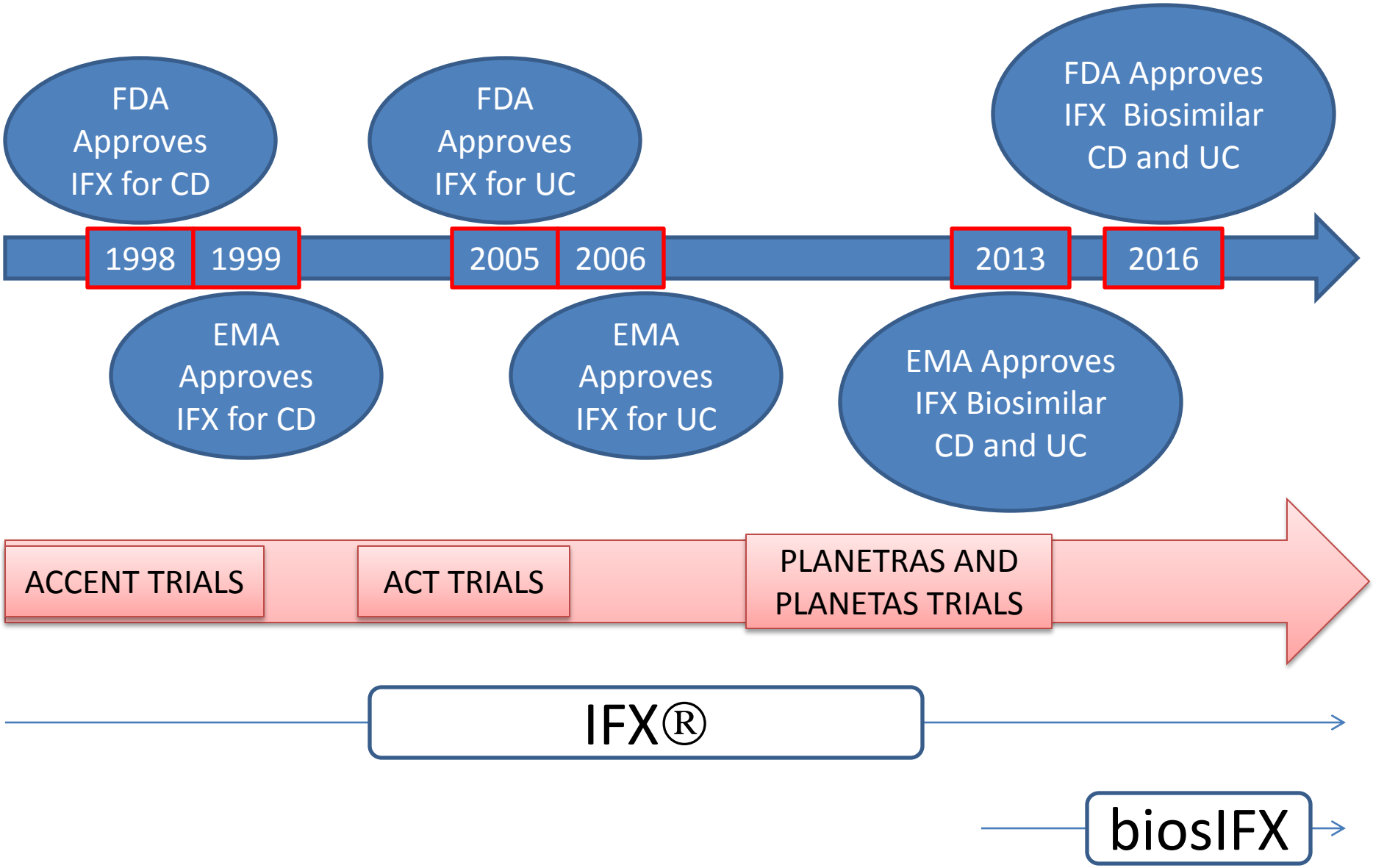
"Δυο δεκαετίες εμπειρίας ενδοφλέβιων anti-TNF παραγόντων"

Γιώργος Μπάμιας
Γαστρεντερολόγος
Λαικό Νοσοκομείο

CONFLICT OF INTEREST

- Έχω λάβει τιμητική αμοιβή από την Aenorasis S.A.

Timeline of i.v. anti-TNF therapy in IBD



Current indications for infliximab use in IBD

ULCERATIVE COLITIS

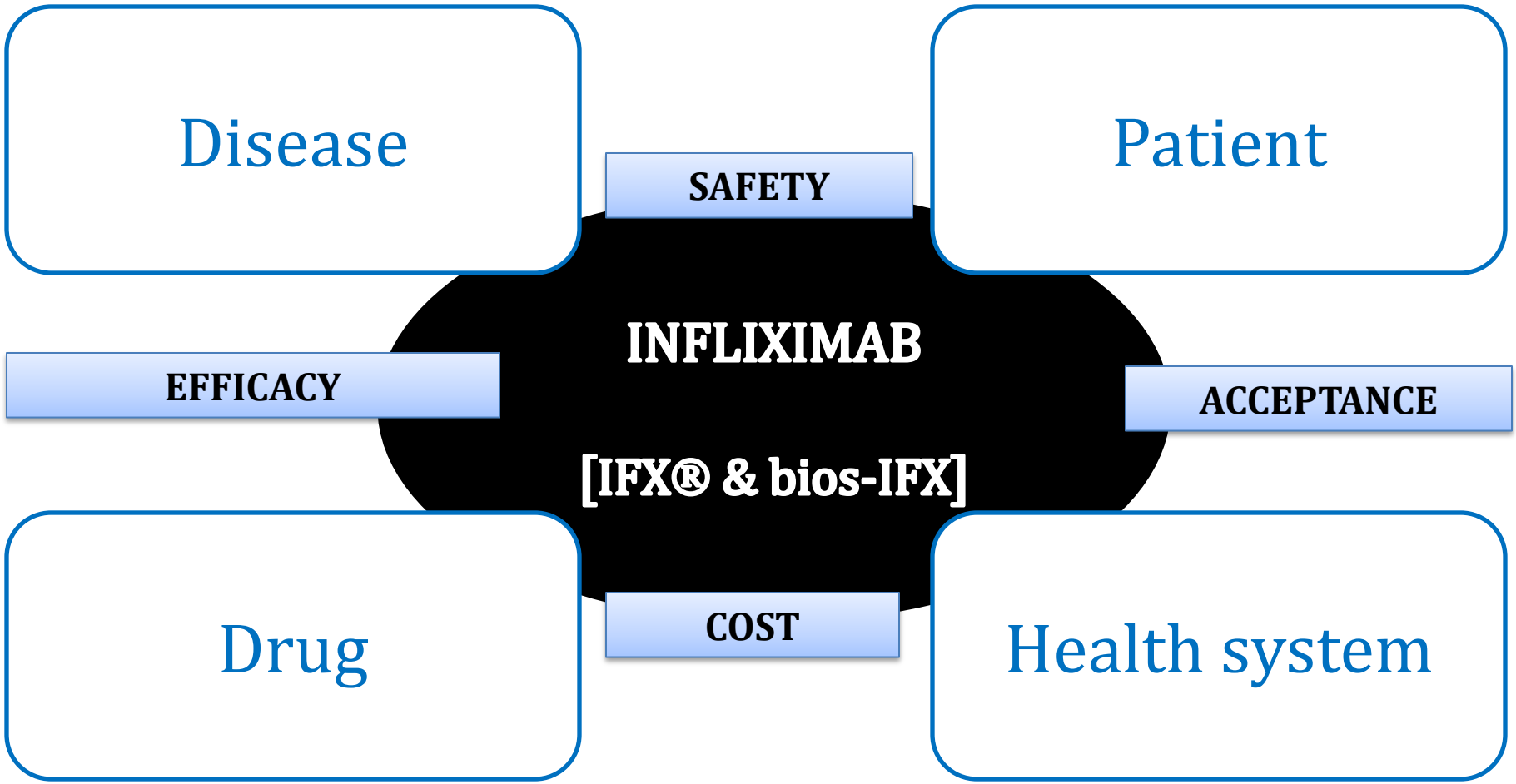
- *Steroid-dependent active ulcerative colitis [ECCO statement 11I]*
- *Oral steroid-refractory active ulcerative colitis [ECCO statement 11J]*
- *Immunomodulator-refractory UC [ECCO statement 11K]*
- *Acute severe UC refractory to 3-days of i.v. corticosteroid administration*

CROHN'S DISEASE

- *Luminal CD refractory or intolerant to steroids [ECCO statement 5C]*
- *Early treatment for patients with factors of poor prognosis [ECCO statement 5G]*
- *Immunomodulator-refractory CD [ECCO statement 6E]*
- *Recurrent refractory simple fistulizing disease not responding to antibiotics [ECCO statement 9F]*
- *Complex perianal fistulizing disease [ECCO statement 9I]*

ECCO Ulcerative Colitis Consensus Update (2016)
ECCO Crohn's disease Consensus Update (2016)

Clinical use of IFX



Evolution of our knowledge

Factors that affect the clinical use of IFX

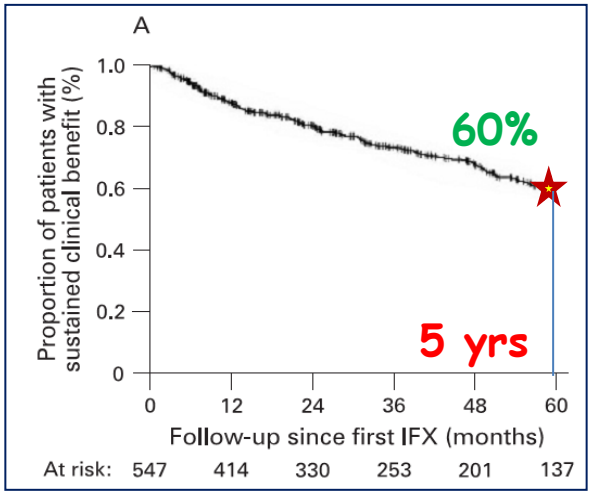
- Mechanism of action
- Clinical indications
- Predictors of response
- Immunogenicity
- Patient preferences
- Adherence
- Cost

