (83.5)
Immunomodulators only	88 (76.5)
Steroids and immunomodulators	74 (64.3)

Efikasan posebno kod antiTNF naivnih

Postepeno počinje da deluje (treba sačekati 14 nedelja)

Efikasnost VDZ

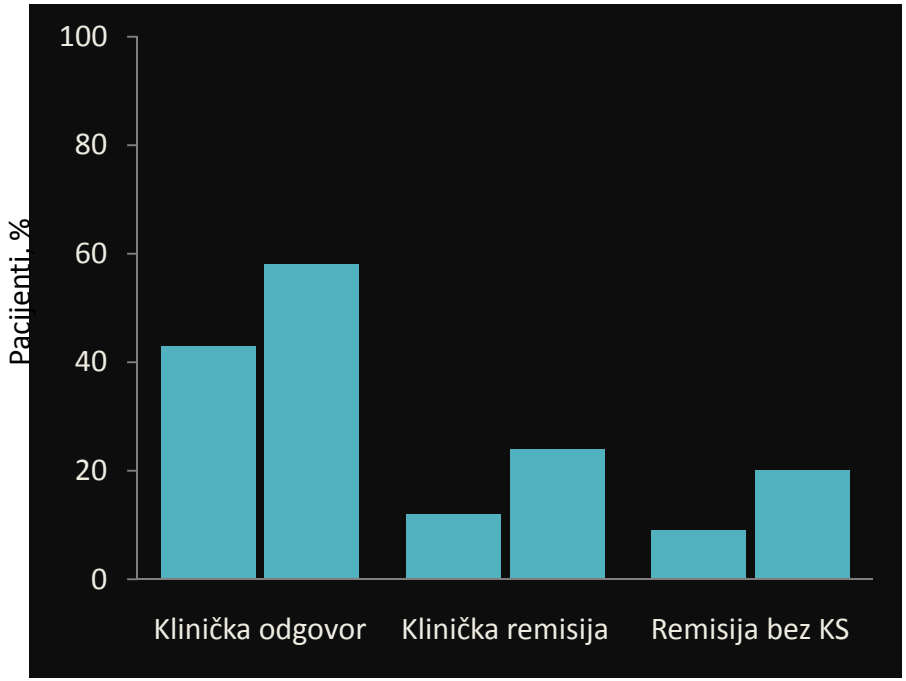
VDZ 300 mg iv indukciona terapija 0, 2, 6, održavanje na 8. nedelja

Praćenje do 14 nedelja

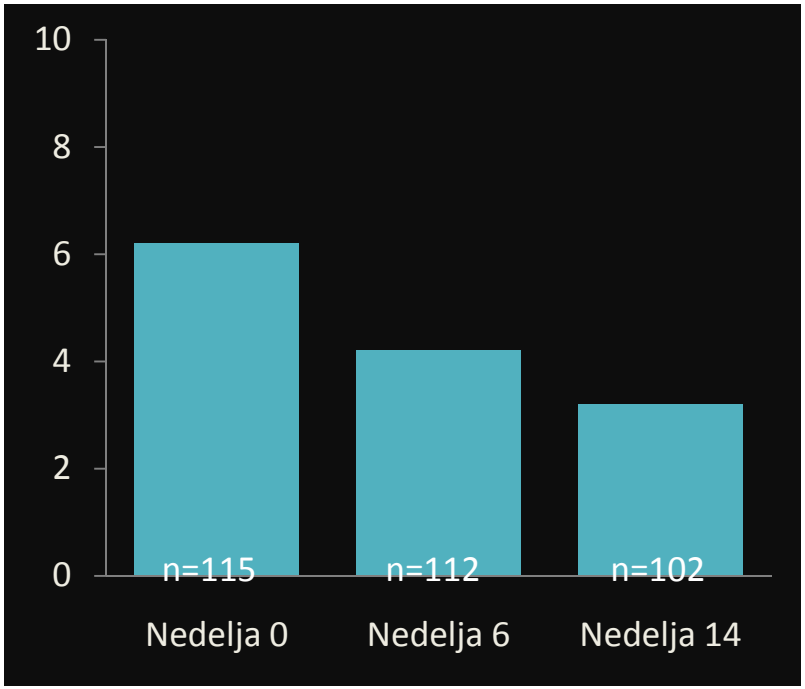
Izgubljeni su tretirani kao *non responderi*

