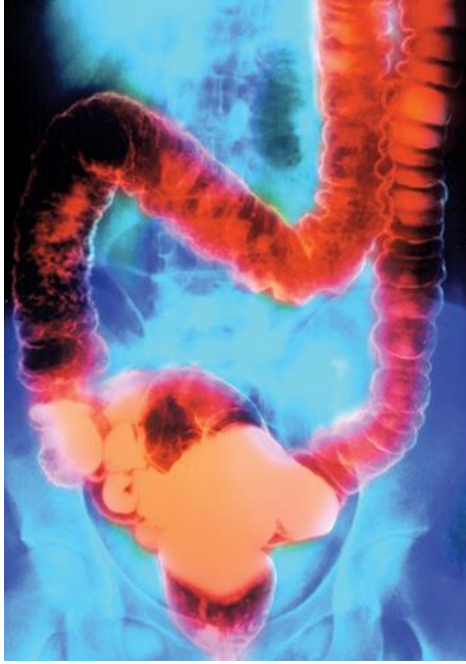


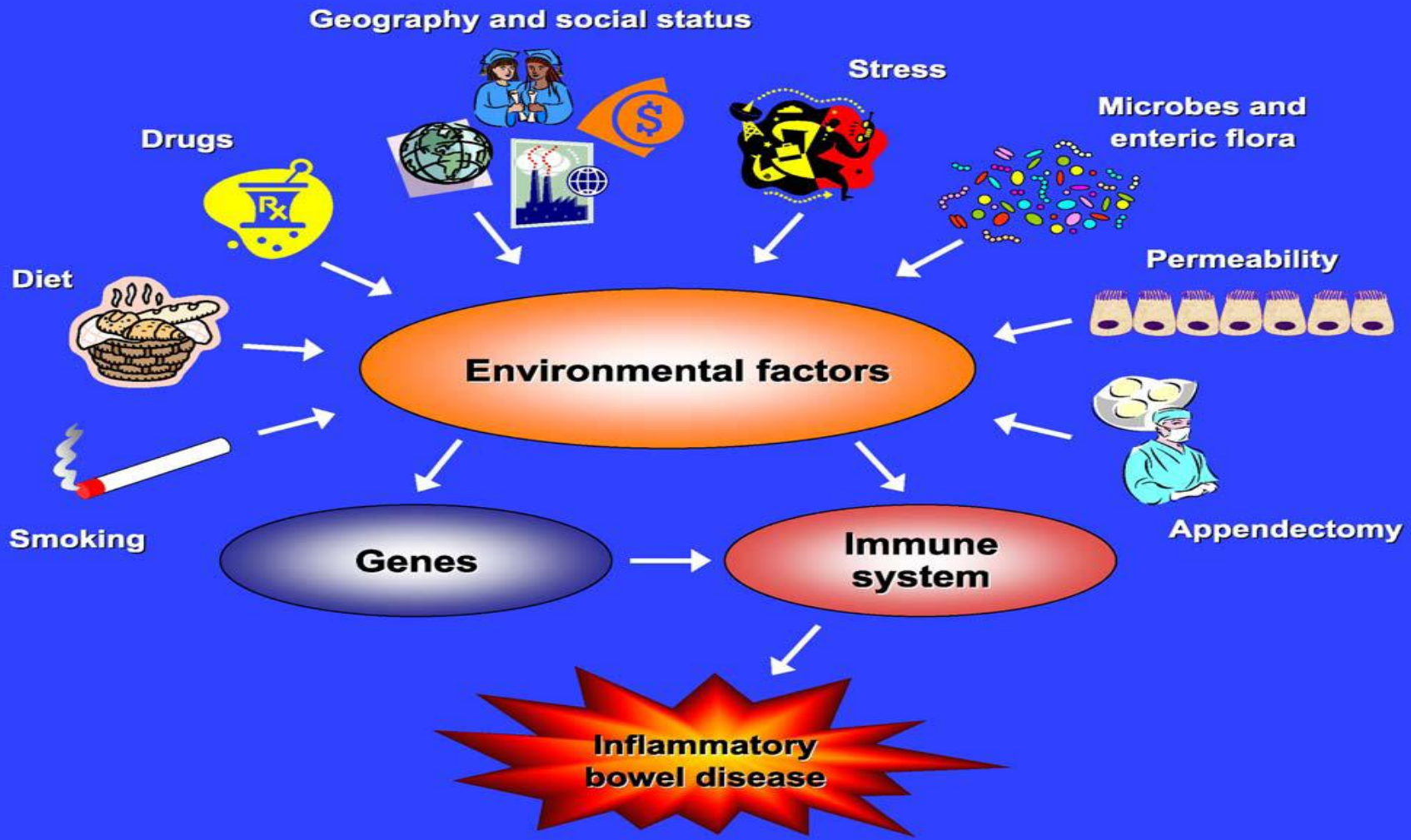
Actualités dans les MICI

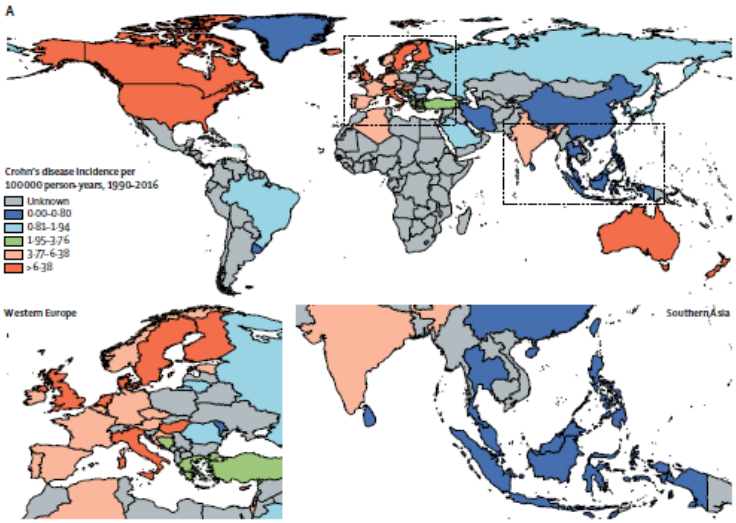
Pr Bruno Bonaz

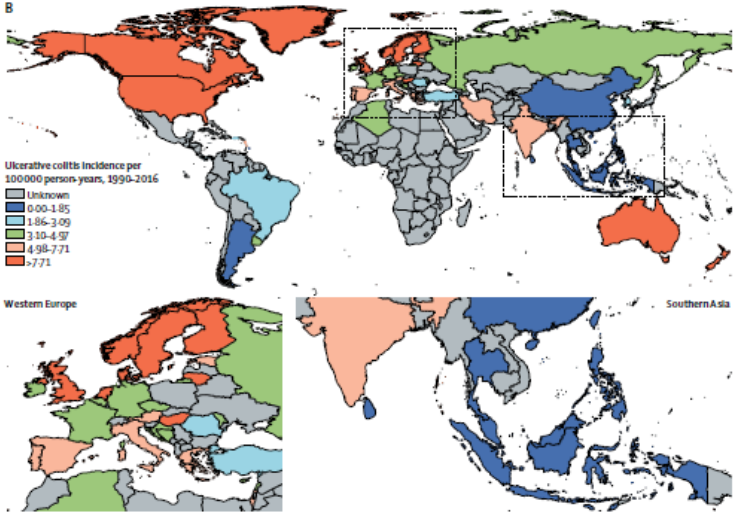
Service d'Hépato-Gastroentérologie

Pôle DIGI-DUNE, CHU Grenoble Alpes

Colloque médical du jeudi, 7 décembre 2017


Geography and social status
Stress
Drugs
Microbes and enteric flora
Diet
Permeability
Environmental factors
Smoking
Appendectomy
Genes
Immune system
Inflammatory bowel disease





"At the turn of the 21st century, inflammatory bowel disease (IBD) has become a global disease with accelerating incidence in newly industrialised countries whose societies have become more westernised. Although incidence is stabilising in western countries, burden remains high as prevalence surpasses 0·3%. These data highlight the need for research into prevention of IBD and innovations in health-care systems to manage this complex and costly disease".

IBD now affects between one in 200 and one in 300 people in high-income country populations.

Since 1990, the incidence has been rising in Africa, Asia, and South America, including, for example, Brazil (11% annual increase for Crohn's disease and 15% for ulcerative colitis) and Taiwan (4% and 5% annual increases, respectively).

All areas of health care are affected by the rapid emergence of such diseases.

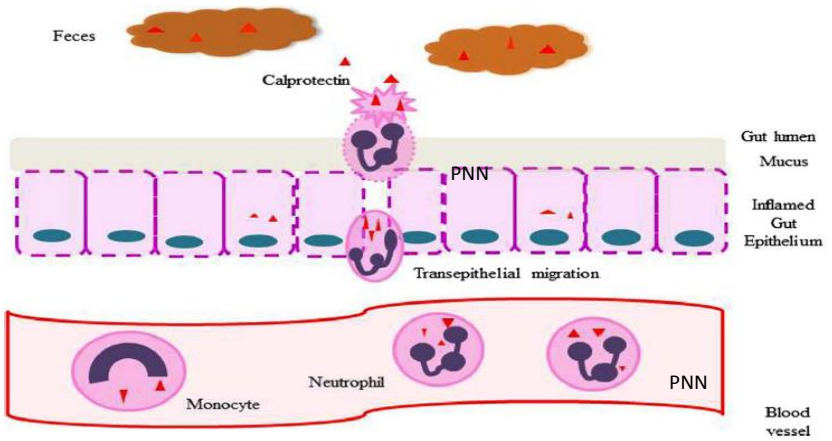
Ng SC et al. Lancet, 2017: Oct 17

Comment faire le diagnostic de MICI

- Clinique : interrogatoire ++++, examen clinique
- Biologie :
  - CRP, calprotectine fécale, ASCA, pANCA
- Imagerie : non invasive ++++
  - IRM : entéro-IRM, entéro-colo-IRM, bili-IRM
  - Echographie standard (ou de contraste)
- Scanner abdomino-pelvien (complications)
- Iléo-coloscopie (±FOGD) :
  - Bilan des lésions, recherche de complications (sténoses, fistules), cicatrisation muqueuse
  - Pas d'appréciation trans-pariétale (MC)
- Combinaison ++++

Calprotectine Fécale

- 60% des protéines cytosol des polynucléaires neutrophiles (PNN)
- Marqueur non invasif d'inflammation intestinale
- Résistance à dégradation dans selles par bactéries coliques
- Stabilité à température ambiante pendant au moins 3 jours
- Peut être réalisée sur 1-2 g de selles
- Technique ELISA
- "CF rapide" : Quantum Blue (12 min)
- Kit de dépistage IBDoc
- Non prise en charge (60€)



Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease

TAINA SIPPONEN[1] & KAIJA-LEENA KOLHO[2]

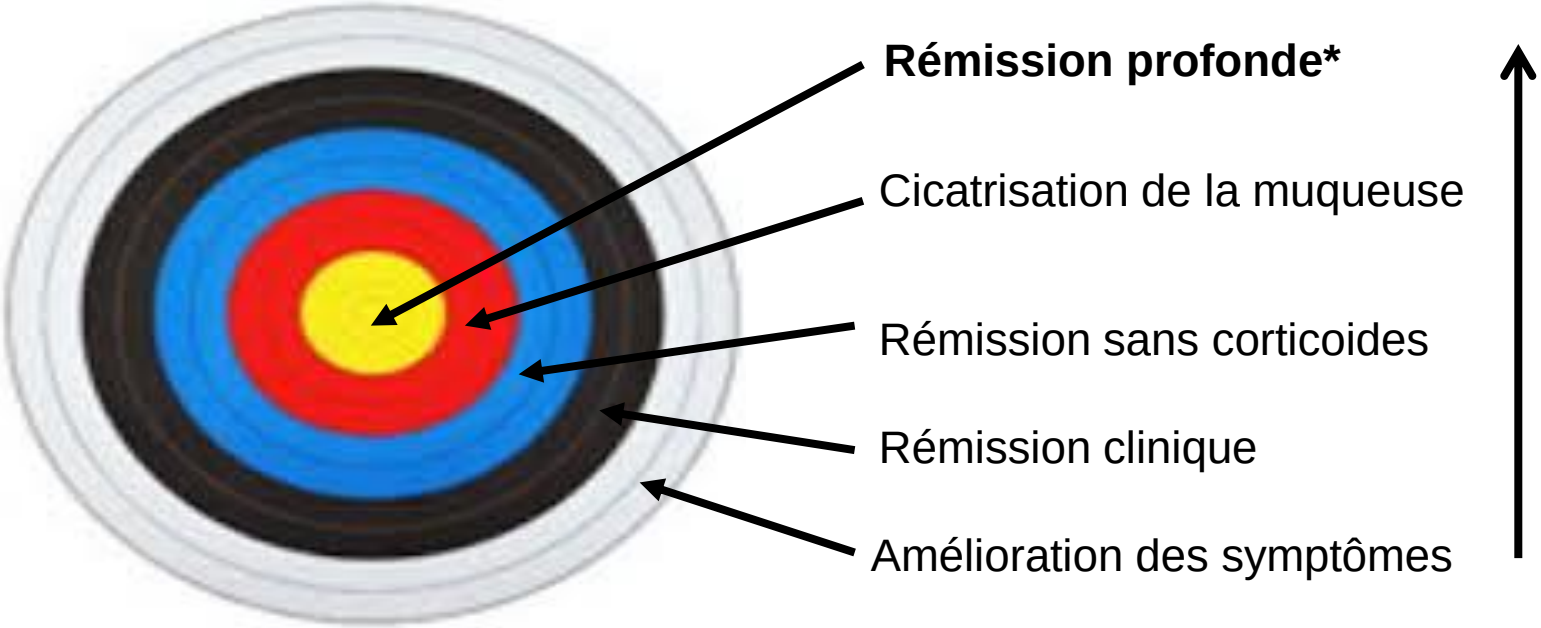
[1]*Department of Medicine, Division of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland, and* [2]*Children's Hospital, Helsinki University Central Hospital, Helsinki, Finland*

- Différence entre MICI et SII
- Différence entre MICI active et inactive
- Réponse au traitement
- Prédire la cicatrisation de la muqueuse
- Prédire la rechute
- Prédire la récidive post-opératoire
- Pouchite
- Colite sévère