"Δυο δεκαετίες εμπειρίας ενδοφλεβίων anti-TNF παραγόντων“

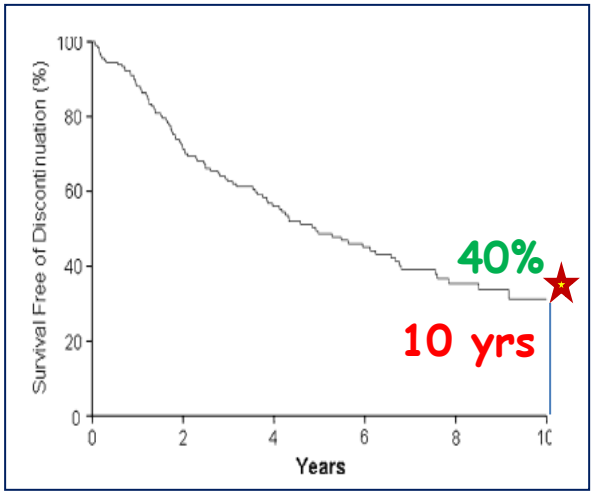
The doctor’s perspective

Efficacy of infliximab in CD

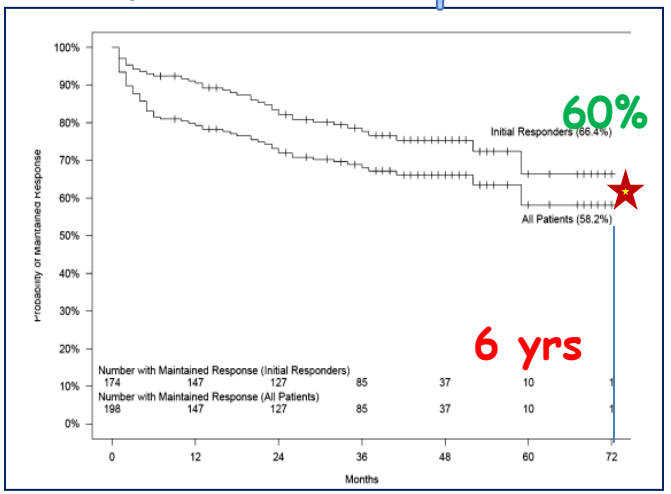
Endpoint: Sustained clinical benefit



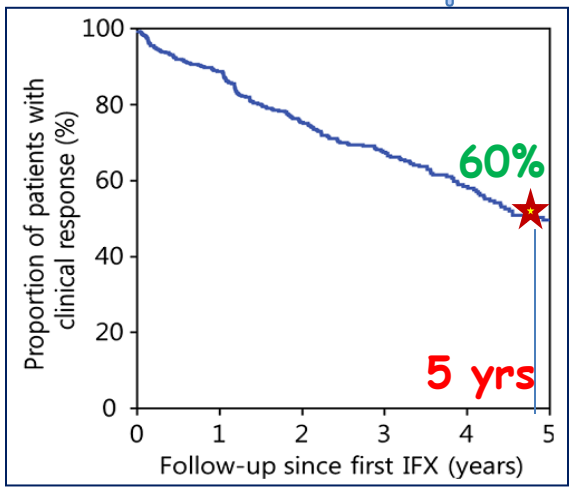
Endpoint: Continuation of IFX



Endpoint: maintained response



Endpoint: Sustained clinical response

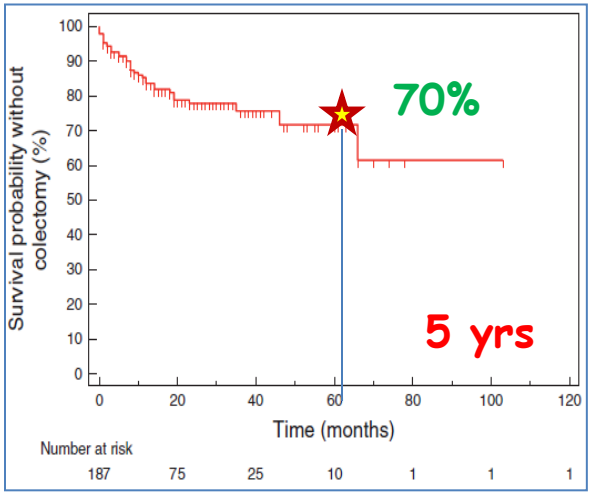


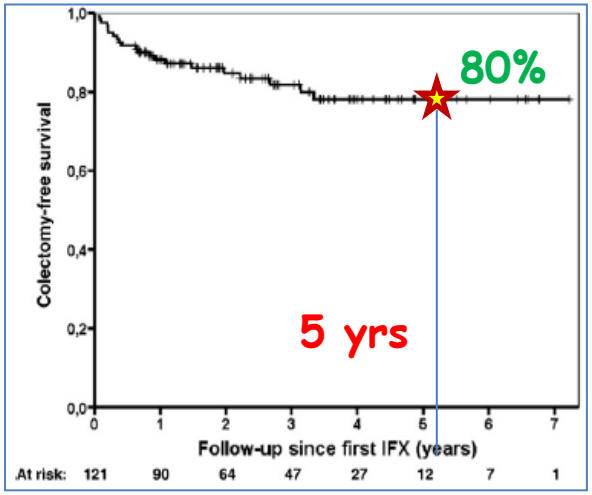
- Moderate to severe CD
- Refractory to Cx ± IS

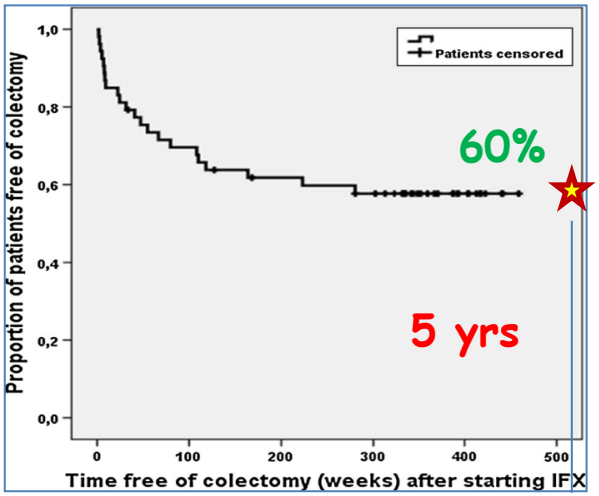
Schnitzler F, Gut. 2009
Seminerio JL, Dig Dis Sci. 2013
Rudolph SJ, Dig Dis Sci. 2008
Park SH, Dig Dis Sci. 2016

Efficacy of infliximab in UC

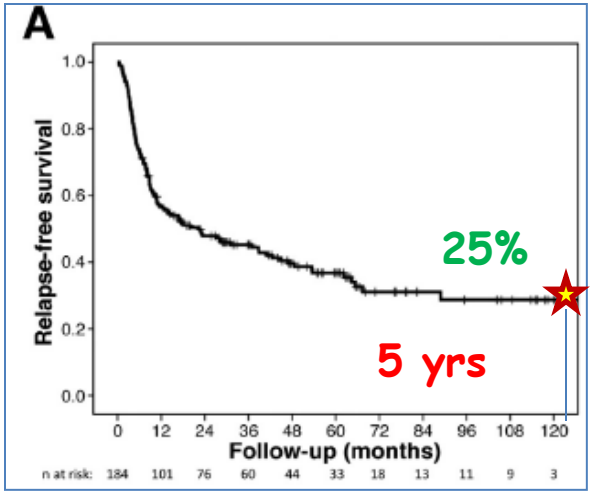
Endpoint: avoidance of colectomy



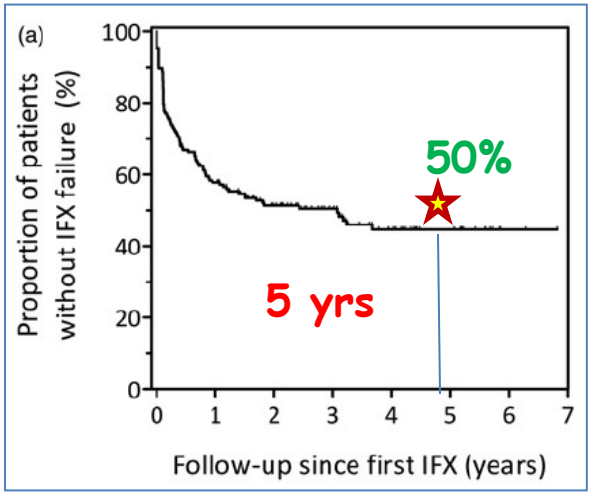




Endpoint: Relapse-free survival



Endpoint: No IFX failure



- Moderate to severe UC
- Refractory to Cx ± IS

Arias MT, Clin Gastroenterol Hepatol. 2015;
Oussalah A, Am J Gastroenterol. 2010;
Garcia-Bosch O, Dig Dis Sci. 2016
Seo MT, Scand J Gastroenterol 2017

How can we improve the efficacy of IFX ?

- *Use IFX in patients with favorable prognostic factors for response*
- *Use IFX in combination with immunomodulators*
- *Use Regular Maintenance Therapy / avoid Episodic treatment*
- *Manage loss of Response*
- *Stop therapy with caution*
- *Special situations (acute severe ulcerative colitis)*

Predictors of response to infliximab in UC

Table 1 Prognostic indicators of response to anti-tumor necrosis factor treatment in ulcerative colitis

At initiation of treatment	During treatment
Clinical and epidemiological parameters	
Severity of the disease	Early clinical response
Younger age	
Duration of colitis < 3 yr	
Ex	
La	
C	
H	
S	
Im	
P	
P	
M	
G	
Endo	
	Mucosal healing
Treatment-related factors	
Pharmacological history	Number of IFX infusions
Exposure to immunosuppressants	Co-administration of immunosuppressants
Response to prior treatment with infliximab	Escalation of anti-TNF therapy
	IFX trough levels
	Antibodies against anti-TNF

Colectomy rates ⇑

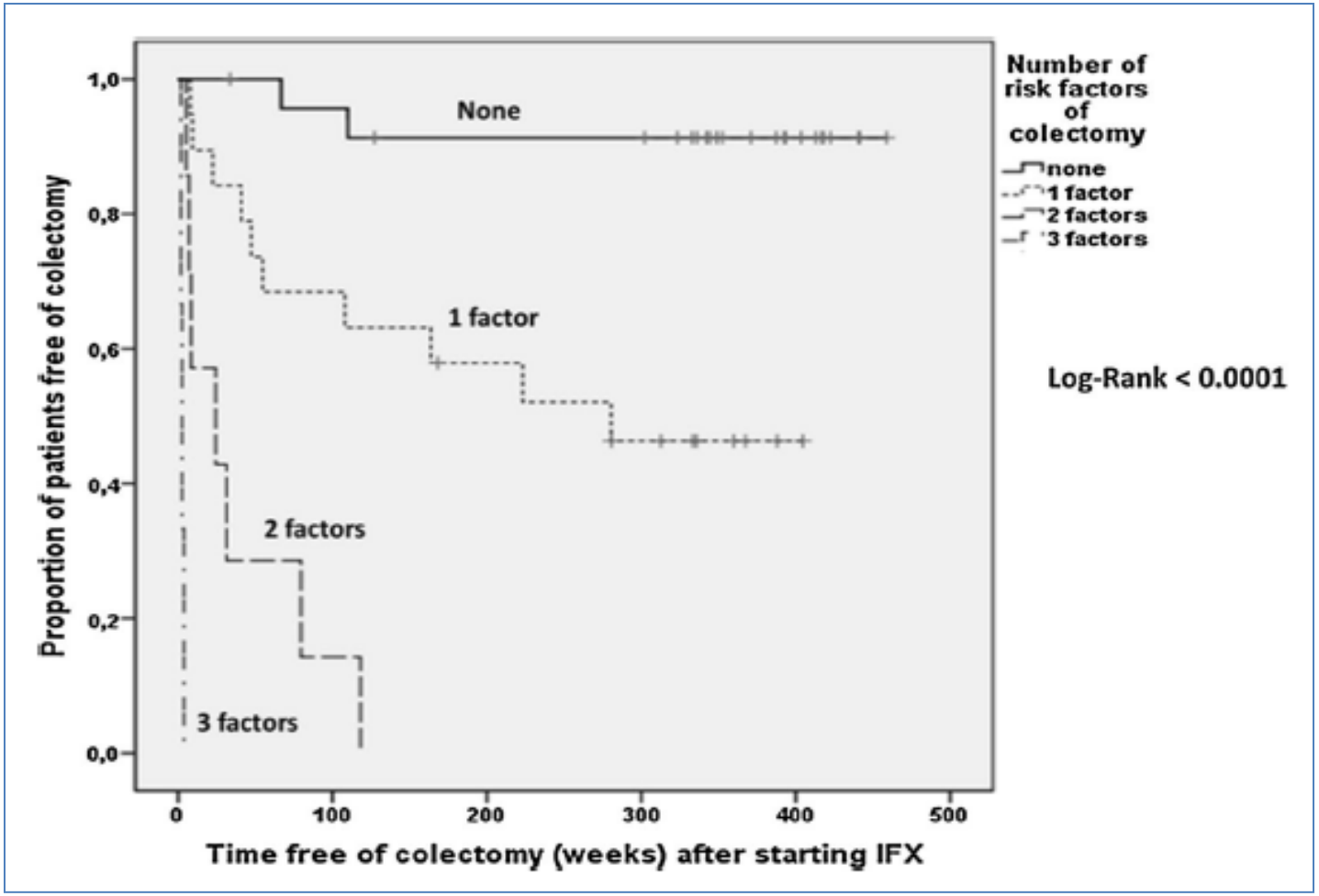
No short-term response to IFX

IFX indication for acute severe colitis

⇑ Baseline level CRP

Zampeli E. World J Gastrointest Pathophysiol 2014

Use IFX in patients with favorable prognostic factors for response



García-Bosch O, Dig Dis Sci. 2016

Predictors of long-term response to infliximab in CD

- ❑ *Drop of elevated baseline CRP to <3 mg/L*
- ❑ *Short-term clinical benefit of IFX treatment*