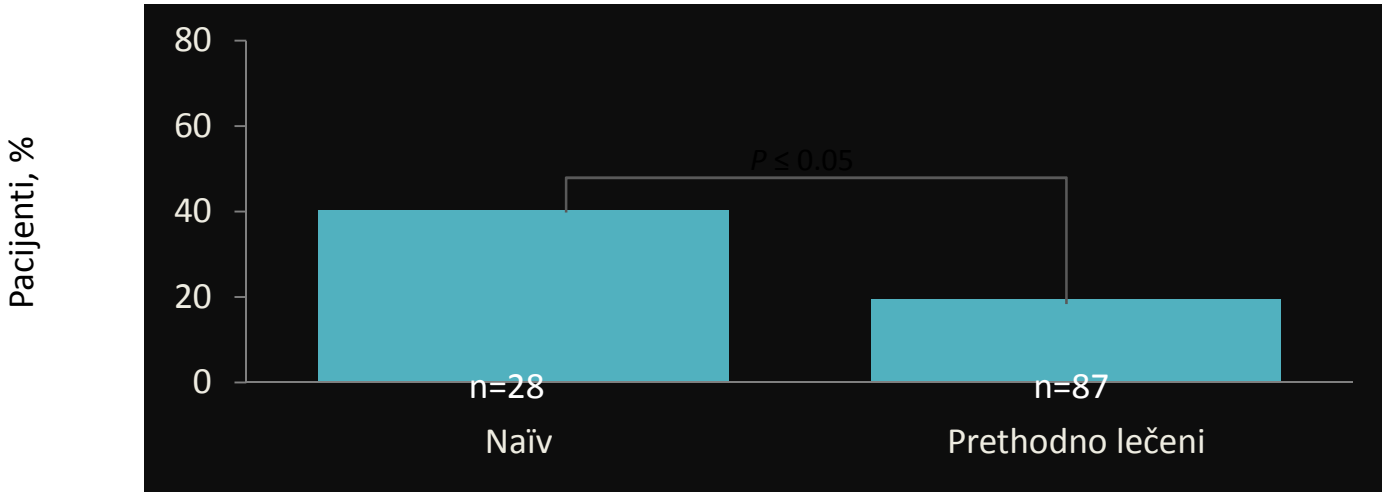
Klinička remisija u 14 nedelji

EU – German Registry (CD/UC)