Normale : <50 µg/g
Cut-off : 250 µg/g

Scand J Gastroenterol 2015; 50: 74–80

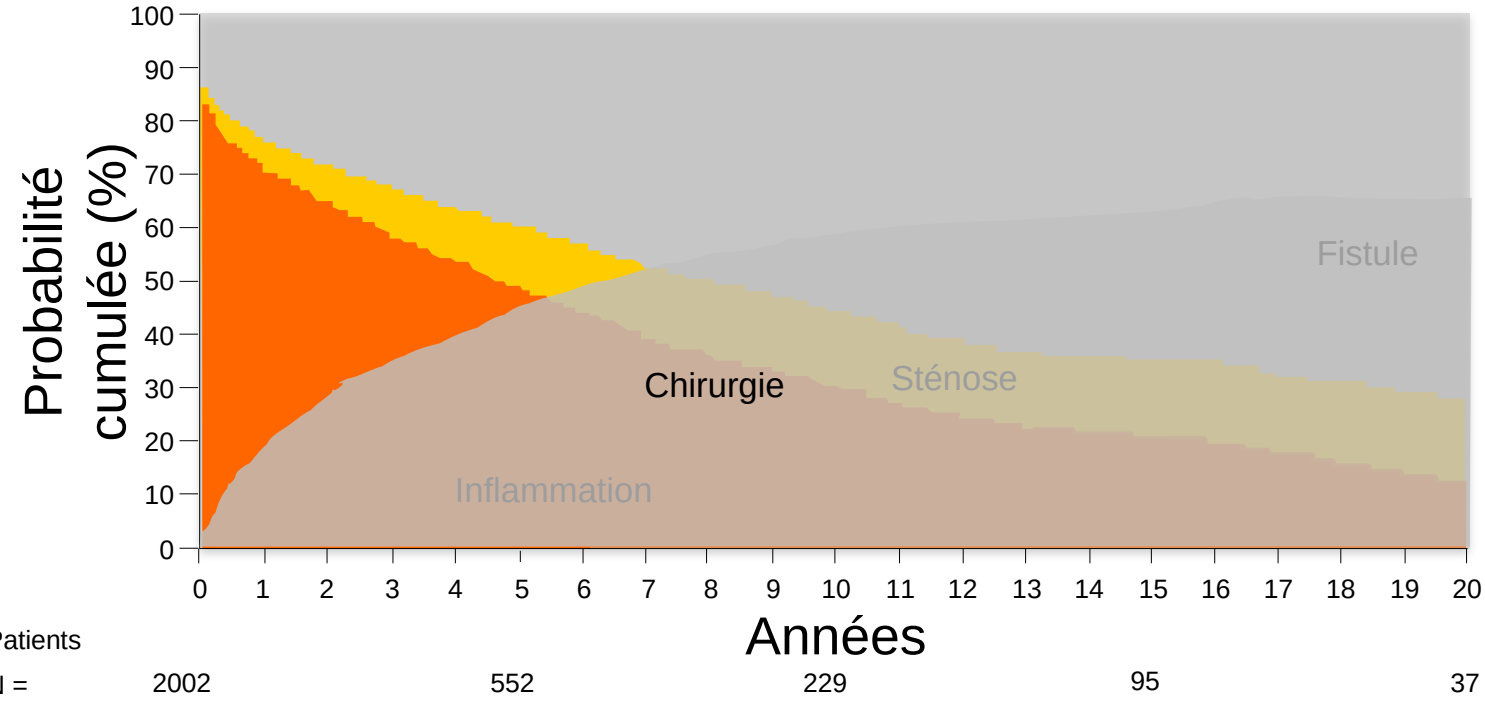
Evolution des buts thérapeutiques dans les MICI



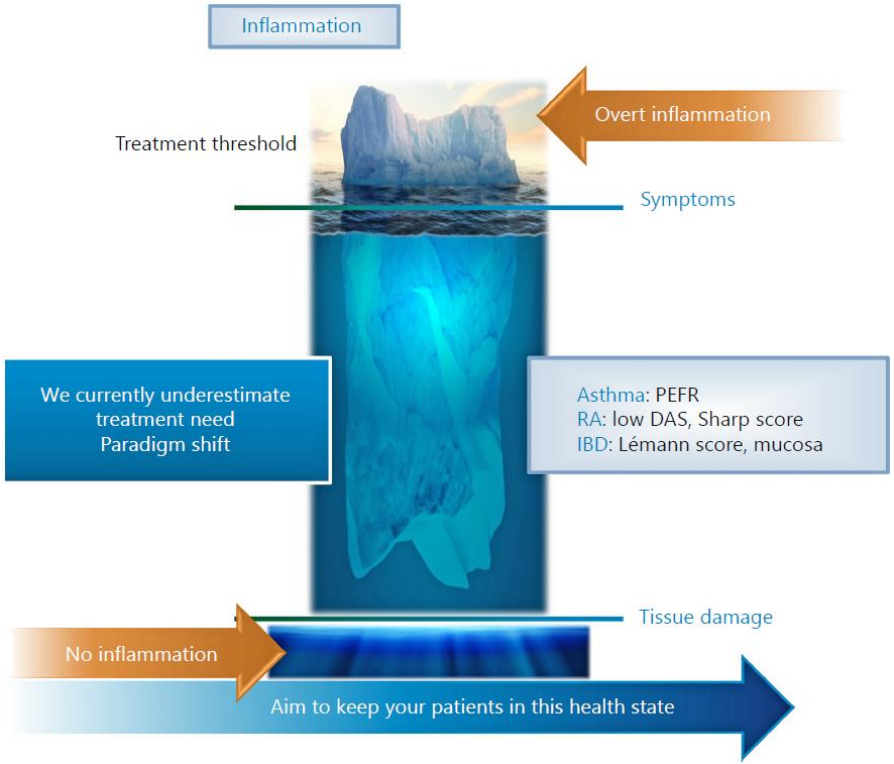
Les stratégies thérapeutiques doivent évoluer de la même façon que les buts thérapeutiques évoluent

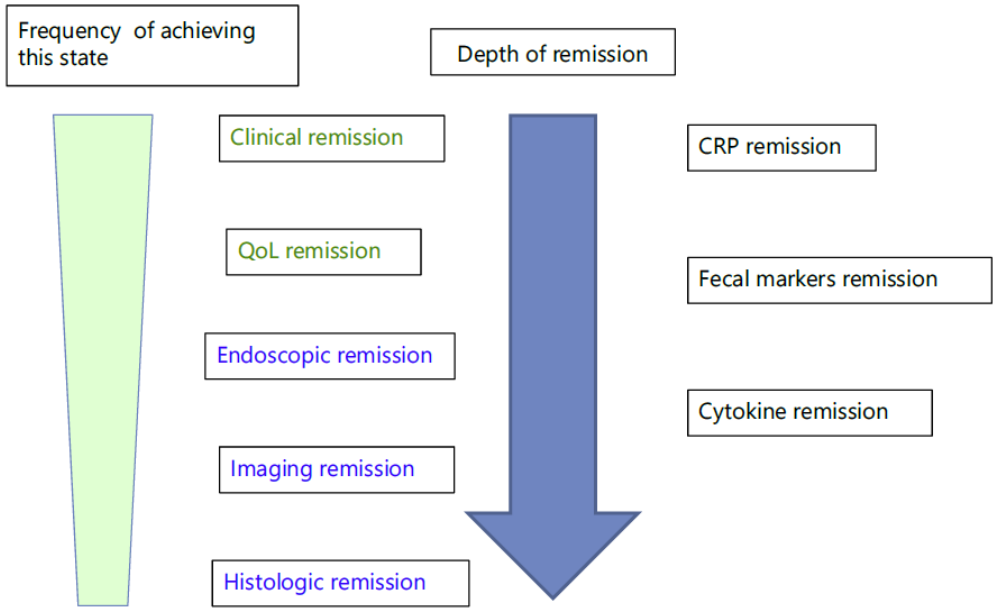
* Clinique (biologique) et endoscopique (histologique)

Histoire naturelle de la maladie de Crohn



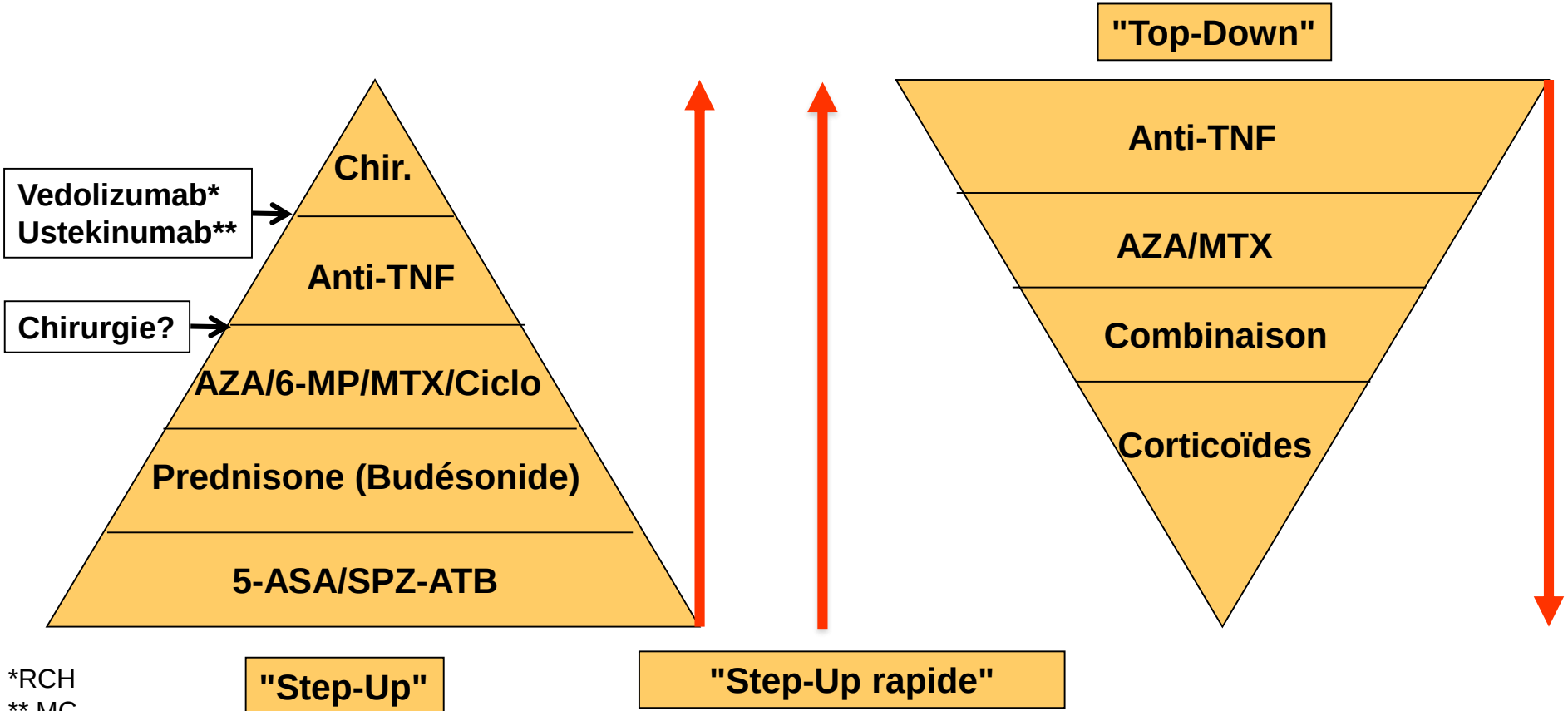
Cosnes J et al. IBD 2002





Iacucci Ma & Ghosh S. Dig Dis 2016;34:160–164

Top-Down ou Step-Up ou Step-Up rapide ??



*RCH
** MC

Four-tier risk stratification

Aggressive disease and poor prognosis
- Young age at onset, extensive disease, early development of fibrostenotic/fistulizing disease, severe endoscopic inflammation

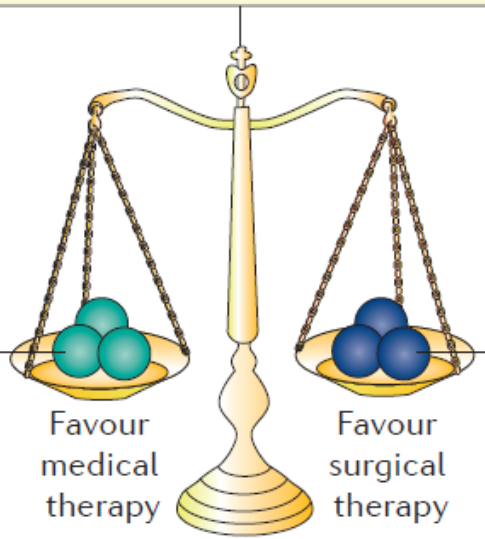
Poor response to biologic therapy
- Young age at onset, female, fibrostenotic/fistulizing disease, prior exposure to anti-TNF agents, prior surgery

Postoperative complication
- Old age, transfusion, hypoalbuminaemia, corticosteroid use, prior bowel resection

Postoperative recurrence
- Young age, prior bowel resection, fistulizing or perianal disease, granulomas or myenteric plexitis on histology

Pros of medicines
- Less invasive and reversible
- Gut sparing
- Disease modifying

Cons of surgery
- Invasive and loss of gut
- Postoperative complications and recurrence
- Cosmesis



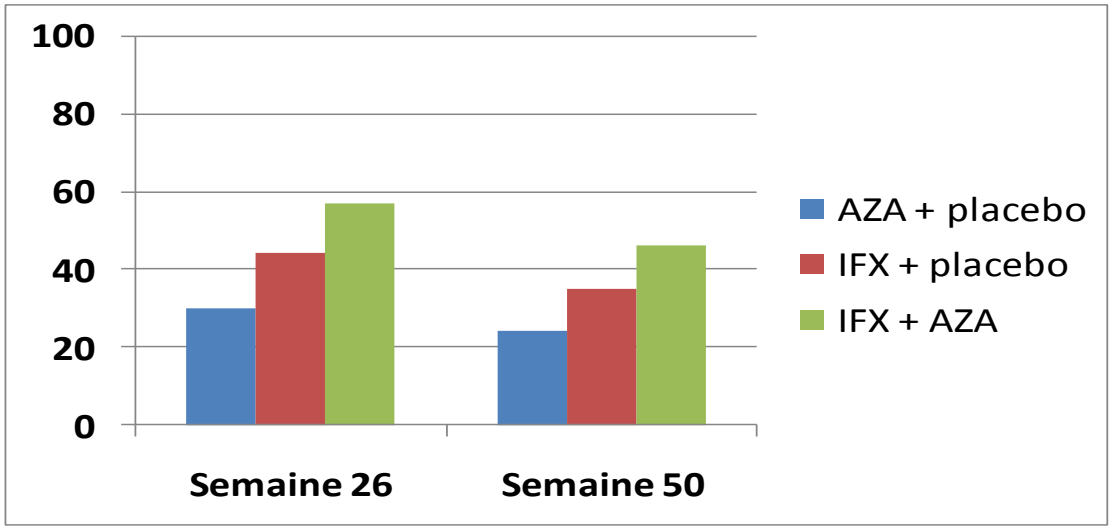
Pros of surgery
- More definitive
- Quick symptom relief
- Cure in some cases

Cons of medicines
- Costs
- Adverse effects
- Adherence
- Risk of dysplasia
- Effect on operative morbidities