- ❑ *>40-y-old at the initiation of IFX*
- ❑ *disease duration <3 years*

- ❑ *Concurrent immunomodulators*

- ❑ *No Smoking*

Schnitzler F, Gut. 2009
Seminerio JL, Dig Dis Sci. 2013
Rudolph SJ, Dig Dis Sci. 2008
Park SH, Dig Dis Sci. 2016

A matrix-based model predicts primary response to infliximab in Crohn's disease

Low BMI, old, & previous surgery high probability for non-response

BMI (kg/m²)						
≥ 25	18.5-24.9	< 18.5	≥ 25	18.5-24.9	< 18.5	
2.5%	8.9%	21.5%	9.4%	28.6%	53.0%	≥ 65
2.0%	7.4%	18.3%	7.8%	24.7%	48.0%	41-64
0.7%	2.8%	7.4%	2.9%	10.5%	24.8%	26-40
0.2%	0.9%	2.5%	0.9%	3.6%	9.4%	≤ 25
No			Yes			
Prior Surgery						

Age (years)

Normal-High BMI, young, & no previous surgery low probability for non-response

Billiet T, J Crohns Colitis. 2015 Dec;9(12):1120-6

Use IFX in combination with immunomodulators

IFX and AZA better than IFX monotherapy in CD

clinical remission	(RR: 1.26; 95% CI: 1.03–1.54)
corticosteroid-free remission	(RR: 1.23; 95% CI: 1.02–1.47)
mucosal healing rates	(RR: 1.50; 95% CI: 1.02–2.19)

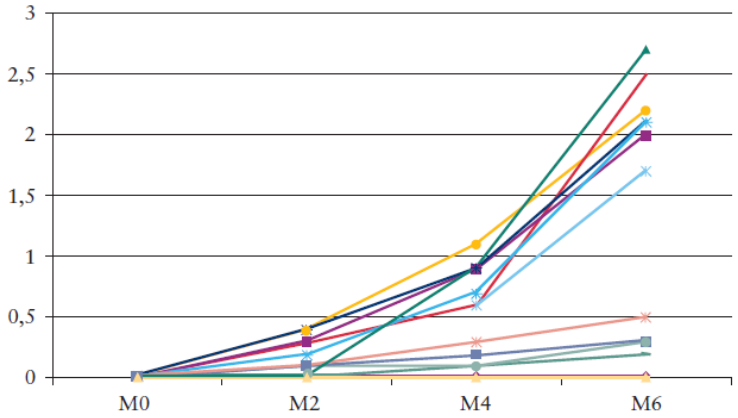
IFX and AZA better than IFX monotherapy in UC

Corticosteroid-free remission	(40% versus 22%, $P<0.05$)

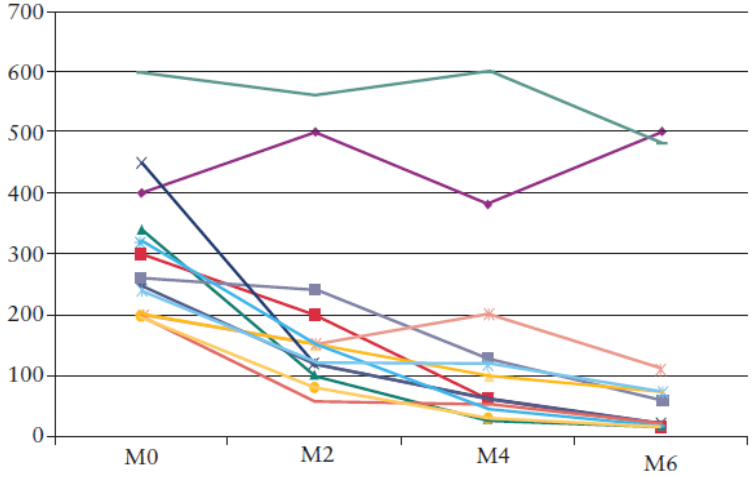
Akobeng AA, Inflamm Bowel Dis 2014;20:2132–2141

Administration of azathioprine in patients who lost response to IFX

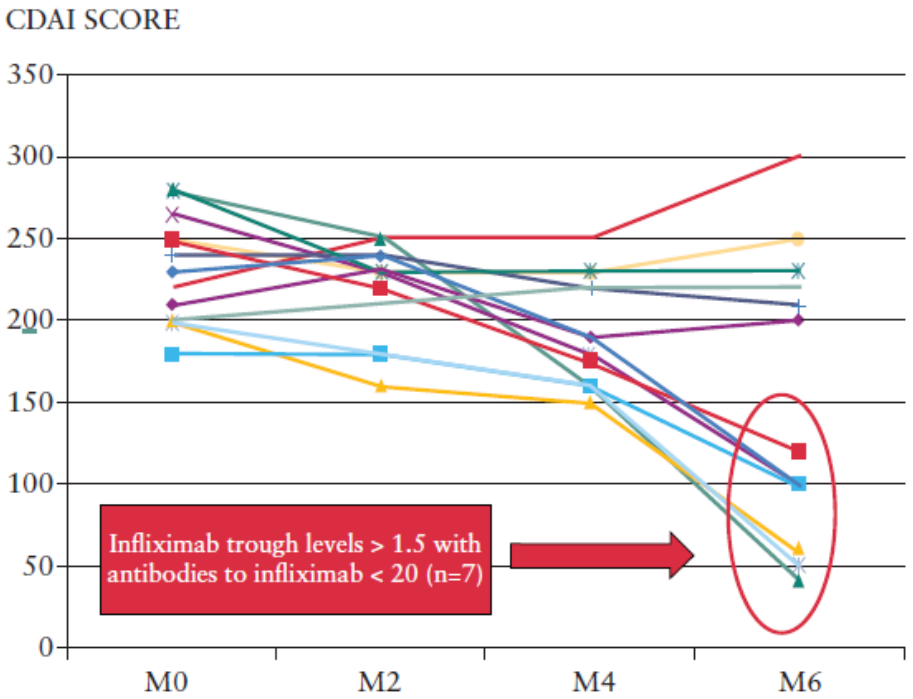
Increase in IFX trough levels



Decrease in ADA



Regain clinical response



Peyrin-Biroulet L, *JCC, 2016*

Manage loss of Response to IFX

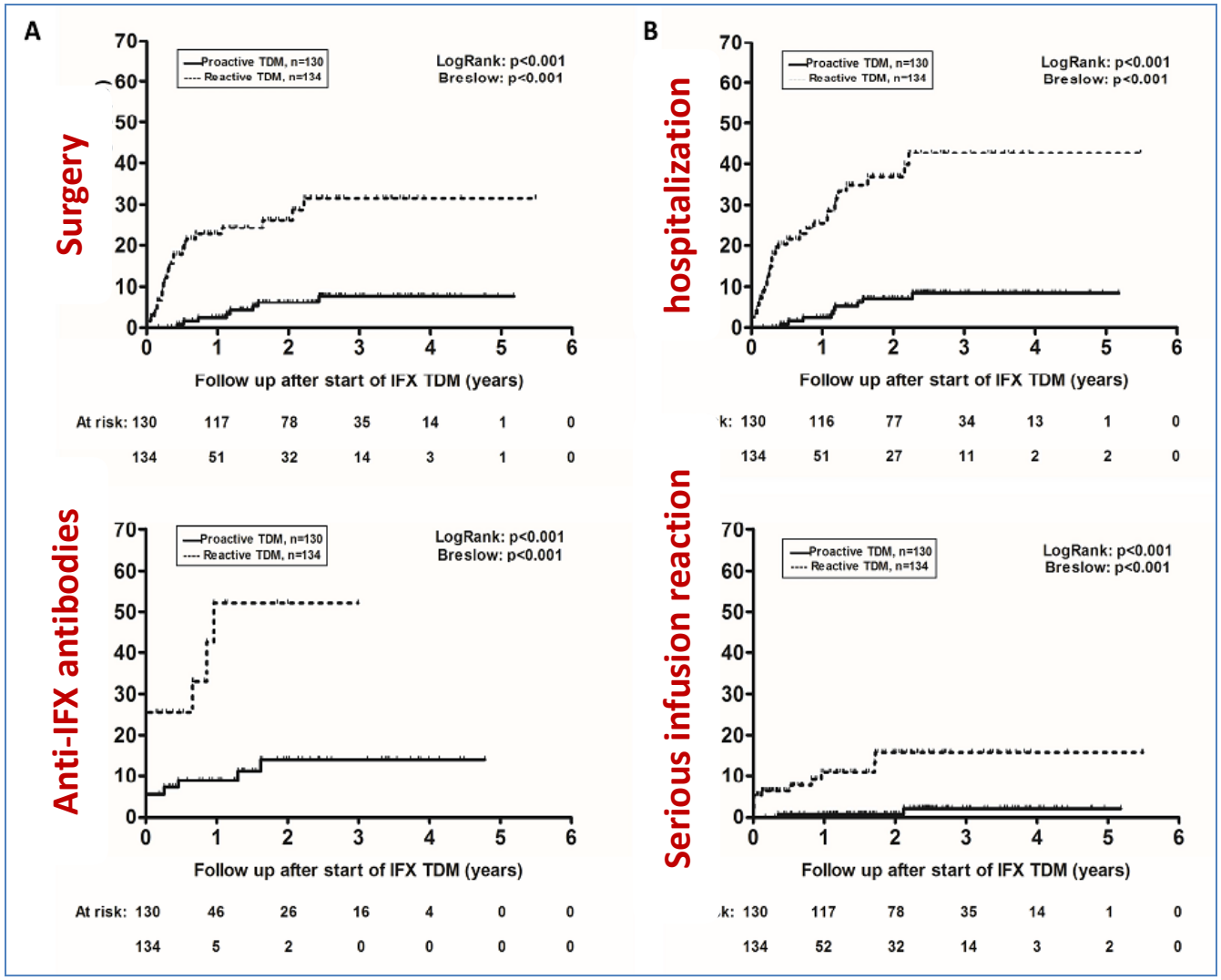
	ATI−	ATI+
IFX < threshold	Optimize dose	Switch (high ATI) or Optimize dose (low ATI)
IFX ≥ threshold	Check endoscopy or Switch	Switch (high activity) or Monitor (low activity)

Subtherapeutic IFX concentrations →
IFX dose escalation > switching to another TNF-a antagonist (86% vs. 33%, *P*=0.02)