UC – Medijana Parcijalnog Mayo Skora





Prethodno lečenje anti-TNFα

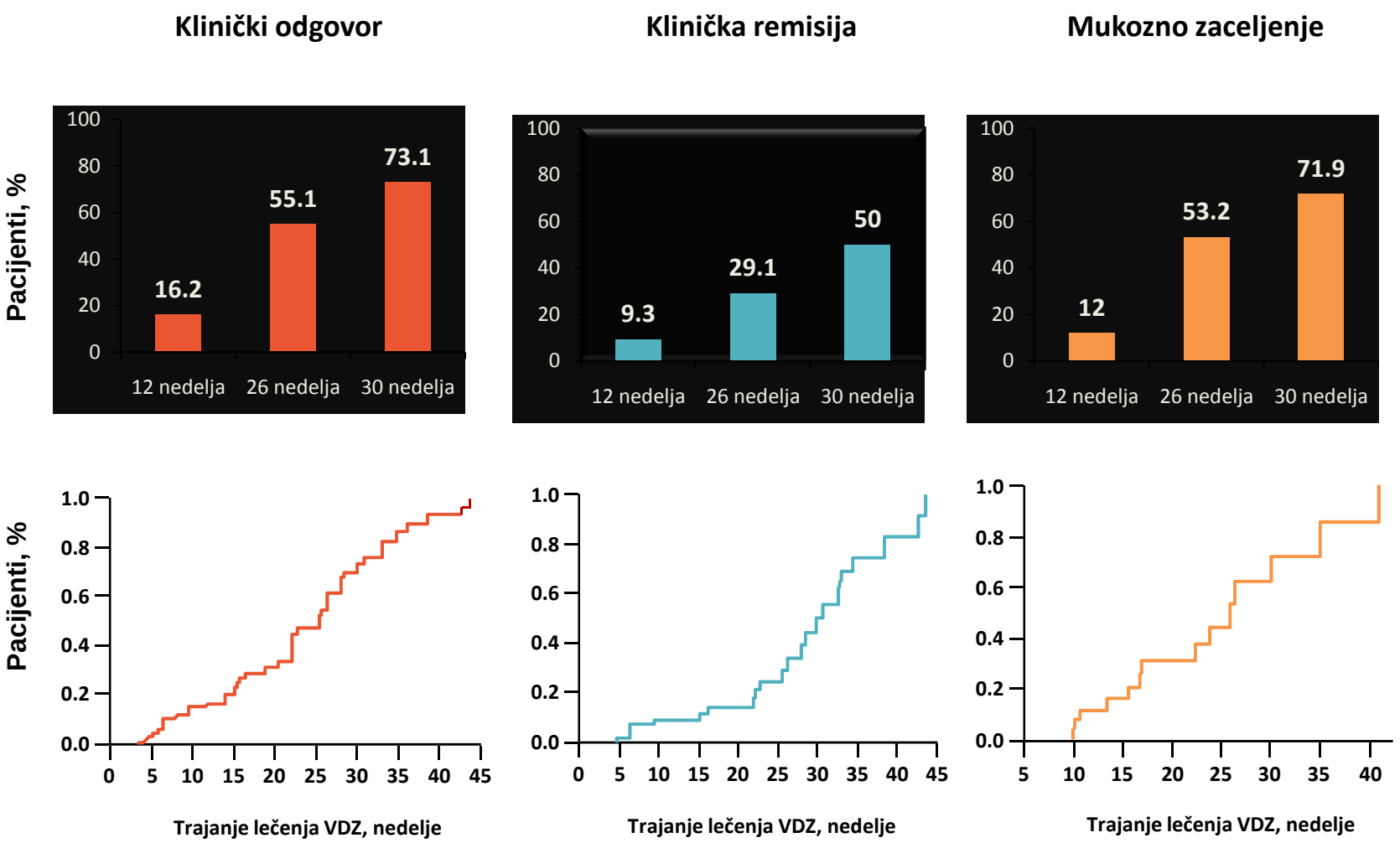
US – Multicenter Consortium (CD/UC)

Vedolizumab u lečenju umereno do teškoaktivne forme IBC
multicentrična studija iz SAD

*Dulai et al **American College of Gastroenterology Scientific Meeting** 2015*

Baseline Characteristics and Treatment Outcomes	UC (n=59)
Mean age, y (SD)	41 (16)
Median disease duration, y (IQR)	6 (3–10)
Male/female, %	63/37
Median follow-up, weeks (IQR)	19 (9–26)
Endoscopy, severe, %	42
Prior hospitalization, %	51
Prior anti-TNF therapy, %	75
Concomitant immunotherapy, %	63
Qualified for GEMINI trial, %	48

Klinički ishod u UC



Dulai PS, et al. Vedolizumab for moderate to severely active inflammatory bowel disease: a multi-center U.S. consortium. *Am J Gastroenterol*. 2015;110:S809. Abstract 1904.