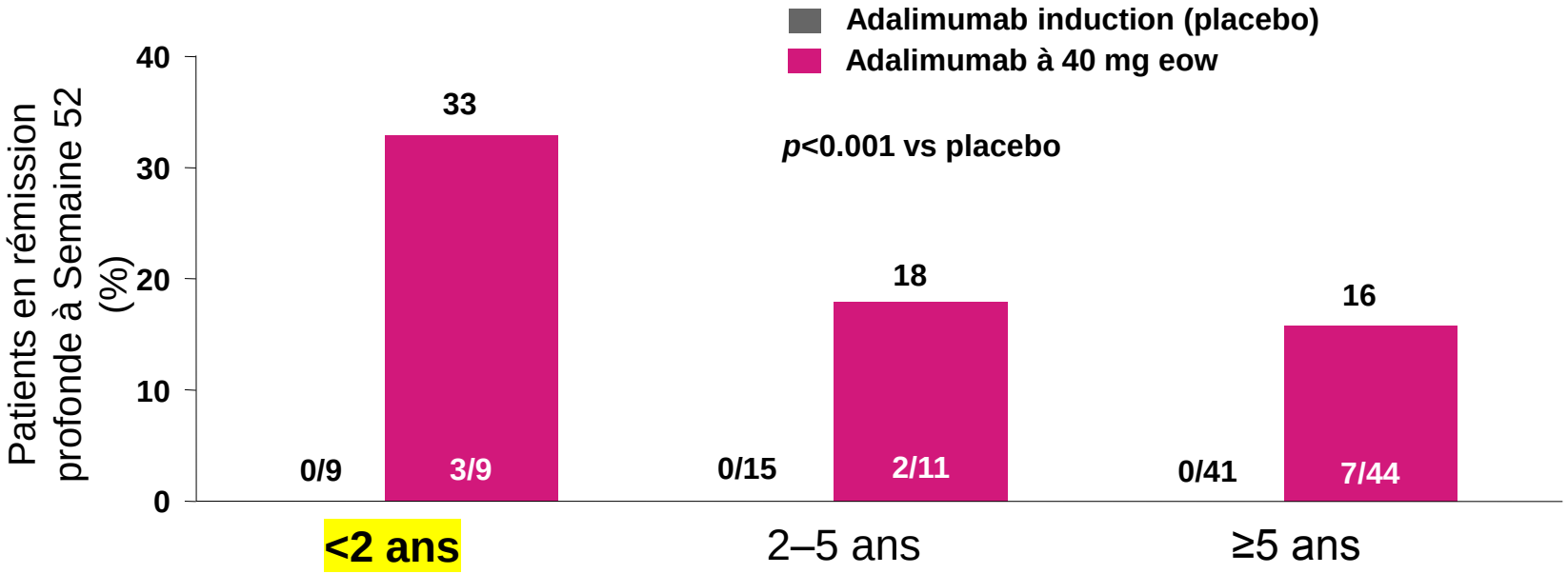
Nat Rev Gastroenterol Hepatol. 2017;14:693-695

Sonic : rémission sans corticoïdes

	AZA + placebo (n=170)	IFX + placebo (n=169)	IFX + AZA (n=169)
Semaine 26	**30%**	**44,4% (p=0,009)**	**56,8% (p<0,001)**
Semaine 50	**24,1%**	**34,9% (p=0,028)**	**46,2% (p<0,001)**



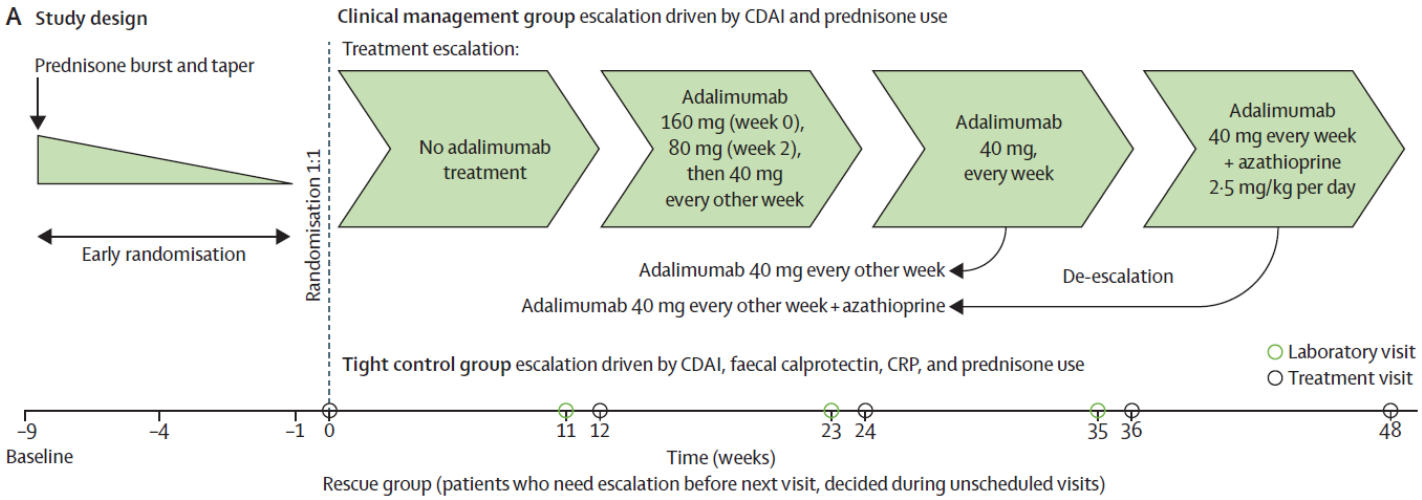
EXTEND : l'utilisation précoce d'ADA est associée à un taux plus important de rémission profonde



Rémission propfonde = rémission clinique (CDAI <150) + cicatrisation de la muqueuse

Colombel JF, et al. UEGW 2010, Barcelona, Spain*, October 23-27:PO400*

CALM study design

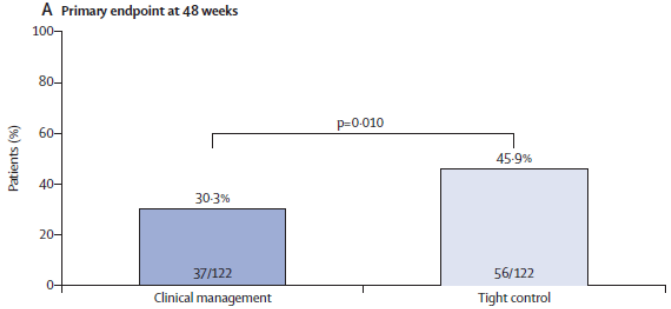


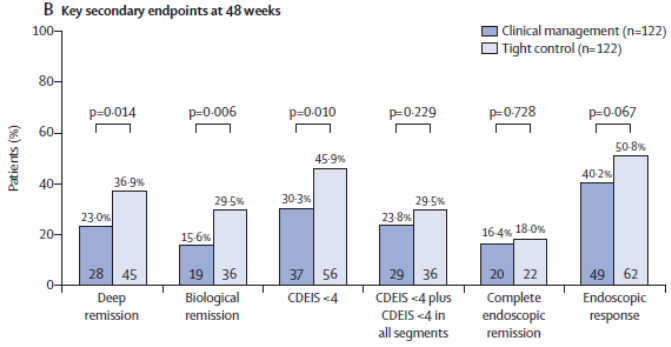
B Treatment and failure criteria

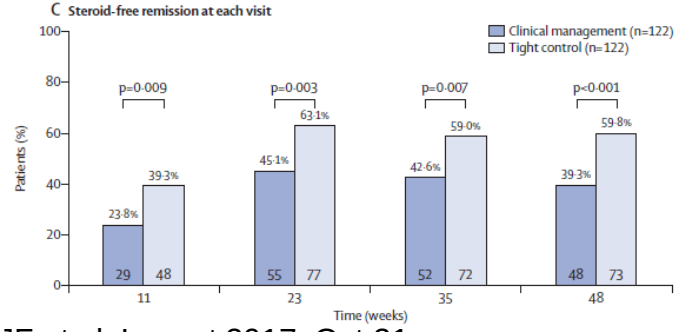
Laboratory visits	Clinical management	Tight control group
Week –1 (before randomisation)	1. CDAI decrease of <70 points compared with baseline or CDAI >200	1. CDAI ≥150 2. CRP ≥5 mg/L 3. Faecal calprotectin ≥250 µg/g 4. Prednisone use
Week 11, 23, and 35 (after randomisation)	1. CDAI decrease of <100 points compared with baseline or CDAI ≥200 2. Prednisone use	1. CDAI ≥150 2. CRP ≥5 mg/L 3. Faecal calprotectin ≥250 µg/g 4. Prednisone use

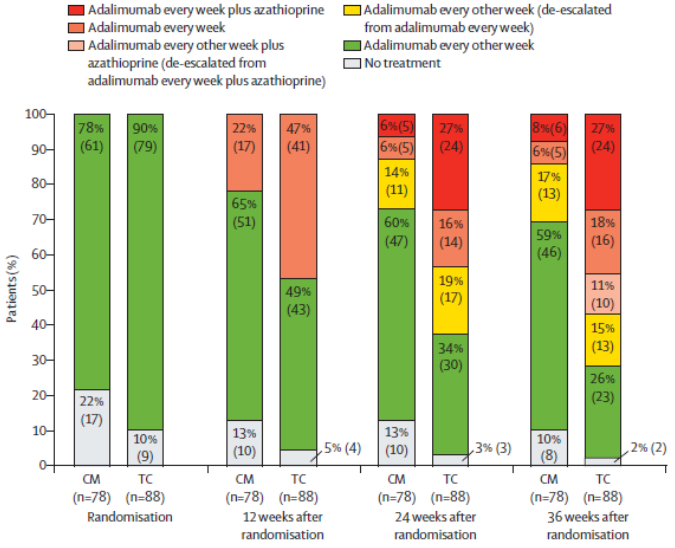
CDAI=Crohn's disease activity index. CRP=C-reactive protein.

Colombel JF et al. Lancet 2017; Oct 31









	Clinical management (n=122)		Tight control (n=122)	
	Patients (%)	Events (events/100 patient-years)*	Patients (%)	Events (events/100 person-years)†
Adverse events	100 (82%)	634 (694·4)	105 (86%)	636 (643·1)
Serious adverse events	25 (21%)	45 (49·3)	22 (18%)	32 (32·4)
Adverse events leading to adalimumab discontinuation	16 (13%)	25 (27·4)	17 (14%)	18 (18·2)
Infection	57 (47%)	110 (120·5)	61 (50%)	116 (117·3)
Serious infection	12 (10%)	15 (16·4)	6 (5%)	7 (7·1)
Opportunistic infection excluding oral candidiasis and tuberculosis	0	0	0	0
Active tuberculosis	0	0	1 (1%)‡	1 (1·0)
Latent tuberculosis	2 (2%)	2 (2·2)	1 (1%)	1 (1·0)
Malignancy	0	0	1 (1%)	1 (1·0)
Deaths	0	0	0	0

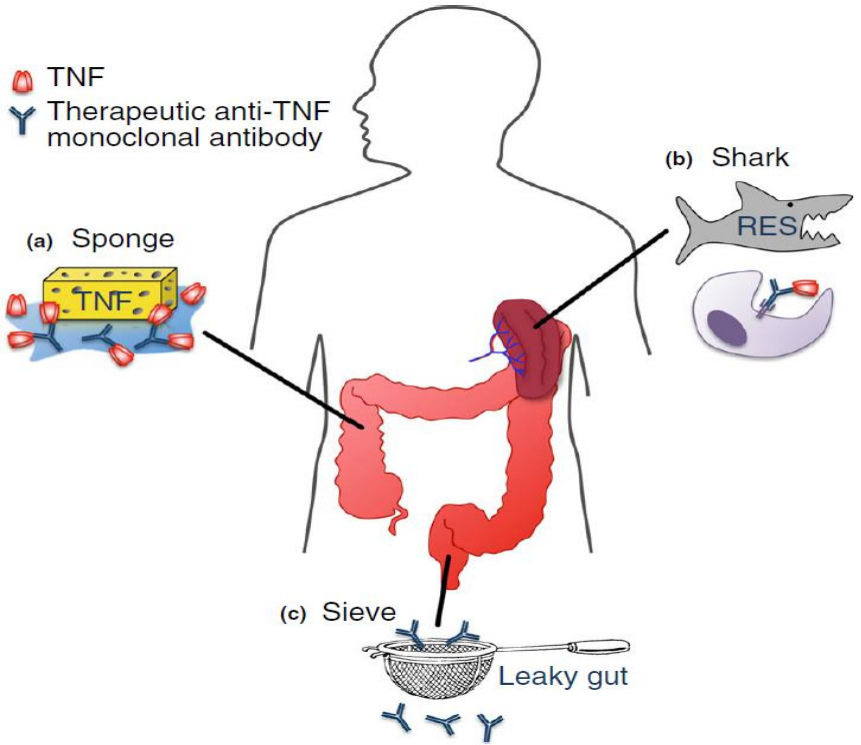
*91·3 person-years of data were obtained in the clinical management group. †98·9 person-years of data were obtained in the tight control group. ‡Pulmonary tuberculosis.

Table 2: **Treatment-emergent adverse events**

Colombel JF et al. Lancet 2017; Oct 31

Facteurs de clairance des anti-TNF

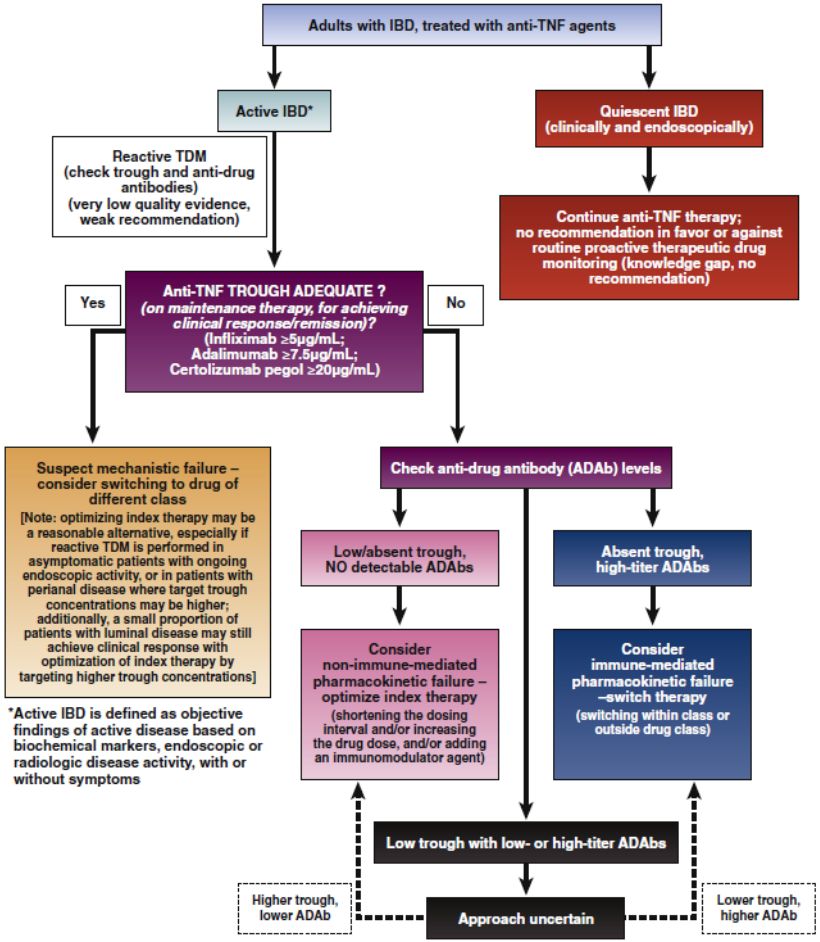
- **Auto-AC (ATI-ATADA)**
- Sexe
- Sévérité de l’inflammation
- Albumine
- CRP
- Poids
- Immunosuppresseurs concomitants