Detectable ADAs →
switching to other agents > dose escalation (92% vs. 17% , *P*=0.004)

Akobeng AA, *Inflamm Bowel Dis* 2014

Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab



Proactive IFX concentration measurement

Reactive IFX concentration measurement

Papamichael K. Clinical Gastroenterology and Hepatology, 2017

ORIGINAL ARTICLE

Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima

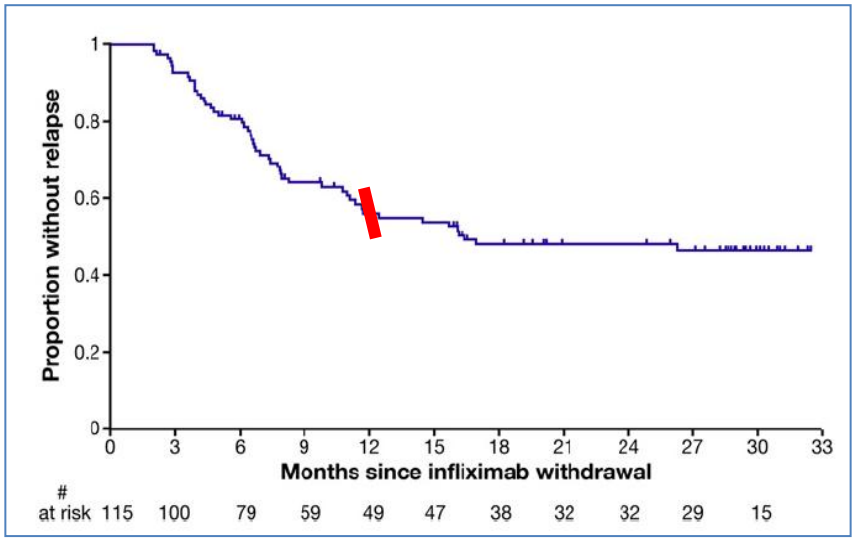
Shomron Ben-Horin,[1] Miri Yavzori,[1] Itai Benhar,[2] Ella Fudim,[1] Orit Picard,[1] Bella Ungar,[1] SooYoung Lee,[3] SungHwan Kim,[3] Rami Eliakim,[1] Yehuda Chowers[4]

Harmonization of Infliximab and Anti-Infliximab Assays Facilitates the Comparison Between Originators and Biosimilars in Clinical Samples

Ann Gils, PharmD, PhD, Thomas Van Stappen, PharmD,* Erwin Dreesen, PharmD,* Ruth Storme, PharmD,* Séverine Vermeire, MD, PhD,† and Paul J. Declerck, PharmD, PhD**

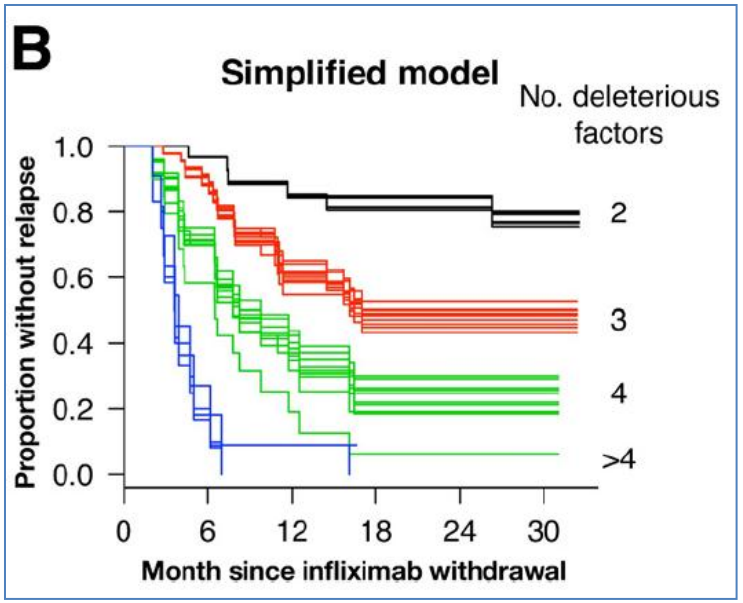
Stop Therapy with caution - CD

Half of patients who stop IFX will relapse within one year



Half of patients who stop IFX will remain in remission after one year

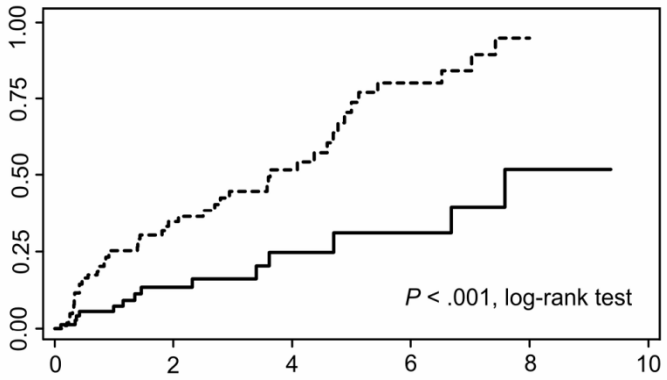
Relapse can be predicted



A. Female
B. Prior surgery
C. WBC < 6 × 10^9/L
D. Hb > 14.5 g/dL
E. hsCRP< 5 mg/L
F. Calpro < 300 µg/g

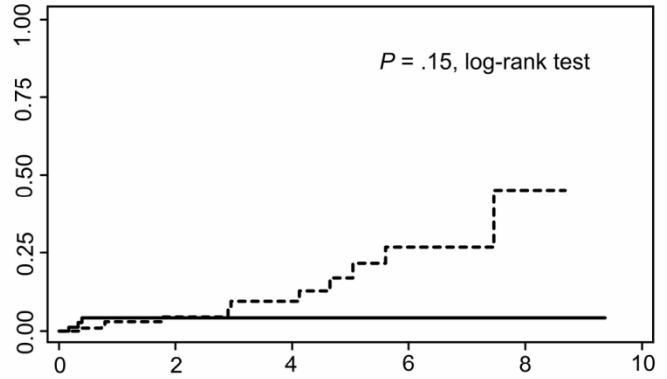
Louis, *Gastro* 2012

Stop Therapy with caution - UC

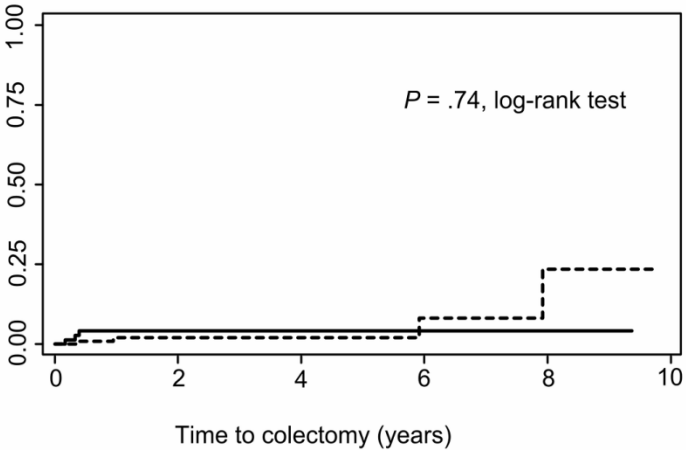


Discontinuation of IFX is associated with

increase in relapse rates



increase in hospitalization rates



increase in colectomy rates

Fiorino G, Clinical Gastroenterology and Hepatology, 2016

Early Trough Levels and Antibodies to Infliximab Predict Safety and Success of Reinitiation of Infliximab Therapy

Filip Baert,[*] David Drobne,[*] Ann Gils,[‡] Niels Vande Casteele,[‡] Scott Hauenstein,[§] Sharat Singh,[§] Steve Lockton,[§] Paul Rutgeerts,[*] and Séverine Vermeire[*]

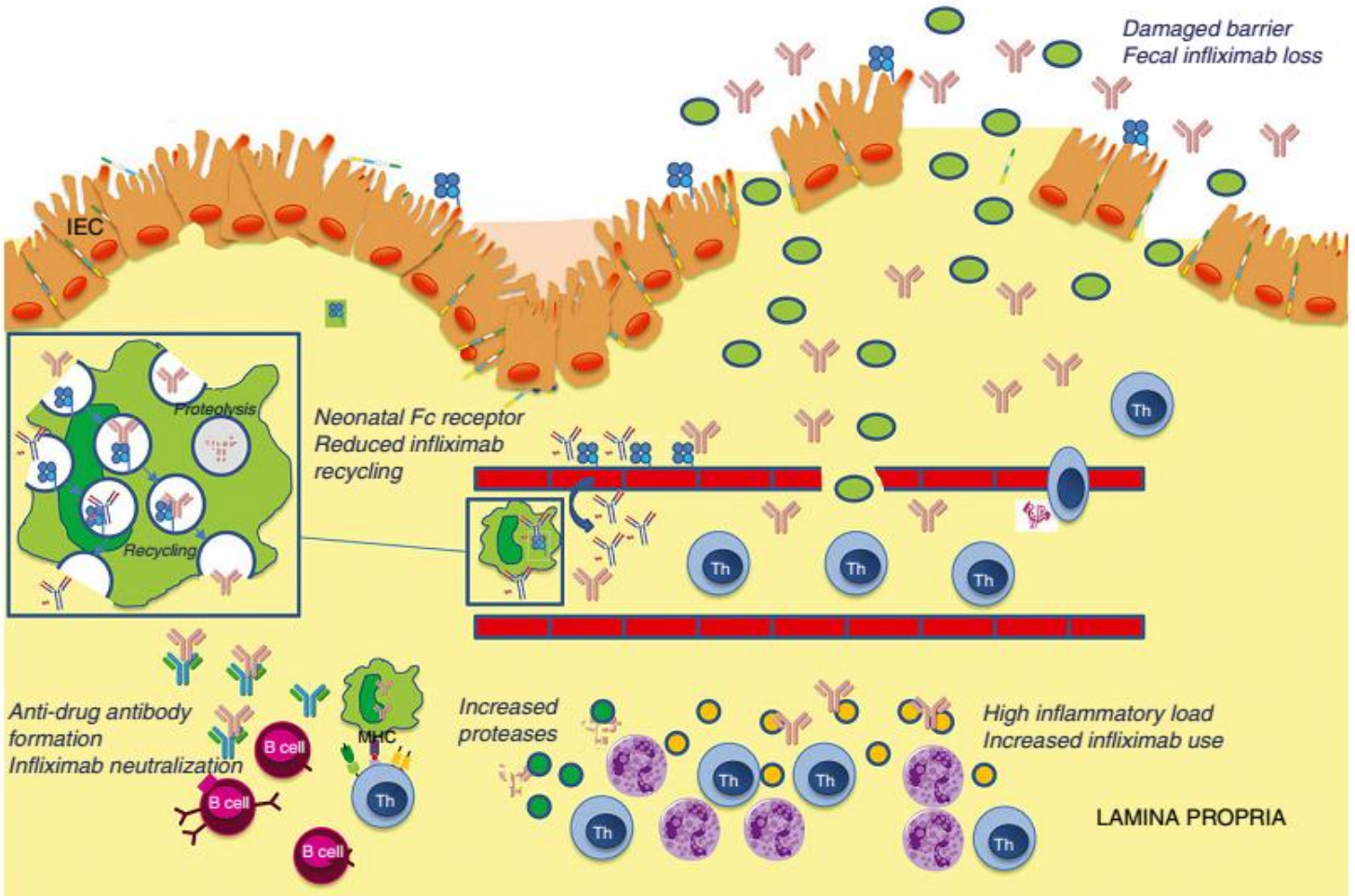
Table 3. Clinical and Biologic Factors Predicting Short- and Long-Term Response of IFX Restarting

Response (%)	Short term	Year 1	End of follow-up period	HR (95% CI); *P* value[a]
ATI T+1 detectable (n = 31)	71%[a]	54.8%	38.7%	0.14 (0.026–0.74); .021
IMM at restart (n = 84)	91.6%[a]	74.7%	66.6%	6.00 (1.3–27); .019
Reason for discontinuation (remission) (n=100)	90%	77.5%	66.6%[a]	2.70 (1.09–6.67); .033
TL T+1 > 2 μg/mL (n = 43)	93%	74%	70%[a]	2.94 (1.18–7.69); .021

Baert F, Clinical Gastroenterology and Hepatology 2014

acute severe ulcerative colitis

enhanced clearance rate of IFX



Hindryckx P. AP& T 2017

acute severe ulcerative colitis
enhanced clearance rate of IFX

high baseline serum CRP (>50 mg/L)
low serum albumin (<35 g/L)
extensive colitis

⇓ IFX concentrations [wks 0 to 6]

Brandse JF, Clin Gastroenterol Hepatol 2016

Patients with acute severe UC had significantly lower week 2 IFX concentrations than those with less severe disease.