- Razlika izmedju **selektivnog** i **sistemskog** biološkog leka

- Infekcije: TBC, oportunističke infekcije, infekcije GIT
- Srčana insuficijencija
- Demijelinizacija
- Stariji bolesnici
- Maligniteti
- Upotreba u toku hirurgije
- Autoimune bolesti
- Žive vakcine
- Oštećenje jetre

Journal of Crohn's and Colitis, 2016, 26–30
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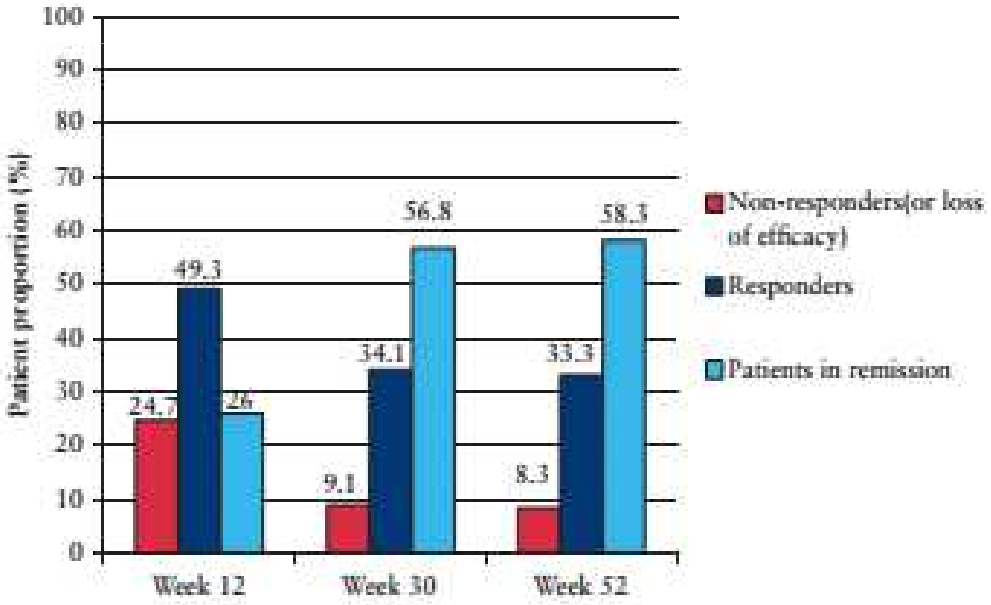
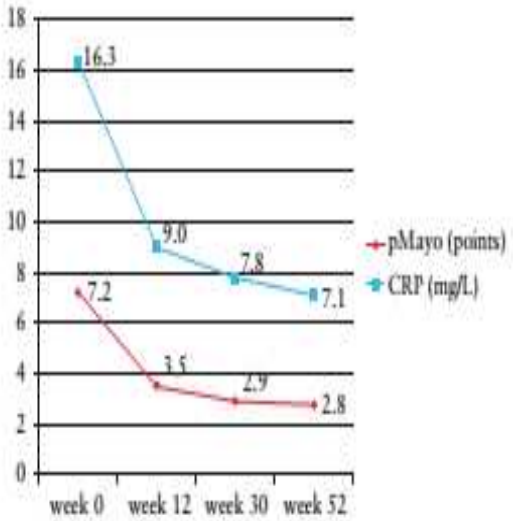
Advance Access publication September 21, 2015
Original Article

Original Article

Efficacy and Safety of Adalimumab in Ulcerative Colitis Refractory to Conventional Therapy in Routine Clinical Practice

Anita Bálint,[a,*] Klaudia Farkas,[a,*] Károly Palatka,[b] Lilla Lakner,[c] Pál Miheller,[d] István Rácz,[e] Gábor Hegede,[f] Áron Vincze,[g] Gábor Horváth,[h] Andrea Szabó,[e] Ferenc Nagy,[a] Zoltán Szepes,[a] Zoltán Gábor,[h] Ferenc Zsigmond,[i] Ágnes Zsóri,[j] Márk Juhász,[d] Ágnes Csontos,[d] Mónika Szücs,[k] Renáta Bor,[a] Ágnes Milassin,[a] Mariann Rutka,[a] Tamás Molnár[a]





HVALA NA PAŽNJI!