Rosen MJ et al. APT 2015; 41: 1094–1103

Therapeutic Drug Monitoring in Inflammatory Bowel Disease

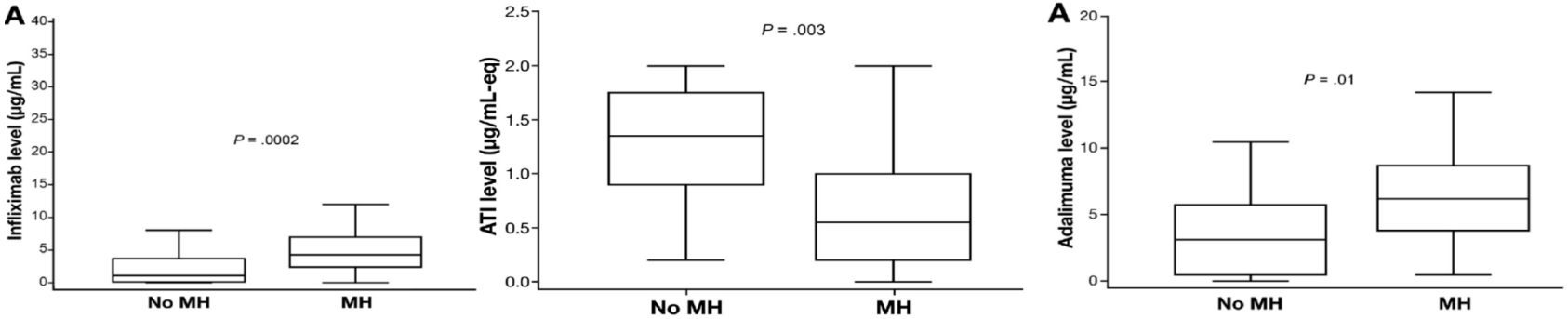
Clinical Decision Support Tool

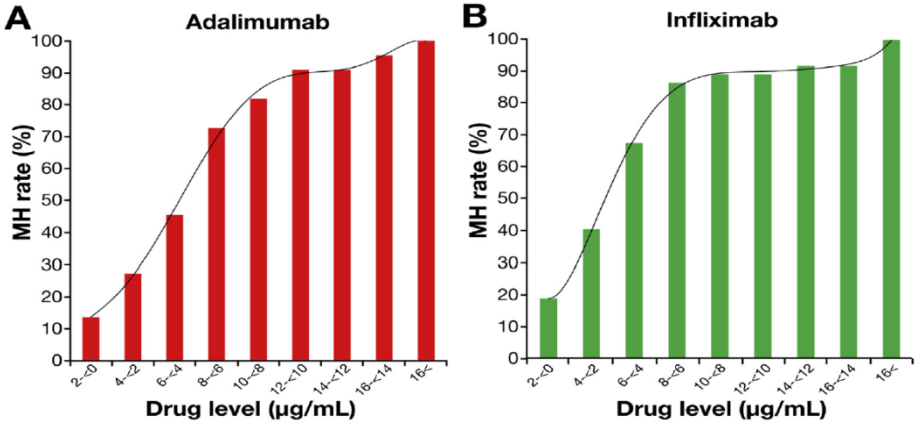


Gastroenterology 2017;153:858-59

Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases

Bella Ungar,* Idan Levy,* Yarden Yavne,* Miri Yavzori,* Orit Picard,* Ella Fudim,* Ronen Loebstein,‡ Yehuda Chowers,§ Rami Eliakim,* Uri Kopylov,* and Shomron Ben-Horin*



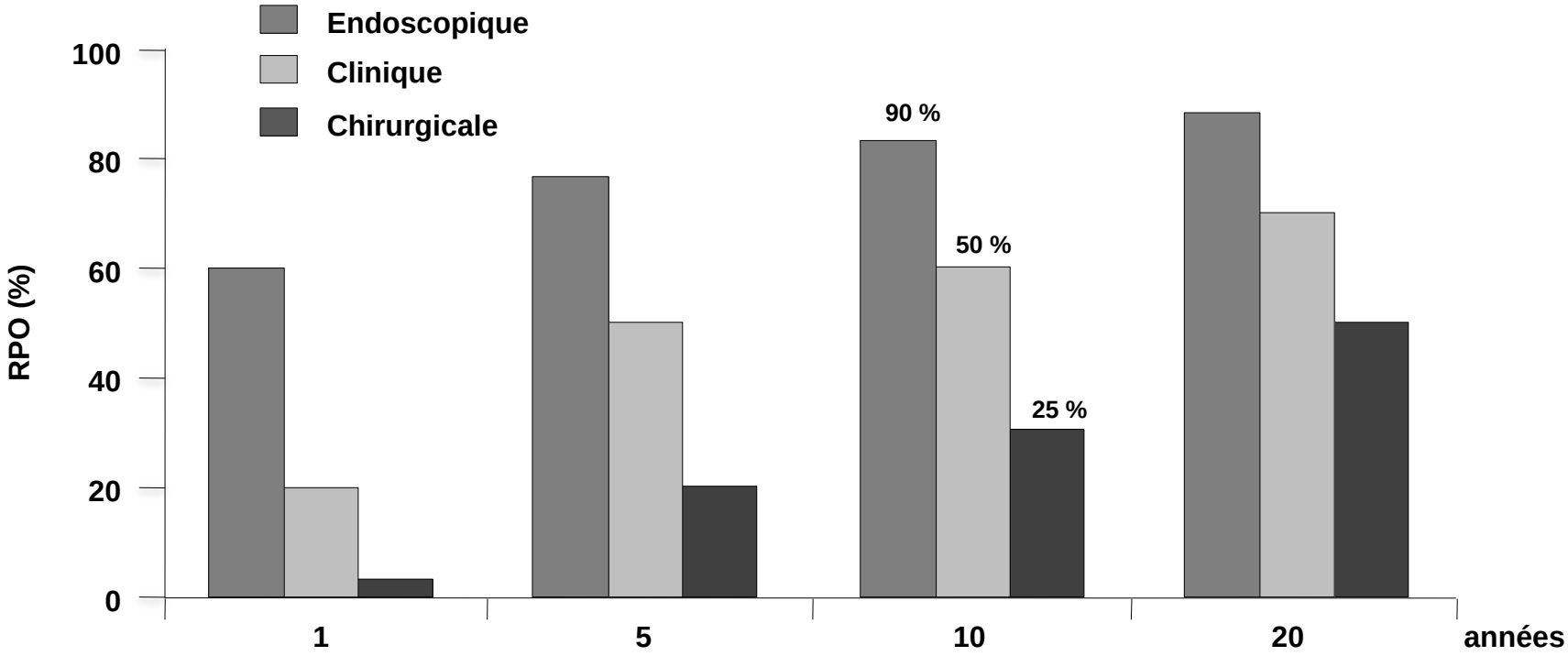


MH: mucosal healing

CGH 2016; 14:550-557

Ne pas laisser passer le temps de la chirurgie
Collaboration médico-chirurgicale +++

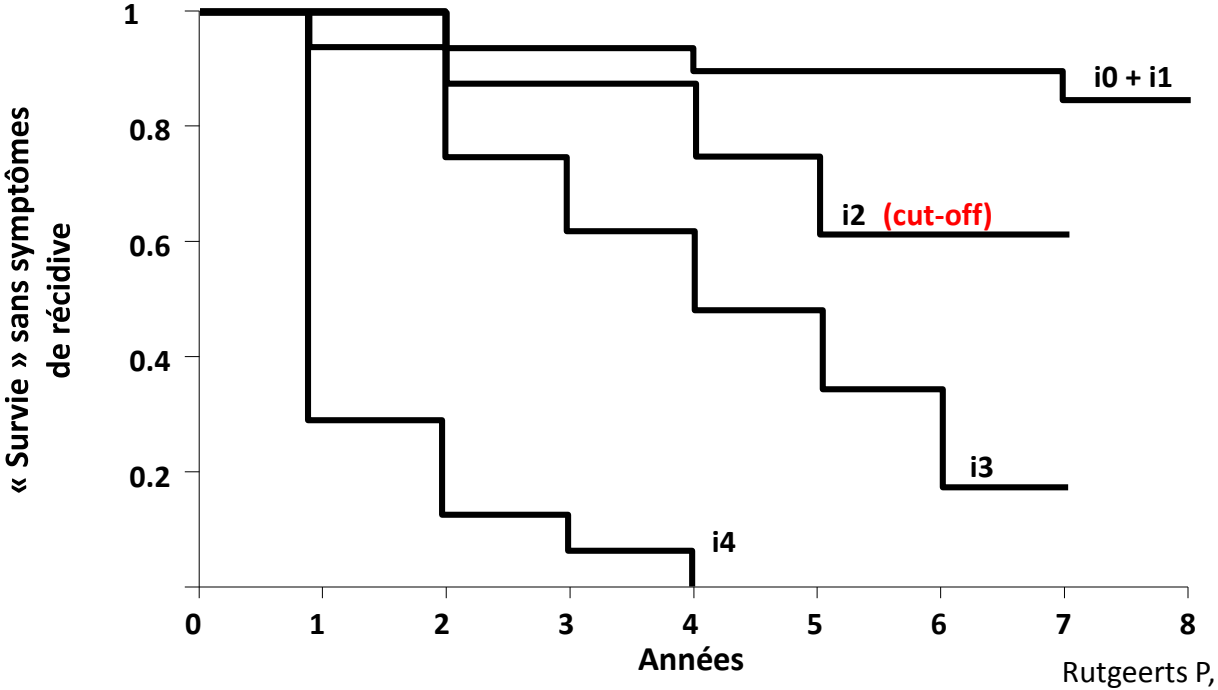
RPO : clinique-endoscopique-chirurgicale

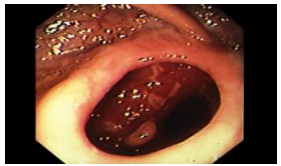


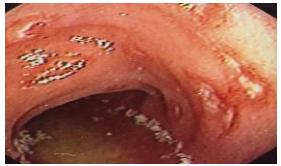
Nos P et al. World J Gastroenterol 2008;14:5540-8

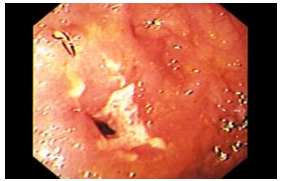
Intérêt prédictif du score de Rutgeerts

i0	Absence de lésions
i1	Ulcérations iléales aphtoïdes peu nombreuses (= 5)
i2	Ulcérations aphtoïdes multiples (> 5) avec muqueuse intercalaire normale ou zones isolées de lésions plus larges ou lésions confinées à l'anastomoses (sur moins de 1 cm de long)
i3	Iléite aphtoïde diffuse avec muqueuse intercalaire inflammatoire
i4	Iléite diffuse avec ulcérations plus larges, nodules et/ou sténose



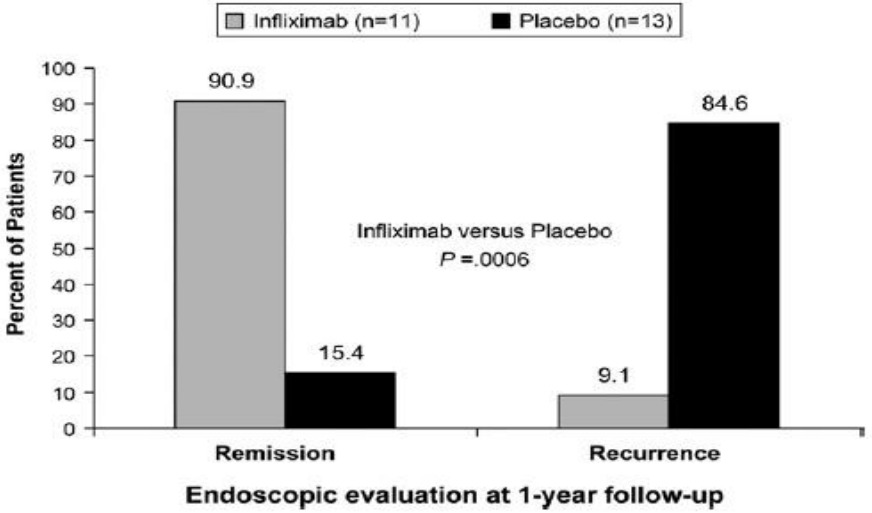


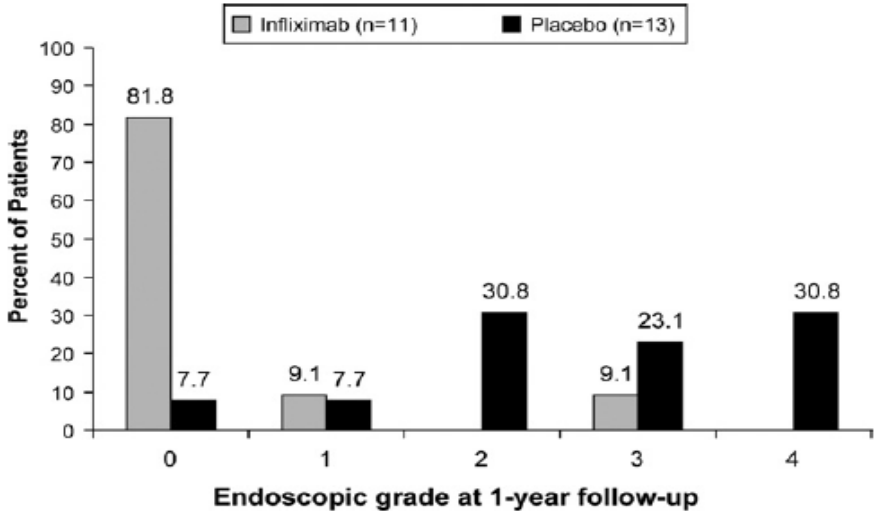




Rutgeerts P, Gastroenterol 1990 ; 99 : 956-63

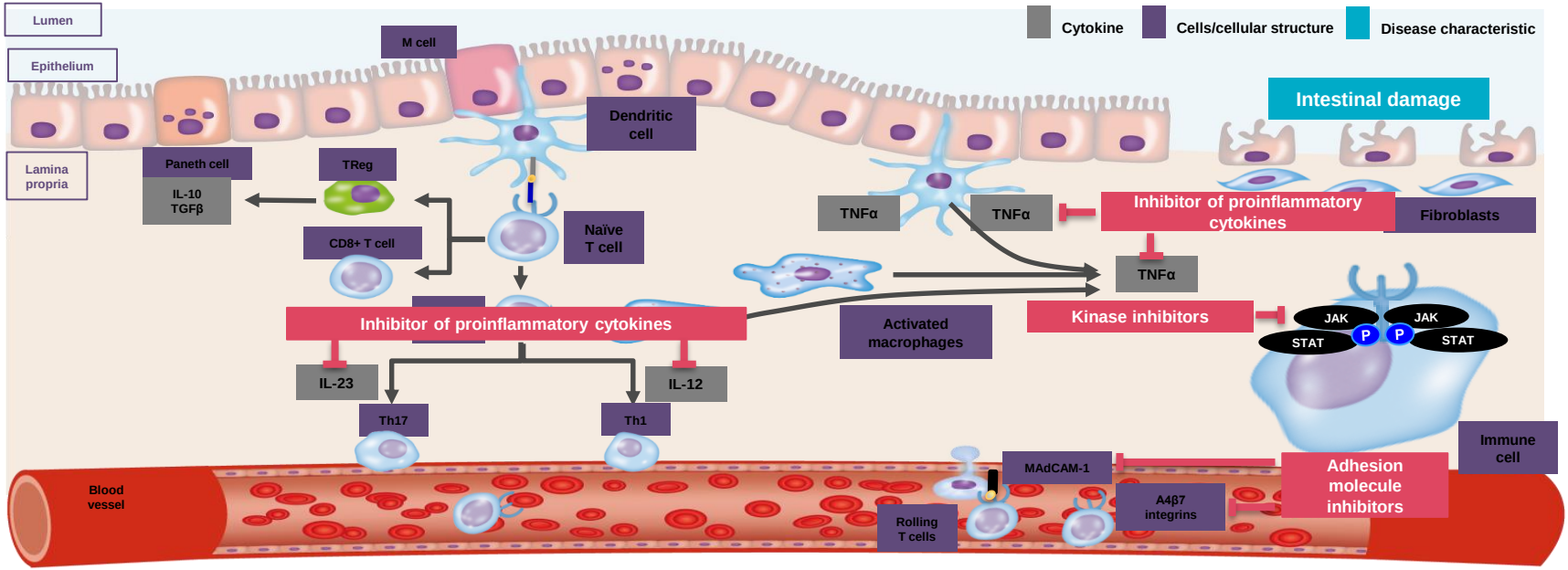
IFX : Prévention récidive post-opératoire après résection iléale





Regueiro M et al. Gastroenterology 2009;136:441–450

Potential sites for biologic inhibition of IBD pathophysiology



IL: interleukin; JAK: Janus kinase; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; STAT: signal transducer and activator of transcription; TGFβ: transforming growth factor-β; TNF, tumour necrosis factor; TReg: regulatory T cell.