Ungar B, Aliment Pharmacol Ther 2016

Acute severe UC with serial measurement of IFX trough concentrations during induction treatment,

8 /13 patients had undetectable IFX

Seow CH, Gut 2010

acute severe ulcerative colitis
association between IFX levels and clinical response

- Detectable serum IFX concentrations [wk 6]
  - ⇒higher rates of clinical and endoscopic remission
  - ⇒lower 24-week colectomy rate (7% vs. 55%; P = 0.001)

- Undetectable IFX serum concentrations during induction
  - ⇒ long-term (30 wks) ADA formation
  - ⇒ treatment failure.

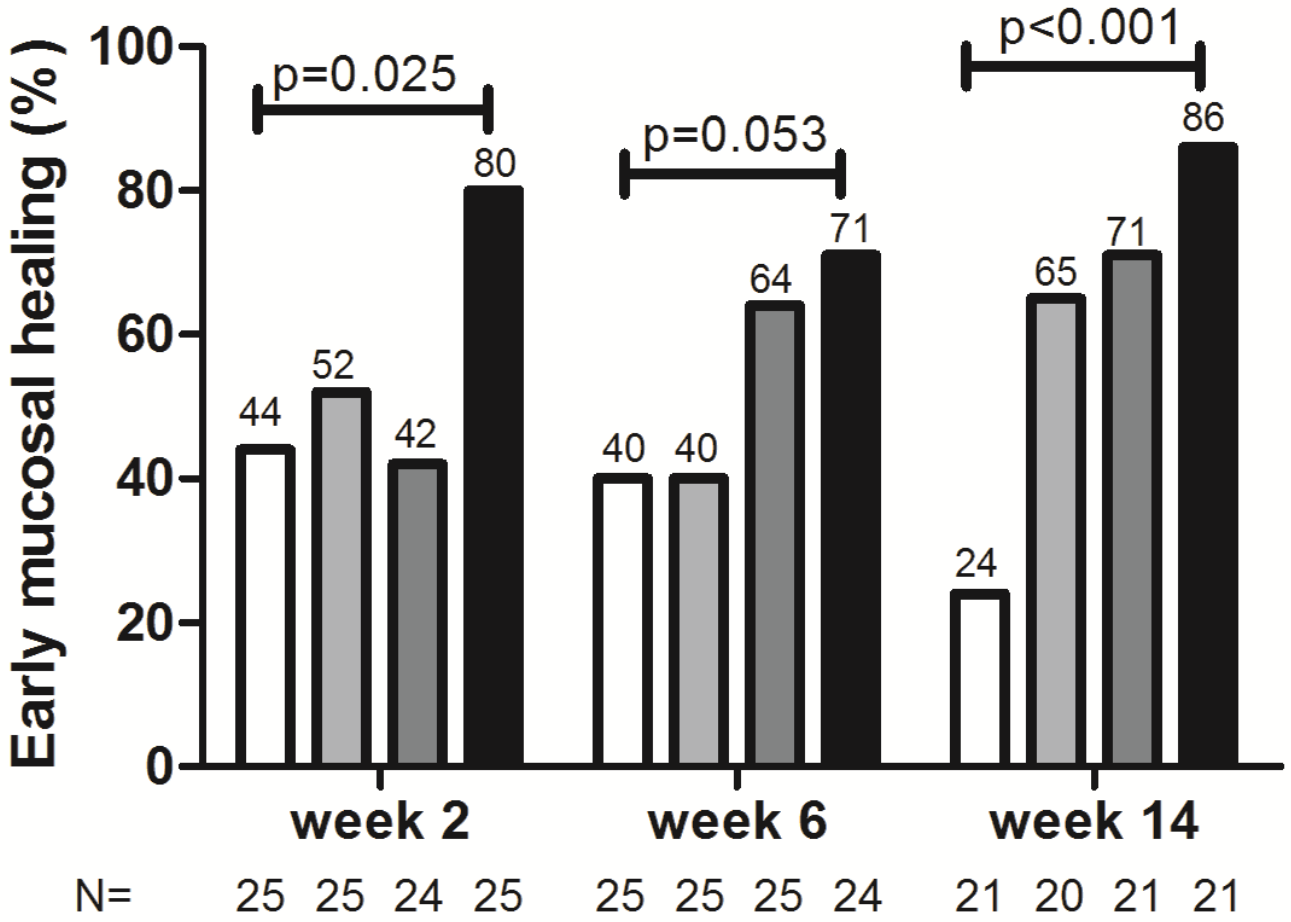
- IFX concentration <16.5 lg/mL [wk 2]
  - ⇒ independent predictor of colectomy

- IFX serum concentrations >2.5 lg/mL [wk 14]
  - ⇒ higher colectomy-free survival [median follow-up: 5 years]

Seow CH, Gut 2010
Kevans D, Gastroenterology 2012; 142: S–384.46.
Papamichael K, J Crohns Colitis 2016
Arias MT, Clin Gastroenterol Hepatol. 2015.

acute severe ulcerative colitis
association between IFX levels and clinical response

Quartile analysis of IFX TC at week 2,6,14 and early MH

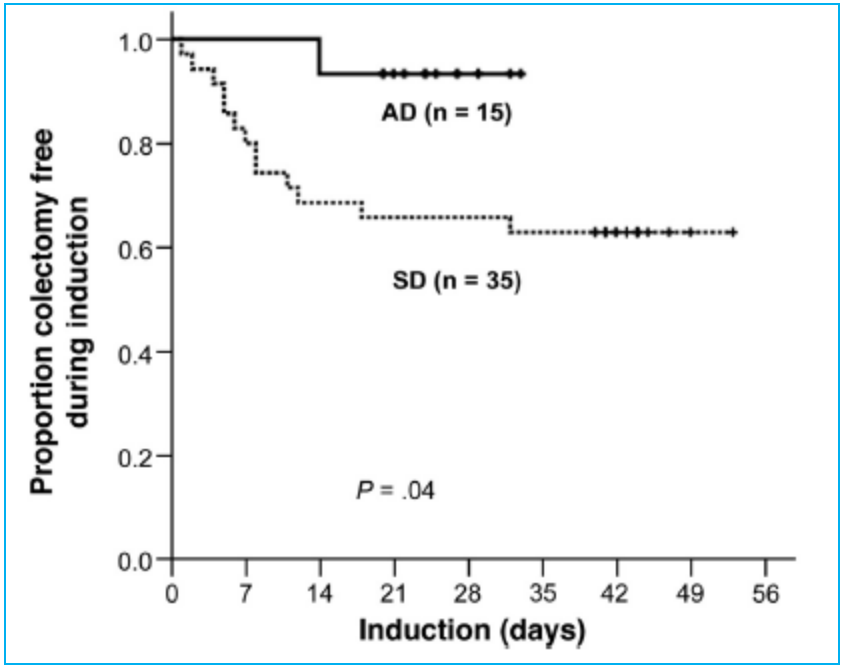


Courtesy of K. Papamichael

acute severe ulcerative colitis
how to improve IFX efficacy

An Accelerated Infliximab Induction Regimen Reduces the Need for Early Colectomy in Patients With Acute Severe Ulcerative Colitis

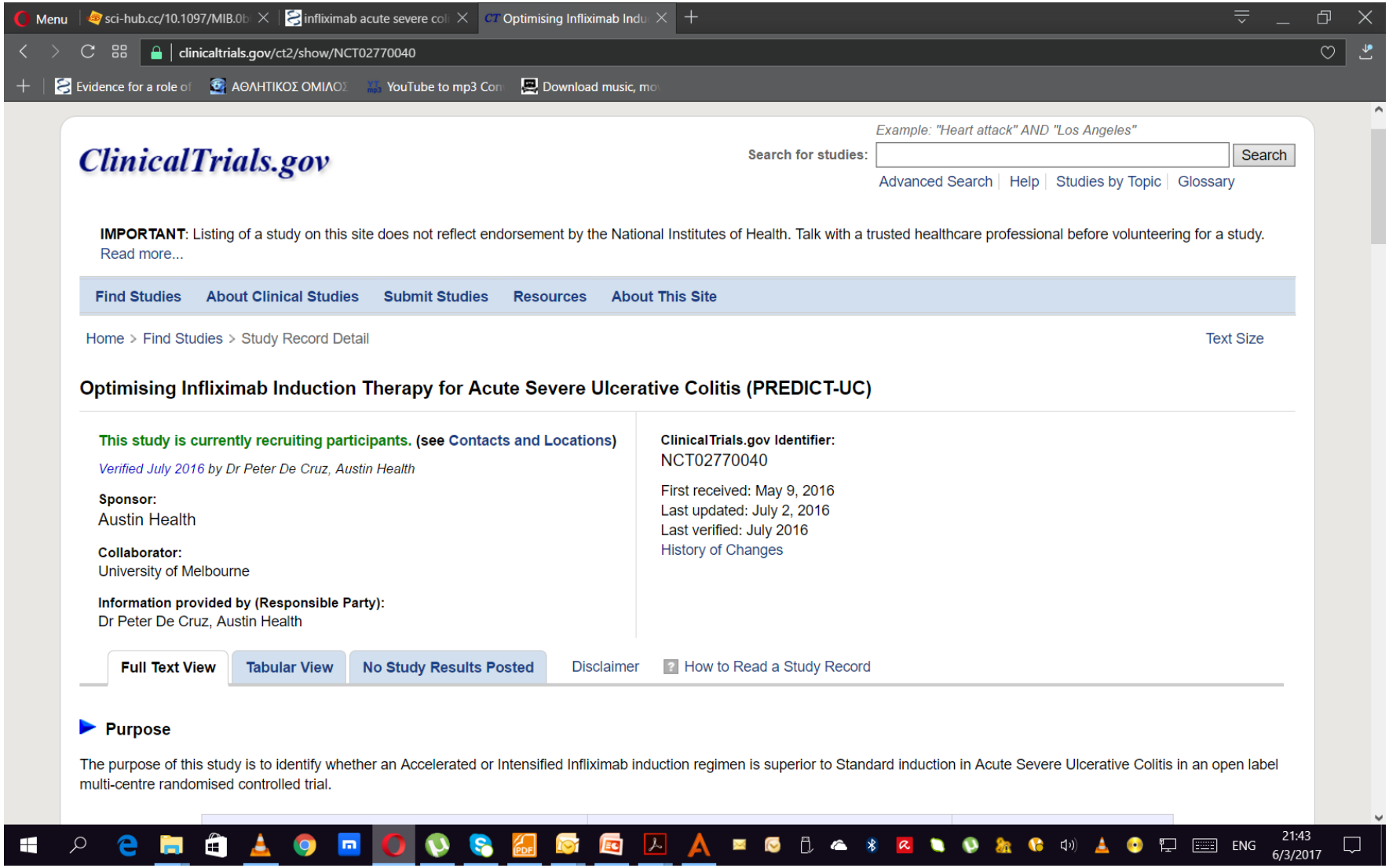
David J. Gibson, Zaid S. Heetun, Ciaran E. Redmond, Kavin S. Nanda, Denise Keegan, Kathryn Byrne, Hugh E. Mulcahy, Garret Cullen, and Glen A. Doherty