Adapted from Danese S, et al. *Nat Rev Gastroenterol Hepatol*. 2015;12:537–45.

Targeting cell activation

Monoclonal antibodies

Target	Compound
TNF	Infliximab Adalimumab
IL12/23 (p40)	Ustekinumab
IL23 (p19)	Rizankizumab
A4β7 / MadCam	Vedolizumab
αEβ7 + α4β7	Etrolizumab
NKG2D	JJ 4500

Small molecules

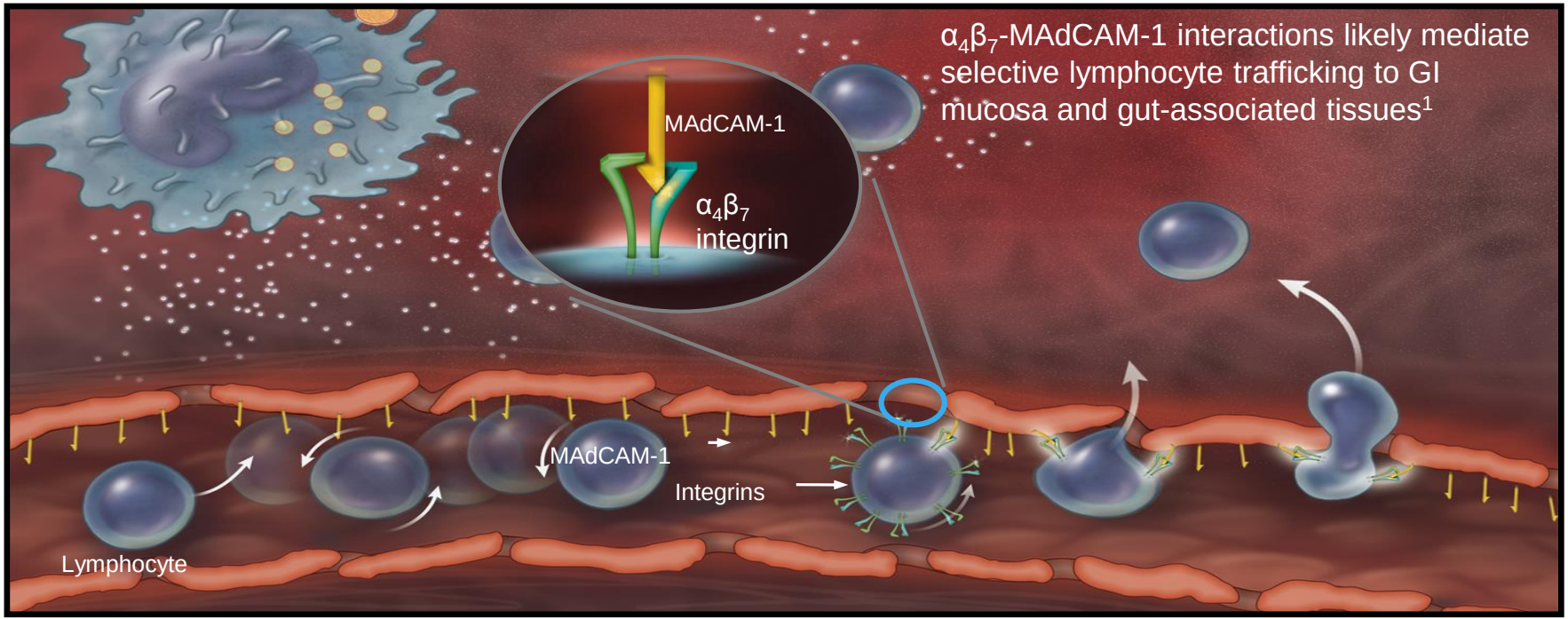
Target	Compound
JAK inhibitor (JAK1/3)	Tofacitinib
JAK 1 inhibitors	Filgotinib Upadacitinib
$S1P_{1R}$	Ozanimod
Smad 7	Mongersen
Phosphodiesterase 4 (PDE4)	Apremilast

UEGW 2017

Vedolizumab : Entyvio®

Mécanisme de l’inflammation intestinale

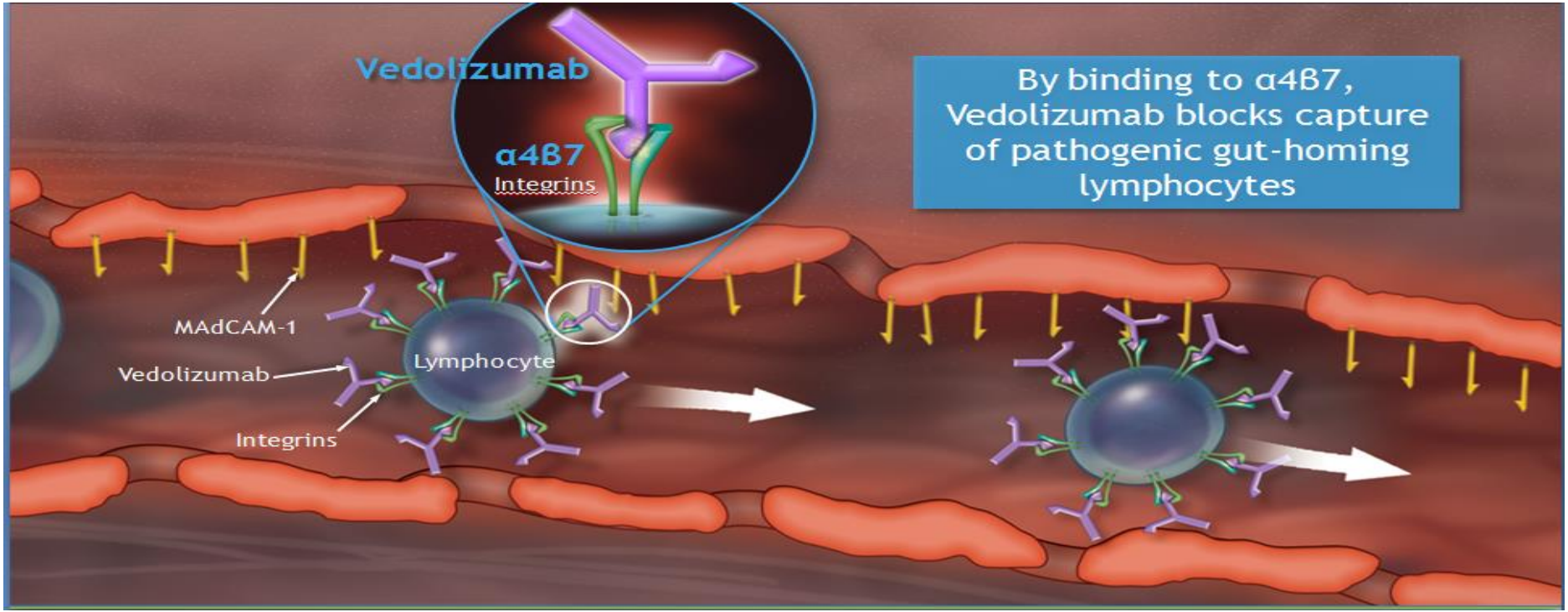
L’intéraction $\alpha_4\beta_7$ integrin/MAdCAM-1 facilite l’inflammation intestinale locale



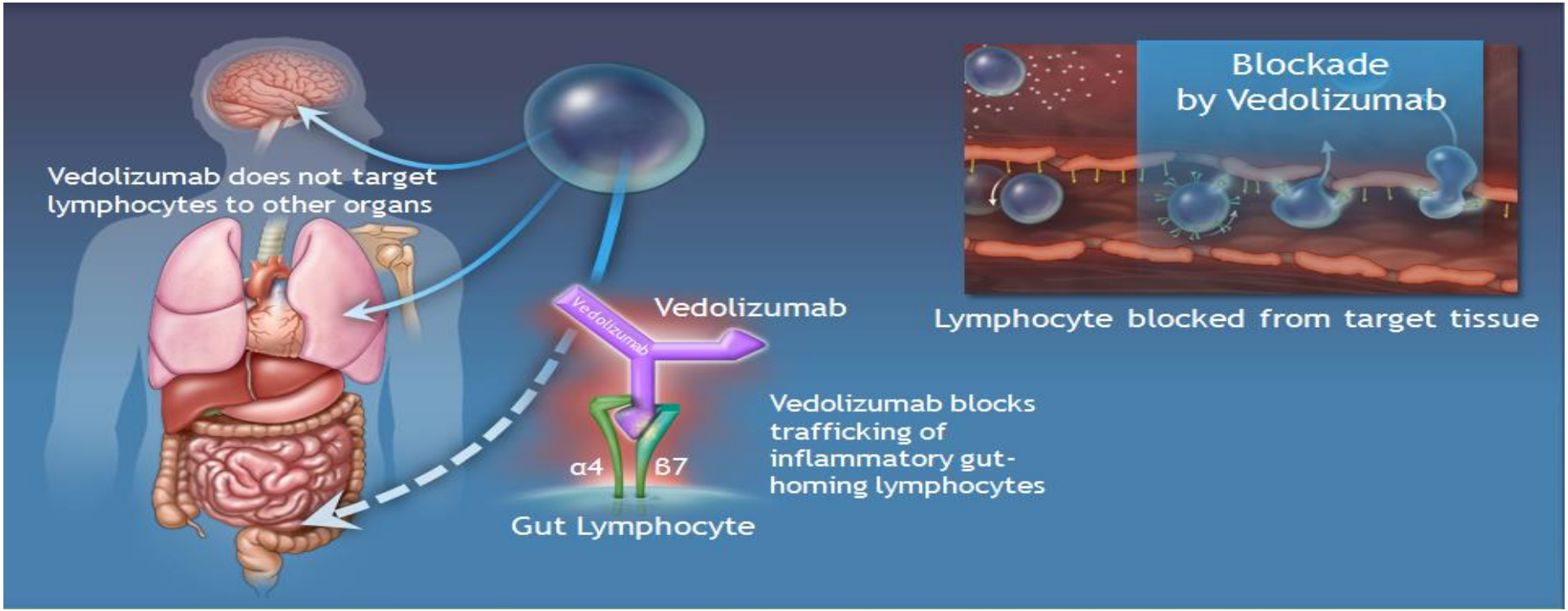
MAdCAM-1: mucosal addressin cell adhesion molecule 1

Briskin M, et al. Am J Pathol 1997;151(1):97–110

Vedolizumab bloque la migration des lymphocytes dans la muqueuse intestinale



Vedolizumab bloque la circulation des lymphocytes vers la muqueuse intestinale



Entyvio® (Vedolizumab) : Indications AMM

Rectocolite hémorragique

- Patients adultes
- Active, modérée à sévère
- Une réponse insuffisante ou une perte de réponse à un traitement conventionnel ou par anti-TNFα
- Ou intolérants à ces traitements

Maladie de Crohn (pas d'AMM en france)

- Patients adultes
- Active, modérée à sévère
- Une réponse insuffisante ou une perte de réponse à un traitement conventionnel ou par anti-TNFα
- Ou intolérants à ces traitements

RCP Entyvio®

Anti-intégrines : Vedolizumab (Entyvio®)

Prix / 300mg:

2961 €

Composition :

- Anticorps humanisé
- Sélectif de l'intestin (anti-intégrine $\alpha 4\ \beta 7$)
- Demi-vie : 25,5 jours

Mode d'administration :

- En IV : HDJ
- Pas de prémédication par hydrocortisone 200mg en systématique.
- Durée de perfusion 30 min + surveillance 2 heures (2 premières perf puis ensuite 1h)

RCUH + MC* quand inefficacité ou intolérance ou CI aux anti-TNF

Posologies :