	β	Standard error	Relative risk (95% confidence interval)	P value
Serum albumin	−0.17	0.06	0.84 (0.75–0.95)	.003
Accelerated IFX	−2.26	1.05	0.11 (0.01–0.83)	.03

Gibson DJ, Clinical Gastroenterology and Hepatology 2014

acute severe ulcerative colitis
how to improve IFX efficacy



"Δυο δεκαετίες εμπειρίας ενδοφλεβίων anti-TNF παραγόντων“

The patient’s perspective

Patient preferences regarding the route of anti-TNF administration

	Prefer I.V.	Prefer S.C.	no preference
Allen et al.	42%	24%	34%
Kim et al.	63.5%	36.5%	
Vavricka et al.	24%	36%	11%

Factors that influence the decision

ease of use

time required for therapy

time interval between application of the drug

scientific evidence for efficacy

and fear of syringes

Factors for i.v. route preference

Uncomfortable with self-injecting

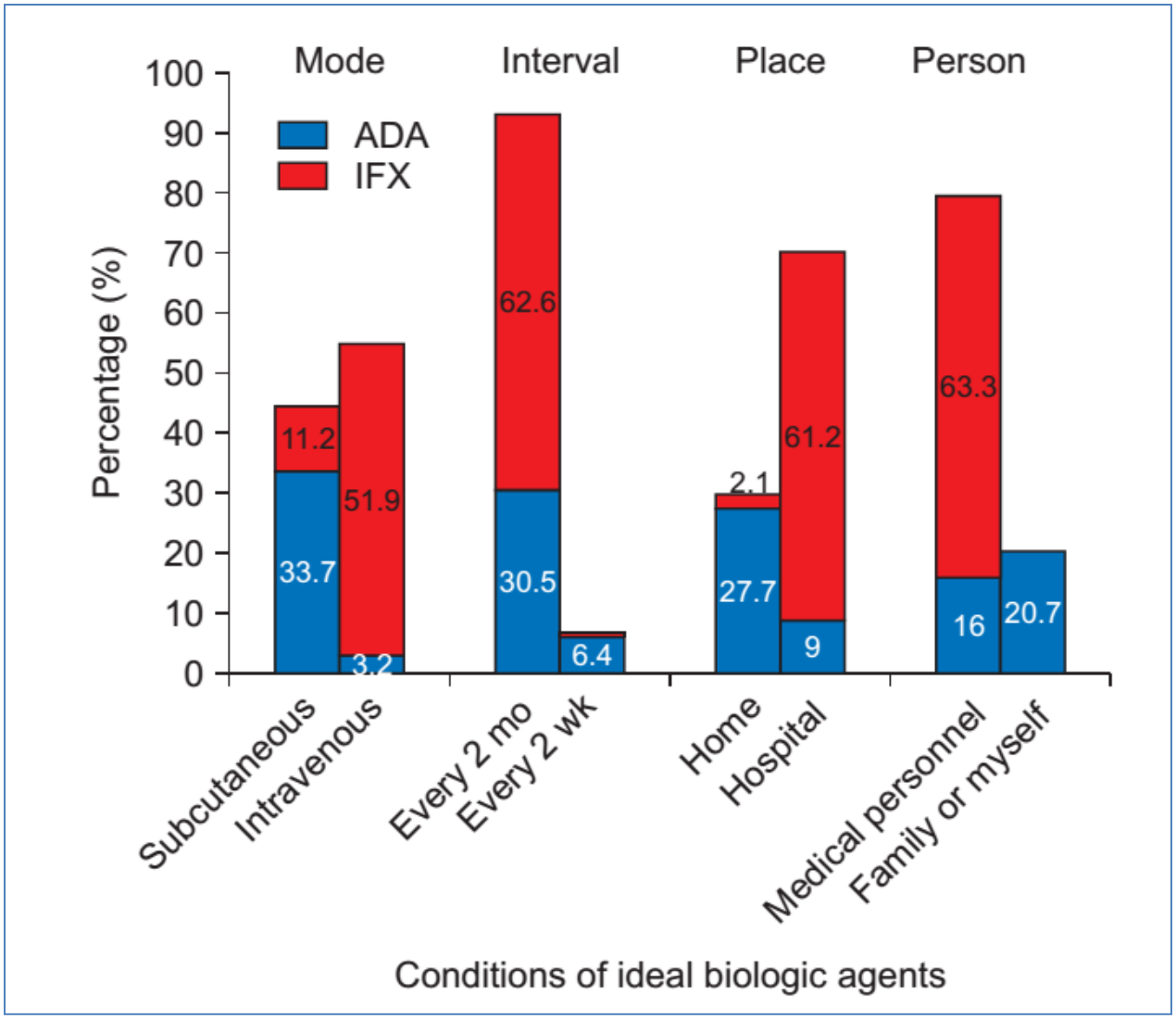
Less frequent administration

Safety of administration in a health-care environment

Presence of medical personnel

Vavricka, Inflamm Bowel Dis 2013;19:1528–1533

What is the ideal biologic agent?

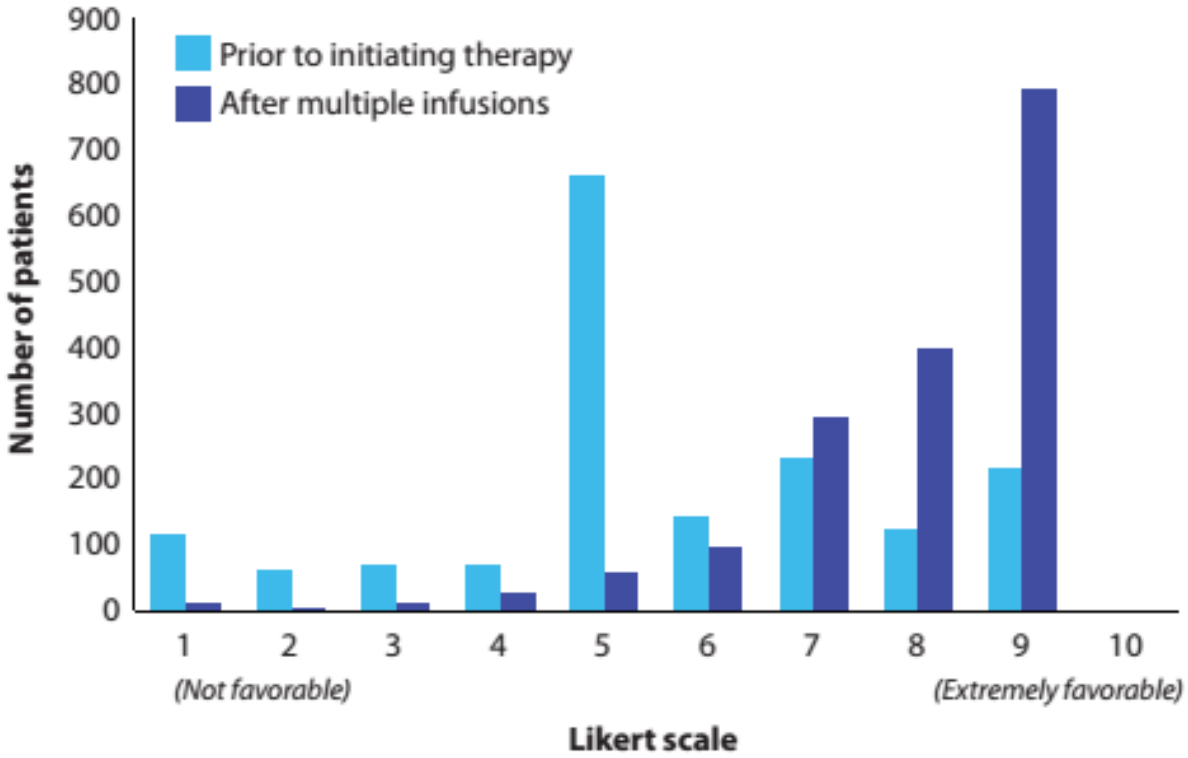


Kim ES, Gut and Liver, 2016

BioAdvance Patient Support Program Survey: Positive Perception of Intravenous Infusions of Infliximab

Jennifer Jones, MD, FRCPC,[1] Mark Borgaonkar, MD, MSc, FRCPC,[2] Jesse Siffledeen, MD, MSc, FRCPC,[3]
Ryan O'Reilly, BSc,[4] Dana Anger, MSc,[5] Dorota Dajnowiec, PhD,[6] Martin Williamson, PhD,[6] Peter Dyrda, BSc, MBA[6]

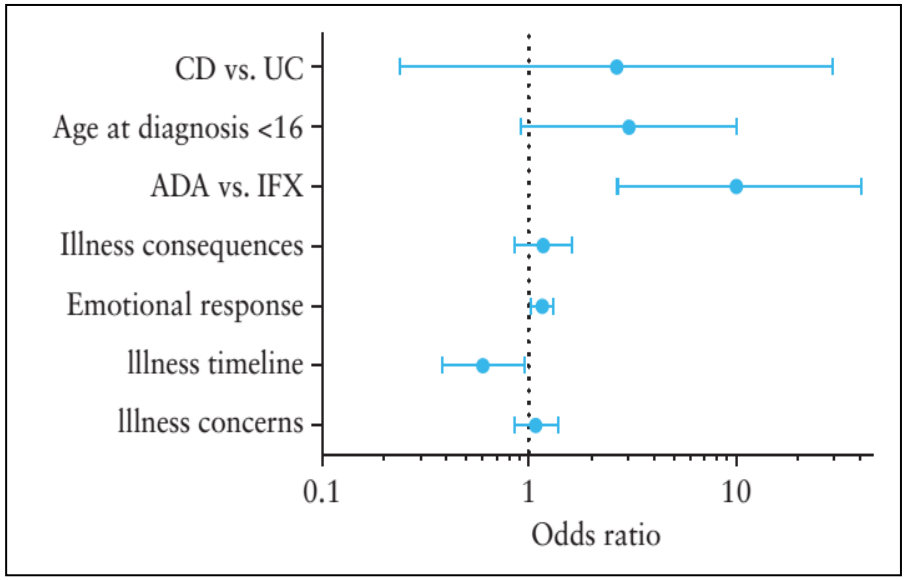
Perception of IV infusion experience before and after initiating treatment with infliximab (N=1,686)