So : 300mg

S2 : 300 mg

S6 : 300mg puis toutes les 8S

Evaluation à S10

possibilité d'optimisation à toutes les 4 semaines

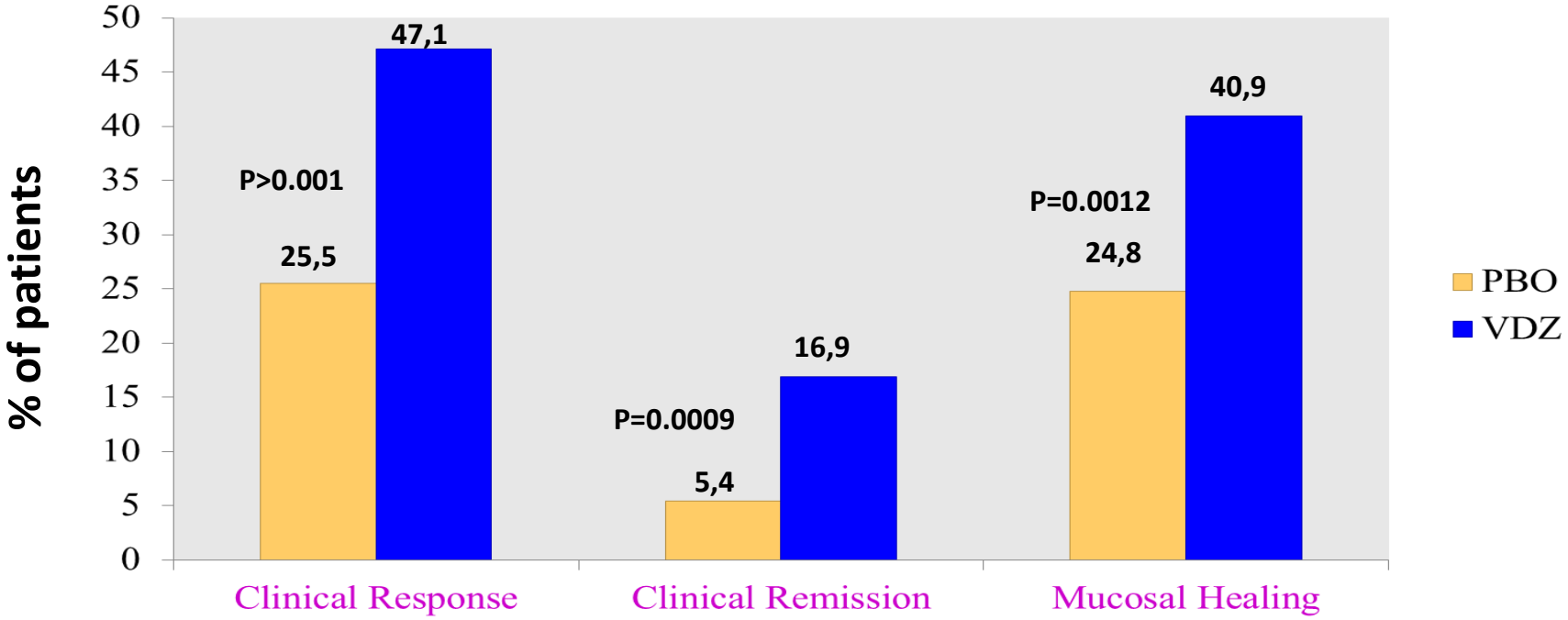
*Pas d'AMM en france

à conserver au frigo

Védolizumab pour l'induction de la remission dans la RCH

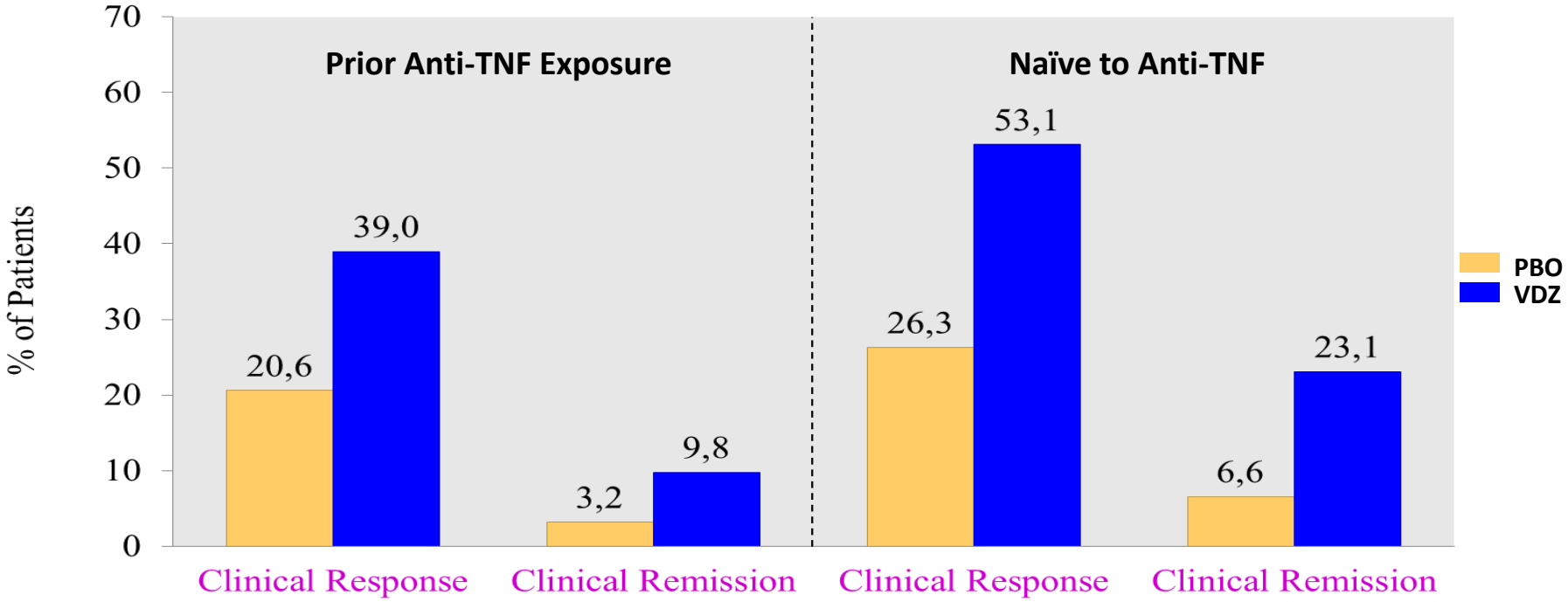
(GEMINI I, Phase III)

Primary endpoint: Clinical response at Week 6



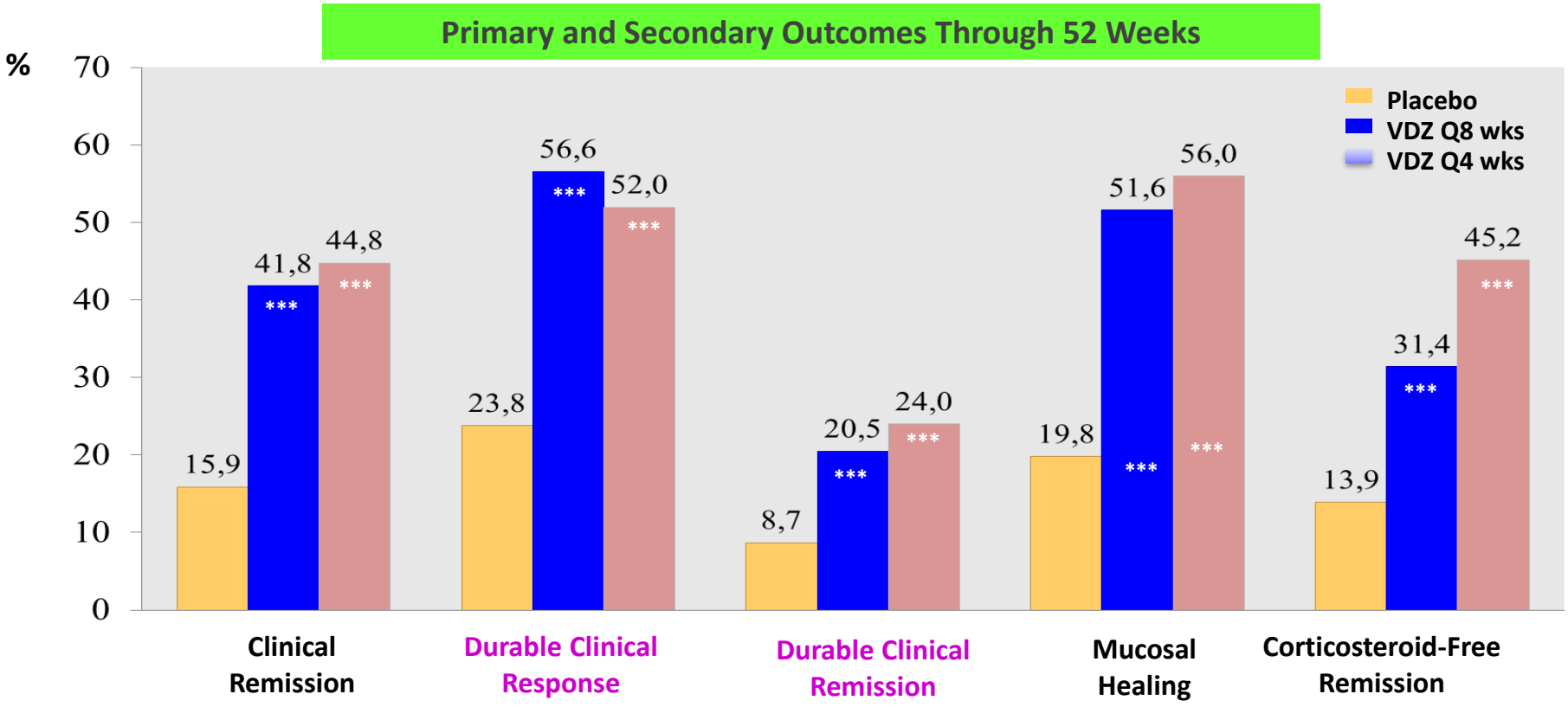
Feagan BG, et al. N Engl J Med 2013

Védolizumab pour l'induction de la remission dans la RCH



Feagan BG, et al. N Engl J Med 2013

Védolizumab pour le maintien de la remission dans la RCH



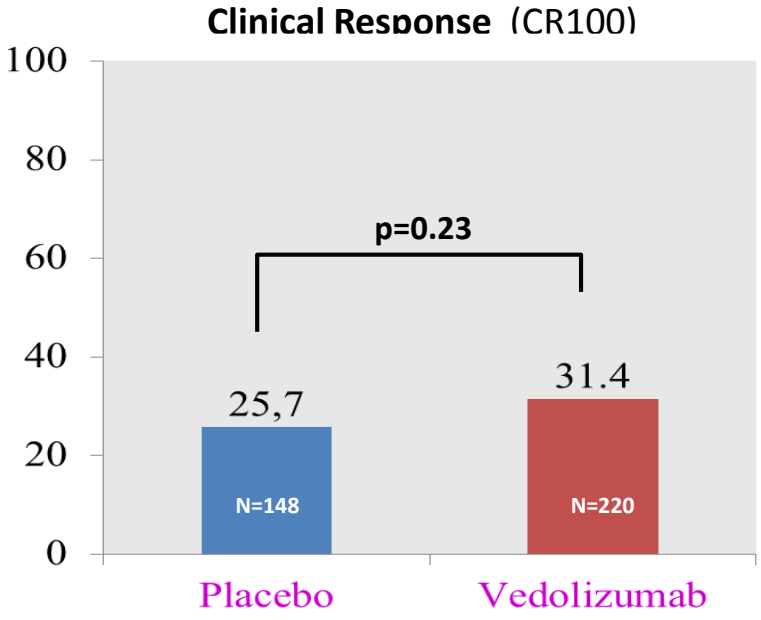
*** p<0.001

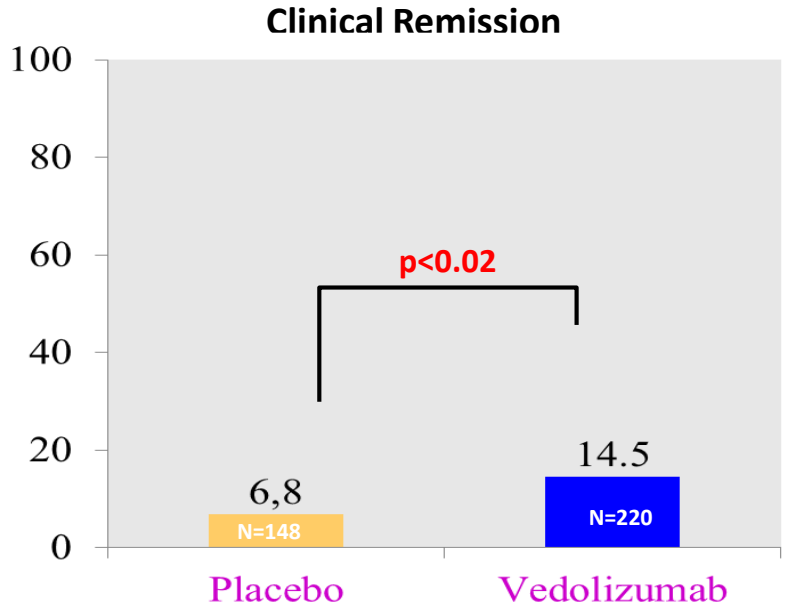
Feagan BG, et al. N Engl J Med 2013

Védolizumab pour l'induction de la remission dans la MC

GEMINI II, Phase III

Primary endpoint: Clinical Response at Week 6

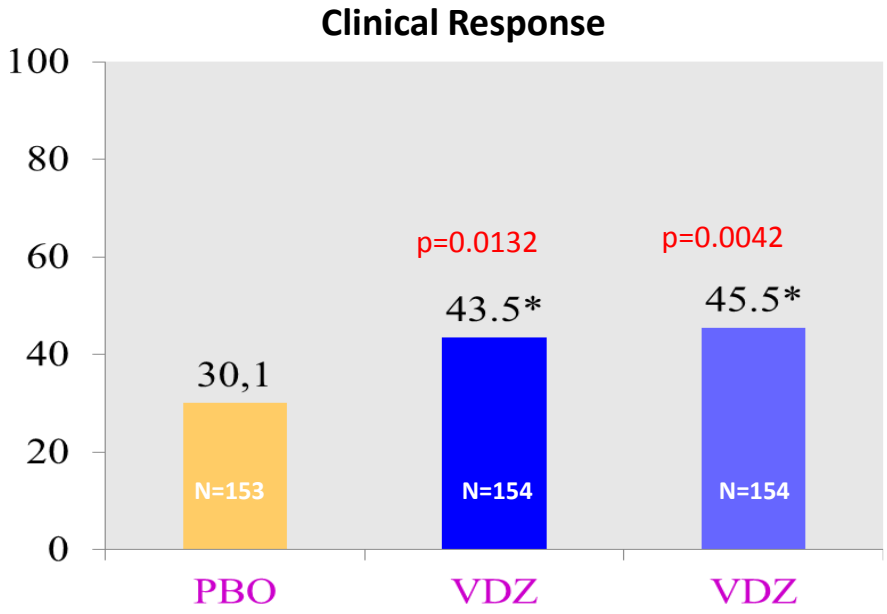


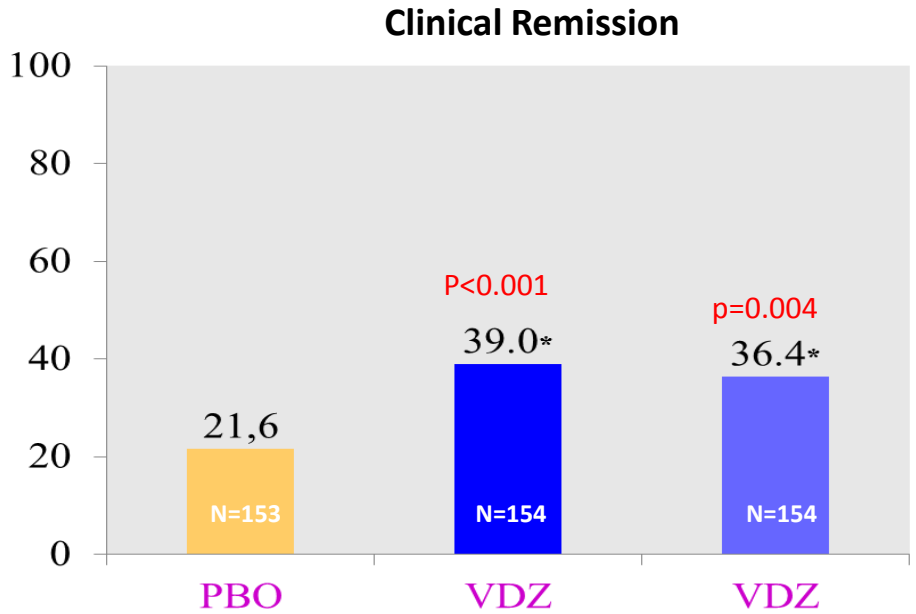


Sandborn WJ et al. N Engl J Med 2013

Védolizumab pour le maintien de la remission dans la MC

Primary and Secondary Outcomes Through 52 Weeks





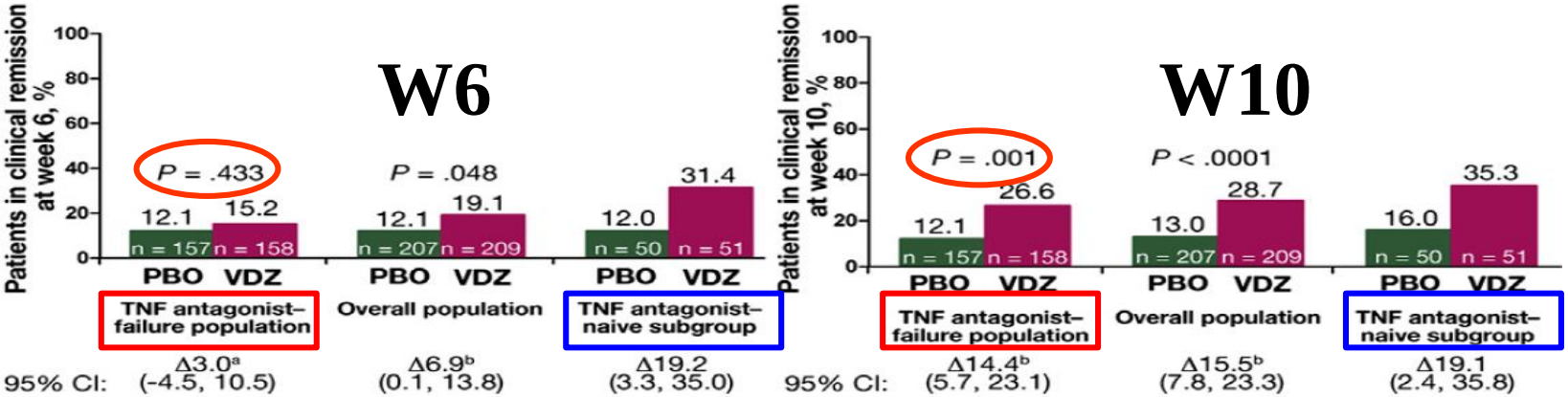
Placebo
VDZ Q8 wks
VDZ Q4 wks

Sandborn WJ et al. N Engl J Med 2013

Gastroenterology 2014;147:618–627

Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed

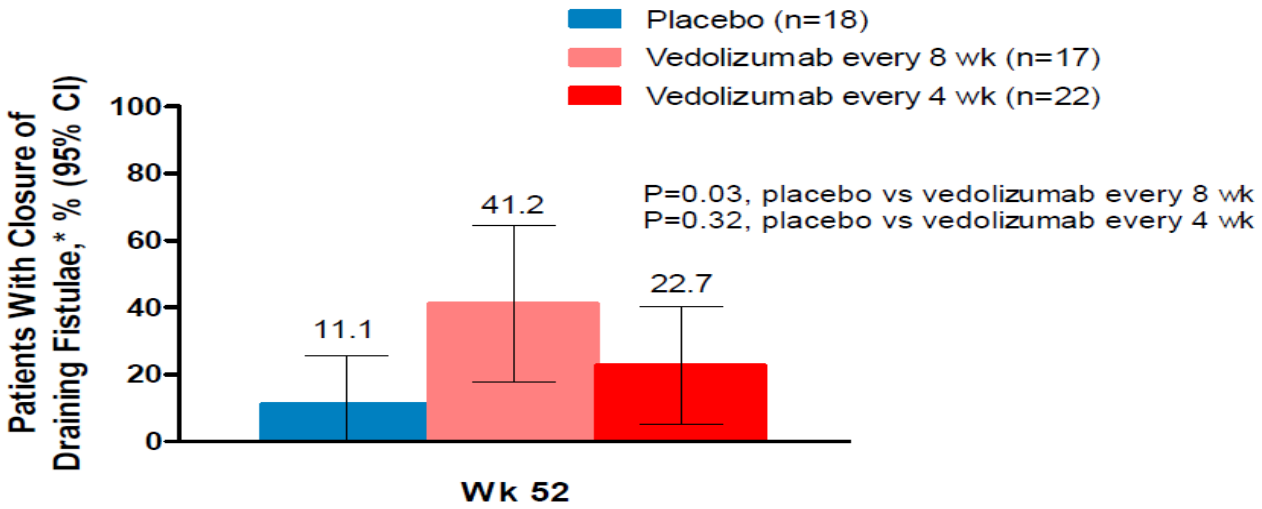
Bruce E. Sands,[1] Brian G. Feagan,[2] Paul Rutgeerts,[3] Jean-Frédéric Colombel,[1,4] William J. Sandborn,[5] Richmond Sy,[6] Geert D'Haens,[7] Shomron Ben-Horin,[8] Jing Xu,[9] Maria Rosario,[9] Irving Fox,[9] Asit Parikh,[10] Catherine Milch,[9] and Stephen Hanauer[11]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

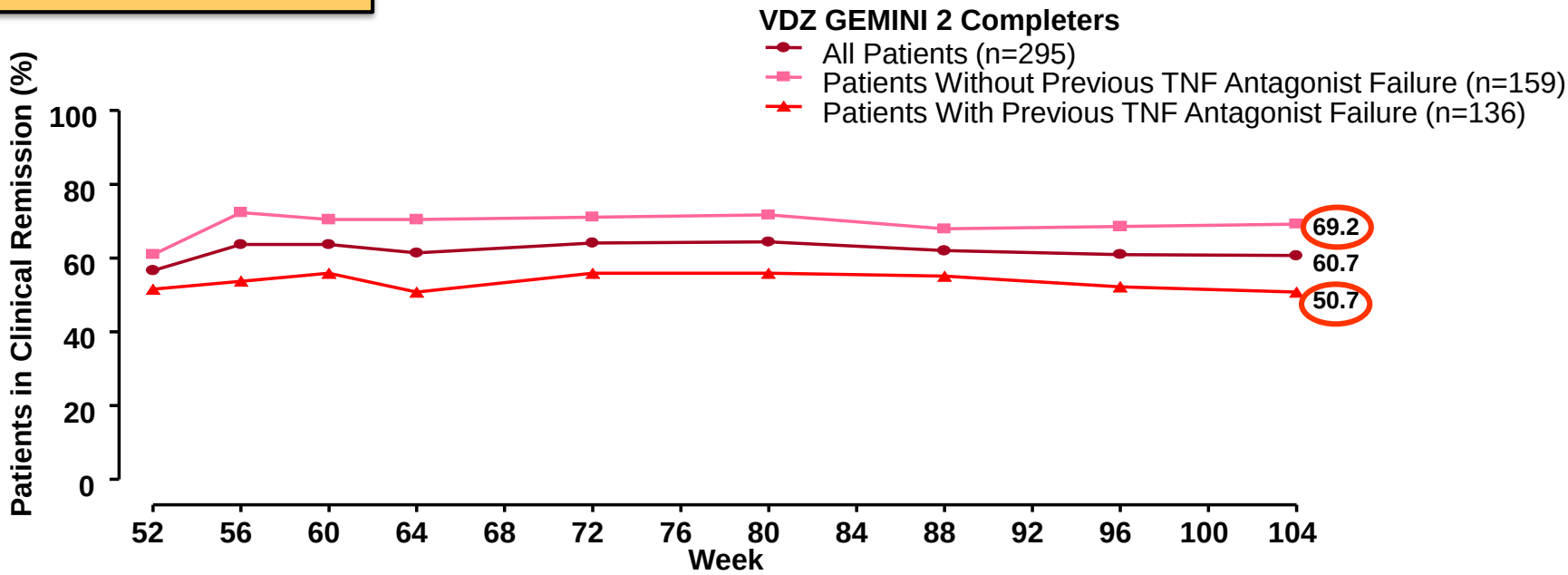
Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease



Long-term Efficacy of Vedolizumab for CD
Efficacy: Clinical Remission

GEMINI LTS
(Open-label VDZ 300 mg Q4W)

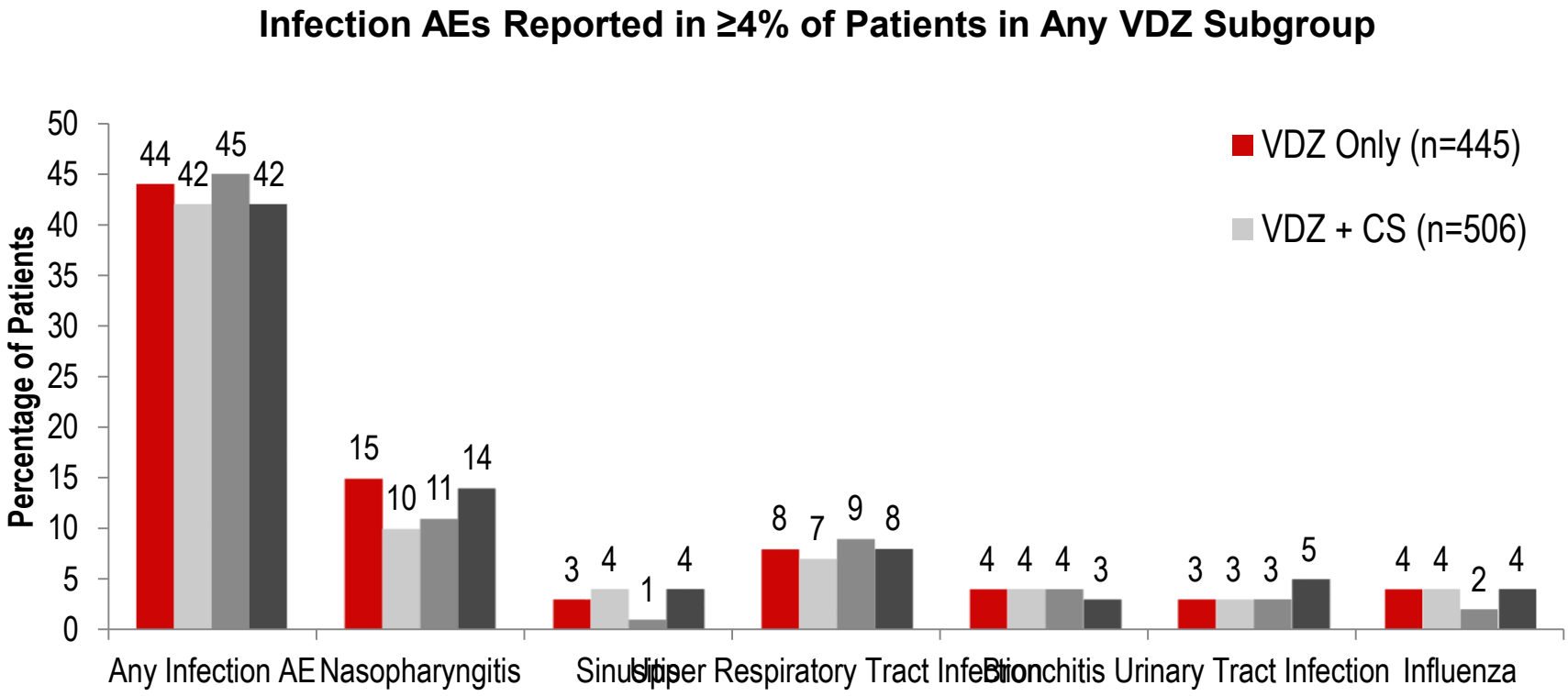
Clinical Remission Over Time



Clinical remission = an HBI score of ≤4 points

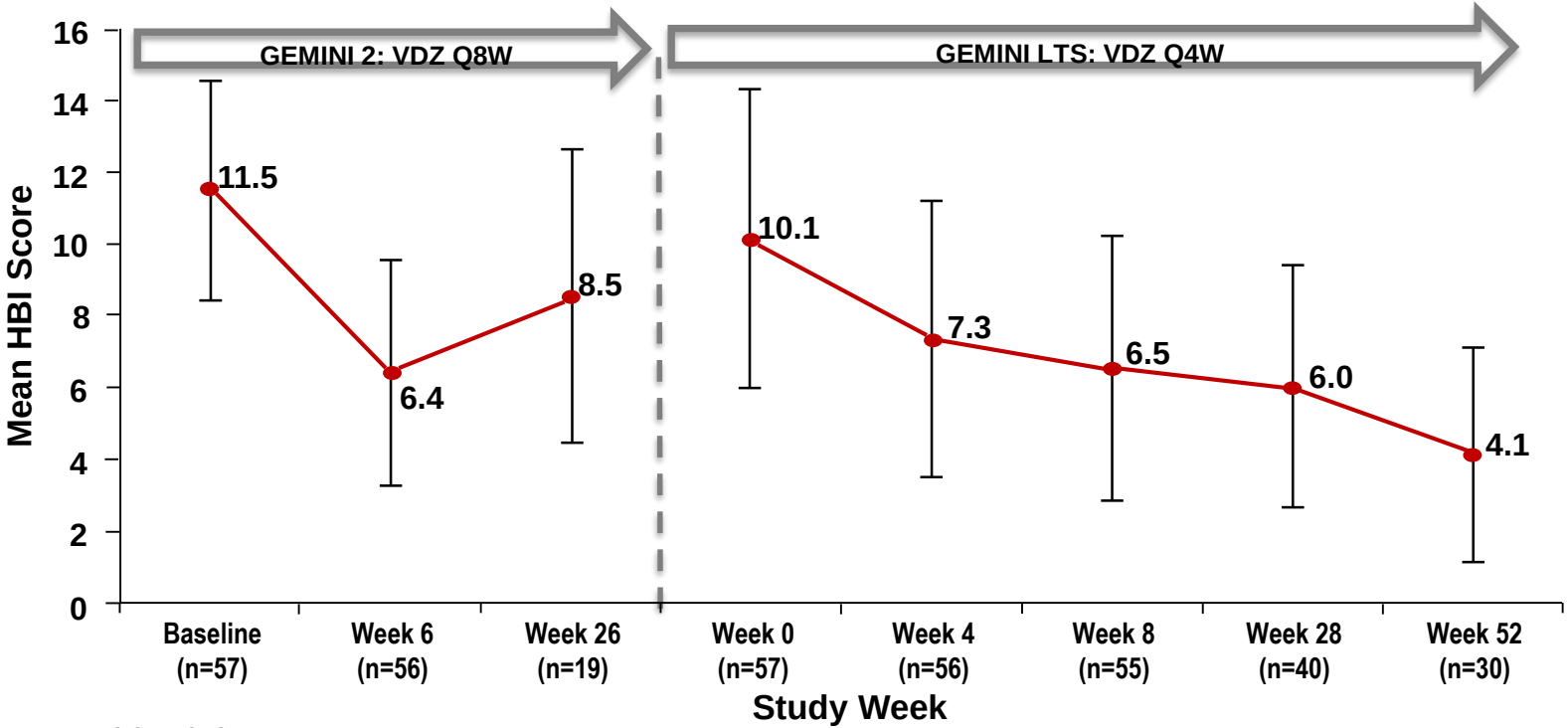
Hanauer et al. Am J Gastroenterol 2014; 109 (Suppl 2): S479. Abstract 1619