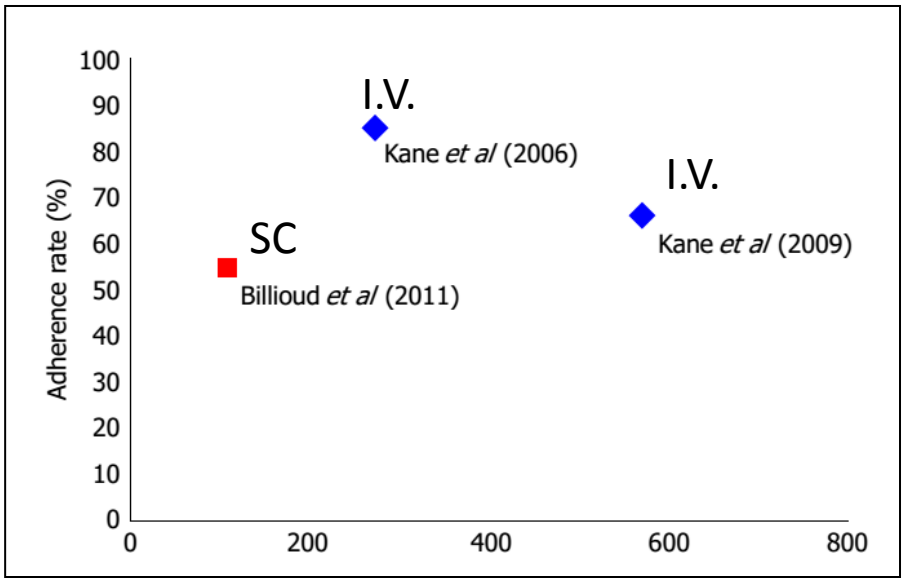


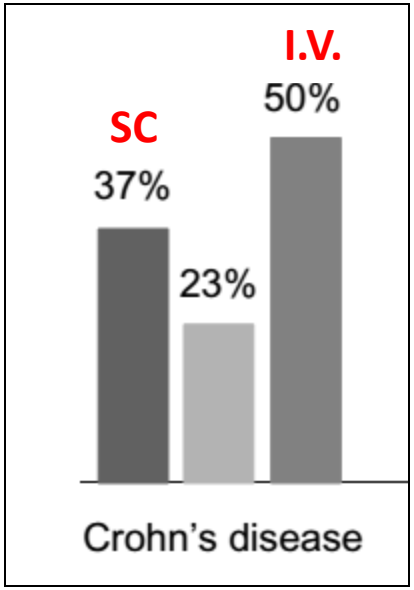
Median (IQR): 5 (5–7) versus 8 (7–9) for before and after initiating IV infusions, respectively ($P<.0001$).
IQR=interquartile range, IV=intravenous

Jones J, MANAGED CARE, FEBRUARY 2017

Adherence rates with anti-TNF therapy in IBD







Pooled adherence in IV-treated patients : 70.7%

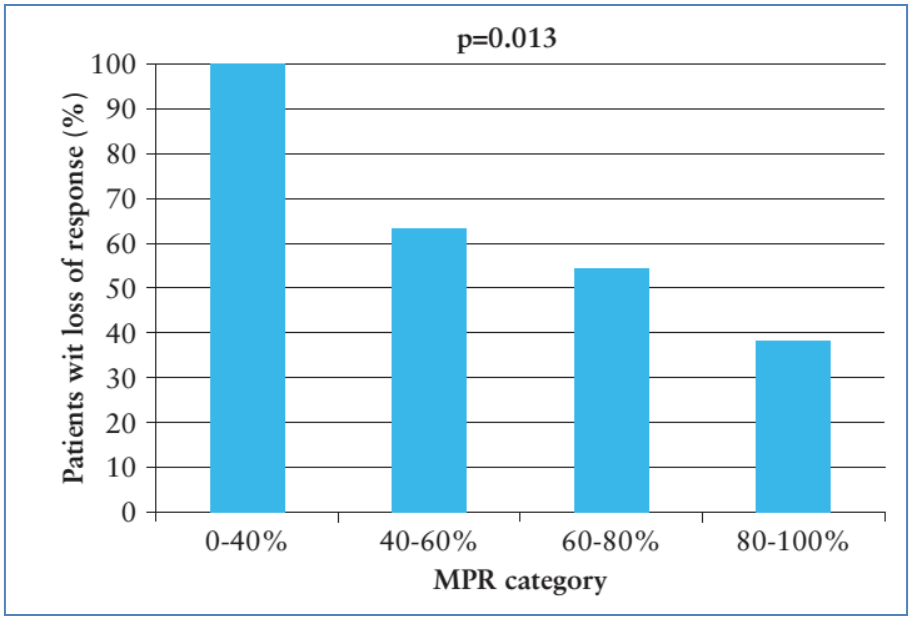
factors for non-adherence to IV route

Female gender,
Smoking,
Constraints related to treatment
Anxiety
Moodiness
Time since first infusion > 18 weeks
Concomitant immunomodulator use

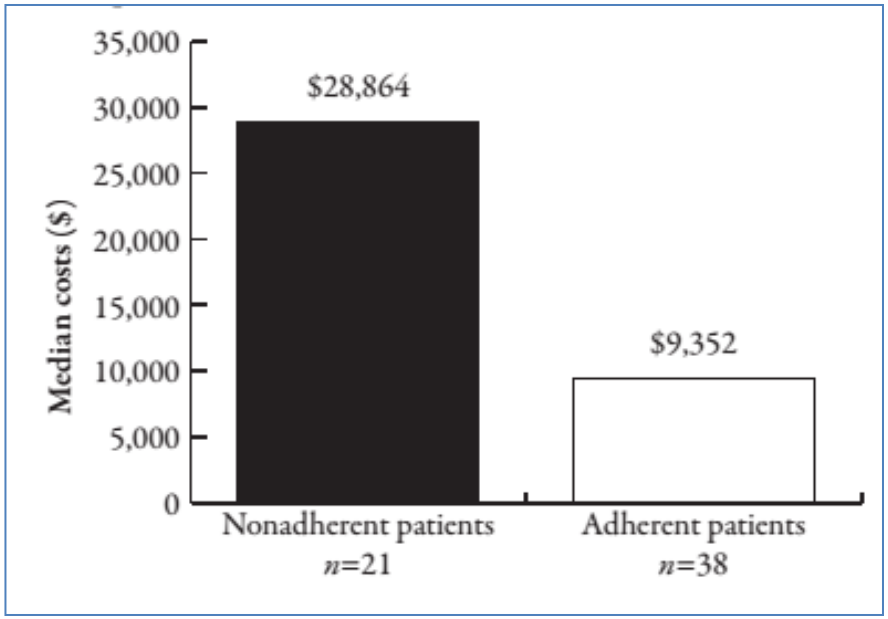
Lopez A, Inflamm Bowel Dis 2013; Fidder HH, WJG 2013

Adherence with I.V. anti-TNF therapy in IBD

Low adherence to i.v. therapy is associated with elevated risk for loss of response



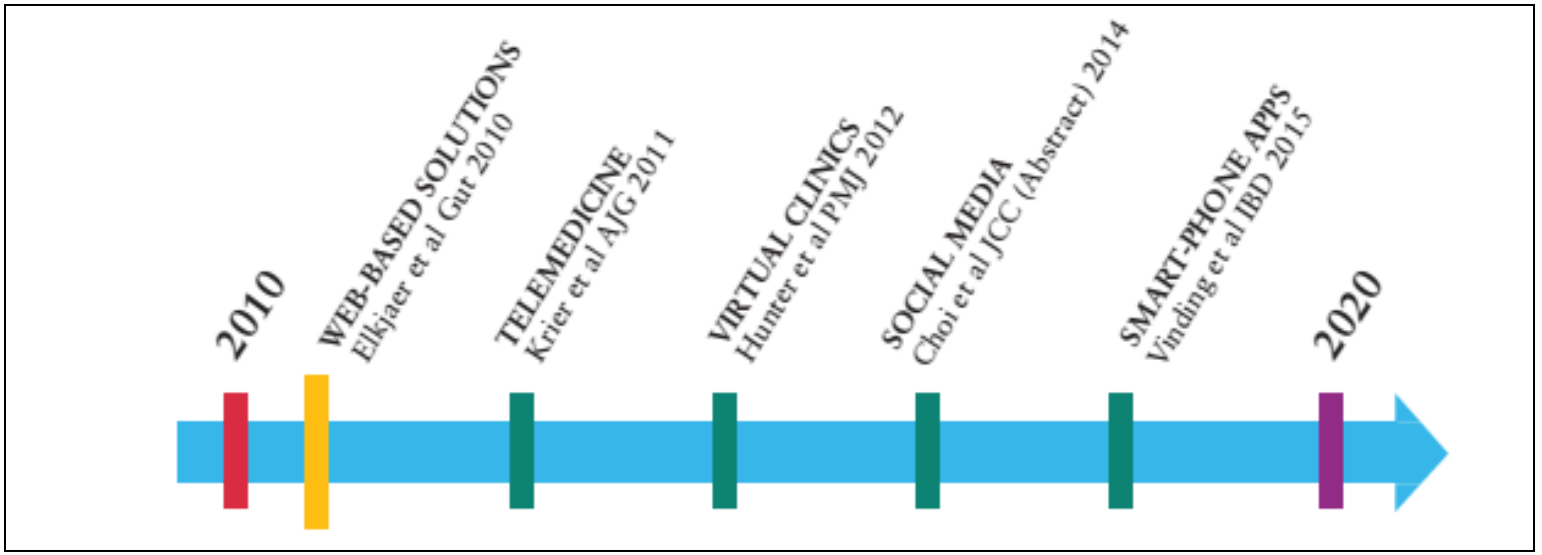
Low adherence to i.v. therapy is associated with elevated costs of treatment



Carter CT, Adv Ther 2011
Feagan B, Journal of Medical Economics 2014
van der Have, Journal of Crohn's and Colitis, 2016

Review Article

EHealth Technologies in Inflammatory Bowel Disease: A Systematic Review



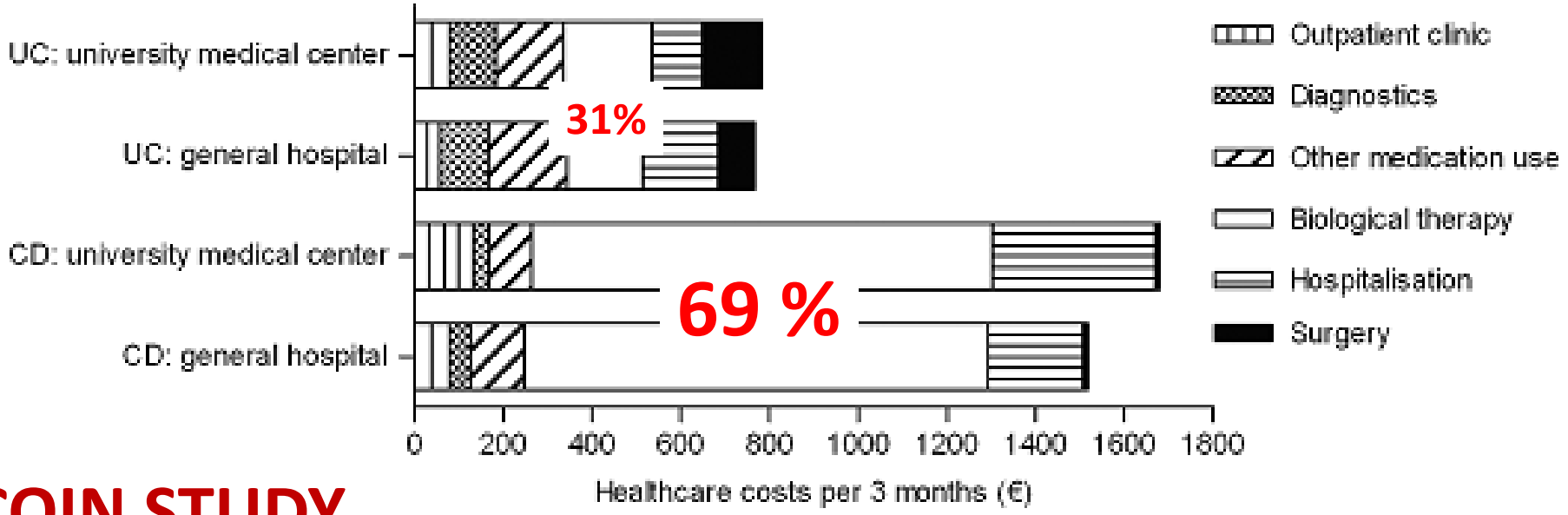
improvements in:

- Relapse duration*;*
- disease activity*;*
- *short-term* ***medication adherence****;*
- *quality of life;*
- *IBD* knowledge*;*
- ***healthcare costs****;*
- *acute visits to outpatient clinic* due to IBD symptoms*;*
- *remote management of up to 20% of an IBD* cohort

"Δυο δεκαετίες εμπειρίας ενδοφλεβίων anti-TNF παραγόντων“

The state’s perspective

Cost of anti-TNF therapy



COIN STUDY

Η φαρμακευτική θεραπεία με βιολογικούς παράγοντες είναι ο σημαντικότερος παράγοντας του κόστους θεραπείας των ΙΦΝΕ

van der Valk ME,et al. Gut2014;63:72–79

Cost of anti-TNF therapy

	Annual cost 2000	Type of costs	Annual cost 2012
Crohn		TOTAL COST	€8004
	€6338	MEDICAL COST	€6501
	62%	SURGERY/HOSPITALIZATION	20%
	18%	DRUGS	71%
Ulcerative	€4819	TOTAL COST	€4092
		MEDICAL COST	€2380
	52%	SURGERY/HOSPITALIZATION	24%
	24%	DRUGS	59%

Accelerated infusion protocols for IFX

Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study

World J Gastrointest Pharmacol Ther2017

The Tolerability and Efficacy of Rapid Infliximab Infusions in Patients with Inflammatory Bowel Disease

Dig Dis Sci 2016

Tolerability of one hour 10 mg/kg infliximab infusions in inflammatory bowel diseases: A prospective multicenter cohort study

Journal of Crohn's and Colitis 2014

Accelerated Infliximab Infusion: Safety, Factors Predicting Adverse Events, Patients' Satisfaction and Cost Analysis. A Cohort Study in IBD Patients

PLoSONE11(11): e0166443

Accelerated infusion protocols for IFX economic impact

Table 4 Infusion time and indirect cost savings: Traditional *vs* short infusion protocol

	w/out SI (min)	w SI (min)	Delta (min)	Saving (min)	Delta %	Hours	Saving indirect costs (€)
Infusion time	300120	254400	-45.72	-45720	-15%	-762	-11.525
Post infusion time	225090	202230	-22.86	-22860	-10%	-381	-5.763
Total time	525210	456630	-68.58	-68580	-13%	-1143	-17.288
Costsaving/patient						-9	-138

Type of cost	Cost per 1-h infusion (€)	Cost per 2-h infusion (€)
Administration	18.02	18.02
Waste disposal	0.06	0.06
Specialist during administration	11.70	11.70
Nurse during administration and monitoring	48.70	125.88
Specialist during IRs	0.05	0.21
Nurse during IRs	0.02	0.28
Total Direct	**78.56**	**156.15**
Loss of productivity due to infusion duration	23.56	63.14
Loss of productivity due to transport from/ to the hospital	31.42	31.57
Total Indirect	**54.98**	**94.71**
Total (Direct +Indirect)	**133.54**	**250.86**

TIME SAVINGS

MONEY SAVINGS

Viola A, *World J Gastrointest Pharmacol Ther 2017*
Mazzuoli S, *PLoS ONE* 11(11): e0166443

Accelerated infusion protocols for IFX patient satisfaction impact

Table III. Factors influencing the overall QoL.

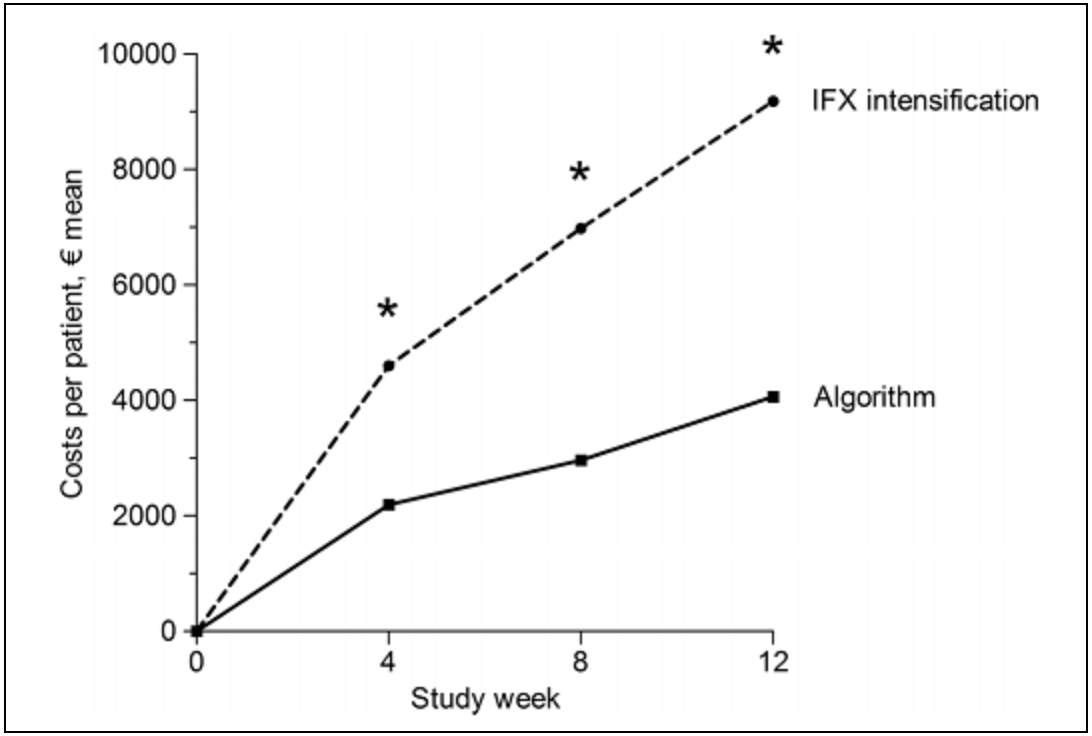
	p	OR	CI 95%
Total number of infusions	0.2	-	-
N. of infusions pre 1-h switch	0.49	-	-
Disease duration (years)	0.92	-	-
Age	0.03	1.023	1.012-1.034
Sex	0.03	2.04	1.775-2.305
Disease (UC or CD)	0.74	-	-
Extension	0.02	0.093	0.078-0.108
Activity score at diagnosis	0.01	7.242	5.895-8.589
Infusion schedule (1h vs 2h)	0.001	0.626	0.531-0.721
Reactions to infusion	0.06	-	-
Smoking	0.31	-	-
Body mass index	0.81	-	-
Other immunomodulators	0.07	-	-
Perianal involvement	0.3	-	-
Prophylaxis prior to infusion	0.42	-	-

UC: ulcerative colitis; CD: Crohn' s disease

Principi M, J Gastrointestin Liver Dis, 2015

ORIGINAL ARTICLE

Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial



Steenholdt C,et al. Gut 2013;0:1–9.

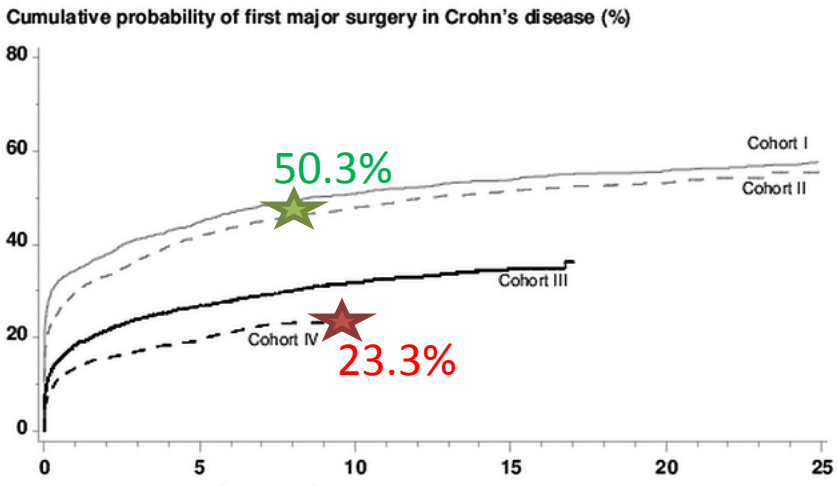
Cost of anti-TNF therapy

Tang, D. H., . et al. Pharmacotherapy 32, 515–526 (2012)

…… infliximab had the highest probability of being the most cost-effective therapy compared with the other biologic agents over 54 weeks…….

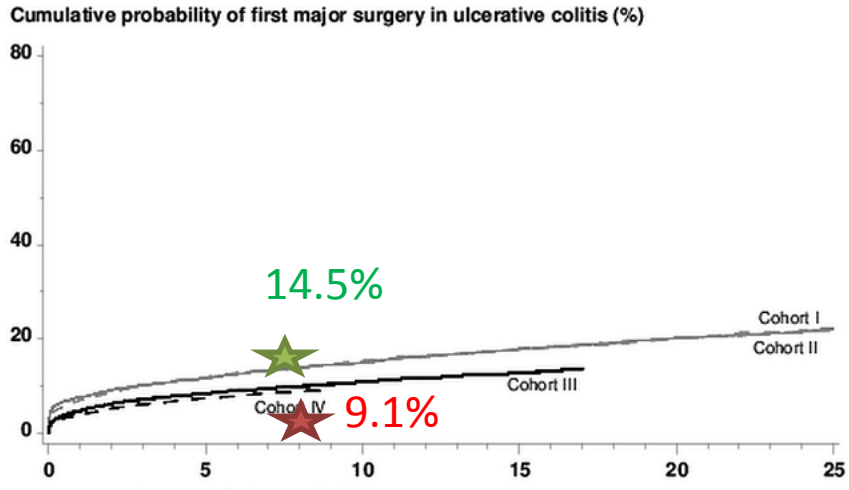
CONCLUSIONS
Long-term effect of anti-TNF agents in IBD

Major surgery for Crohn
50.3% ⇒ 23.3%



CP.	1 y.	5 yrs.	9 yrs.
Cohort I (1979–86)	34.4%	44.7%	50.3%
Cohort II (1987–94)	29.6%	41.7%	46.8%
Cohort III (1995–02)	18.4%	26.7%	31.1%
Cohort IV (2003–11)	13.6%	19.6%	23.3%
P–value	<.001	<.001	<.001

Major surgery for ulcerative
14.5% ⇒ 9.1%



CP.	1 y.	5 yrs.	9 yrs.
Cohort I (1979–86)	7.7%	11.7%	14.5%
Cohort II (1987–94)	7.0%	11.8%	14.8%
Cohort III (1995–02)	4.7%	8.4%	10.4%
Cohort IV (2003–11)	4.0%	7.5%	9.1%
P–value	<.001	<.001	<.001

1995-2002 2003-2011

Rungoe et al. GUT 2014

CONCLUSIONS
future challenges