Safety of Vedolizumab Alone or With Concomitant Meds in UC or CD: Infection AEs (Pooled Data From GEMINI 1&2)



Loftus E et al. Am J Gastroenterol 2014; 109 (Suppl 2): S478. Abstract 1617

Effects of Increased Vedolizumab Dosing Frequency on Disease Activity in CD: Mean HBI Scores

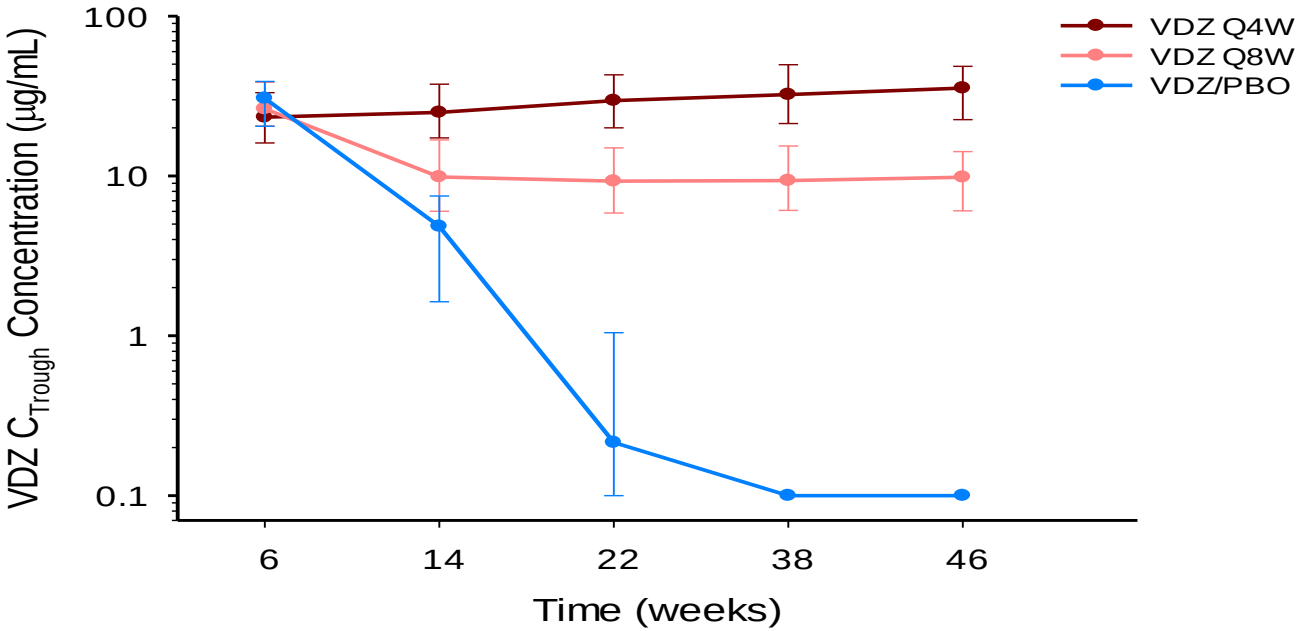


HBI = Harvey-Bradshaw index.
Data are presented for the efficacy population (n=57), which included patients with at least 1 post-baseline efficacy assessment.

Sands et al. Am J Gastroenterol 2014; 109 (Suppl 2): S478-S479. Abstract 1618

GEMINI I: Vedolizumab in Ulcerative Colitis
Vedolizumab Trough Levels ≥ 10 µg/mL for Both Q4W and Q8W

Vedolizumab Mean (SD) C_{trough}–Time Profiles in Patients With UC (n=654)

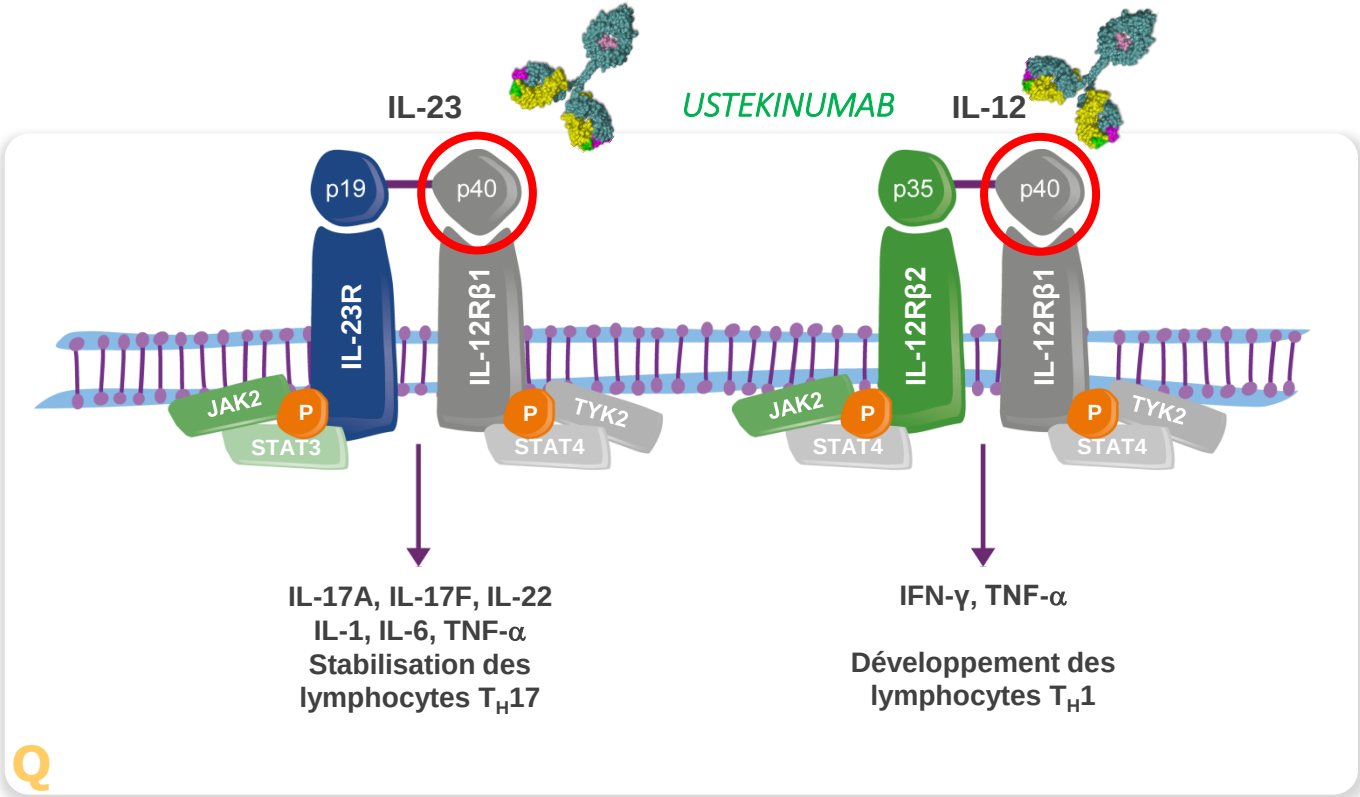


PBO= placebo; VDZ = vedolizumab; Q4W = every 4 weeks,; Q8W = every 8 weeks

Adapted from: Rosario M et al. CCFA Meeting Dec 2013: P140

Anti IL-12/23
Ustekinumab : Stellara®

Comment agit l'Ustekinumab ?



JAK : Janus Kinase
STAT : Signal Transducer and Activator of Transcription
TYK : Tyrosine Kinase

Teng M. Nature Medicine. 2015 ; 21, 7 : 719-729.

- **AMM Européenne – 11 novembre 2016**

L'ustekinumab est indiqué dans le traitement de la maladie de Crohn active modérée à sévère chez les patients adultes présentant une réponse insuffisante, une perte de réponse ou une intolérance à un traitement conventionnel ou par anti-TNFα, ou qui présentent une contre-indication médicale à ces traitements.

SMR	important chez les patients en échec (réponse insuffisante, perte de réponse ou intolérance) d'un traitement conventionnel (corticoïdes ou immunosuppresseurs) et d'au moins un anti-TNF ou ayant des contre-indications à ces traitements

HAUTE AUTORITÉ DE SANTÉ

30 septembre 2017 JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE Texte 165 sur 182

Avis et communications

AVIS DIVERS

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Avis relatif aux prix de spécialités pharmaceutiques publiés en application de l'article L. 162-16-6 du code de la sécurité sociale

NOR : *SSAS1727004V*

En application de la convention entre le comité économique des produits de santé et la société JANSSEN-CILAG et en application de l'article L. 162-16-6 du code de la sécurité sociale, le tarif de responsabilité de la spécialité mentionnée ci-dessous, et figurant sur la liste prévue à l'article L. 162-22-7 du même code, est celui figurant dans le tableau ci-après majoré de la TVA :

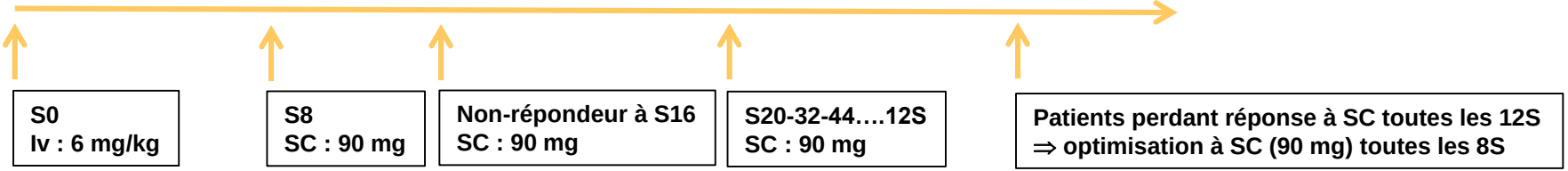
Code UCD	Libellé	Laboratoire exploitant	Prix de vente HT par UCD aux établissements de santé (en €)
34008 942 502 0 3	STELARA 130 mg (ustekinumab), solution à diluer pour perfusion	JANSSEN-CILAG	2308,620

2308,620 E

JO du 30 septembre 2017

Ustekinumab : Pharmacocinétique

- IV ou SC : ½ vie de 3 semaines
- Après SC : concentration sérique la plus élevée à 7-14 jours
- Profil pharmacocinétique comparable en dermatologie, rhumatologie, gastroentérologie
- Pas d'interaction médicamenteuse significative décrite



Programme de développement clinique de l'ustekinumab dans la maladie de Crohn

Programme UNITI – Phase 3 - 2 études d'induction

UNITI-1 : Echec sous anti-TNF (n=741)

- Placebo IV (N=247)*
- Stelara® 130 mg IV (N=245)*
- Stelara® ~6 mg/kg IV (N=249)*

UNITI-2 : Echec à traitement conventionnel: GC ou IM (n=628)

- Stelara® 130 mg IV (N=209)*
- Stelara® ~6 mg/kg IV (N=209)*
- Placebo IV (N=209)*

Une étude de maintenance

IM-UNITI
Etude de maintenance randomisée

Répondeurs

- 90 mg SC / 8 sem
- 90 mg SC / 12 sem
- Placebo SC

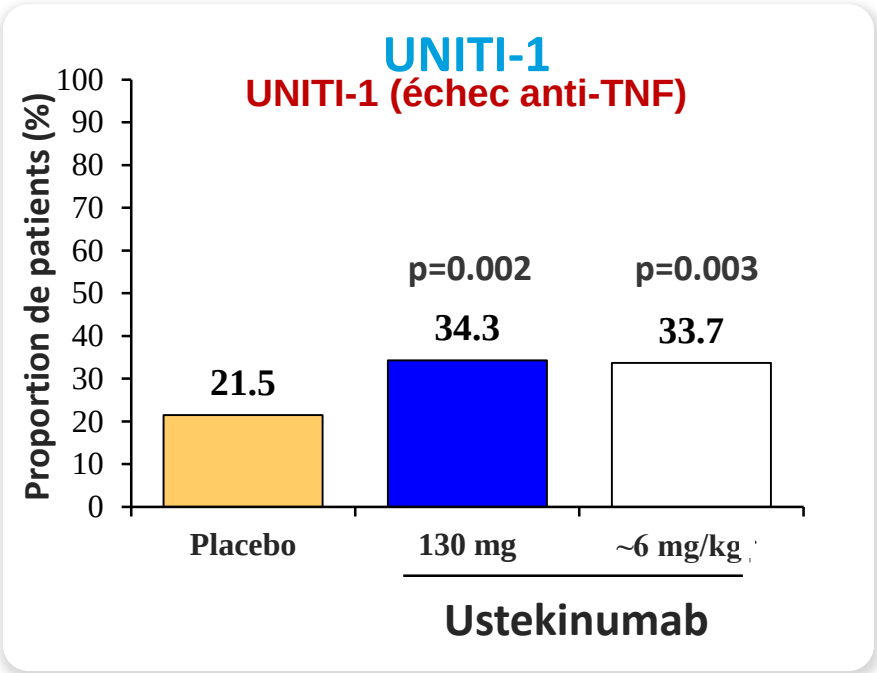
Répondeurs

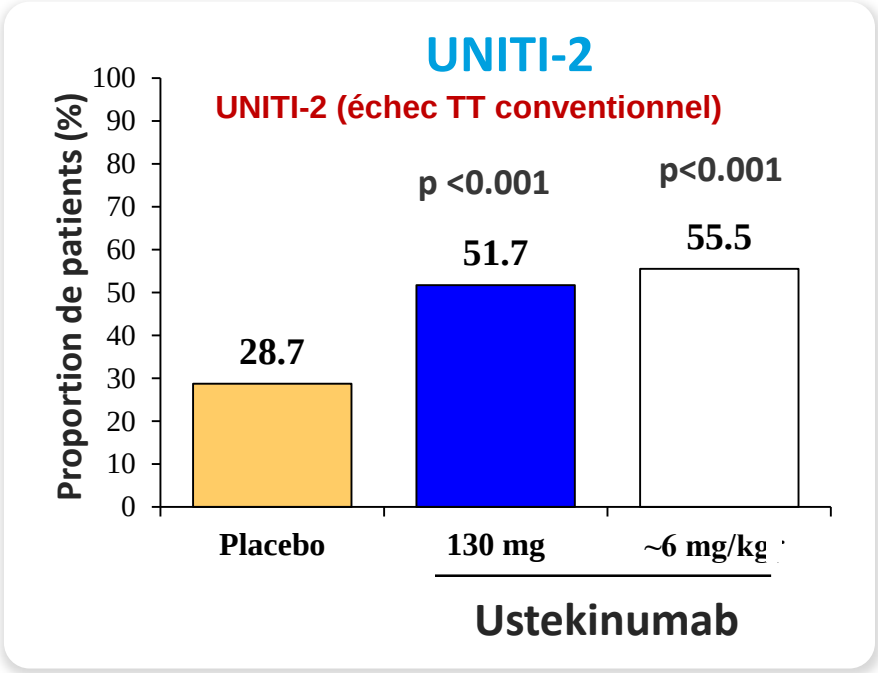
Etude de maintenance sur 44 semaines : suivie par une phase d'extension à long terme (jusqu'à 4 ans)

Adapted from Rutgeerts P, et al. ECCO 2016.Abstract no. OP014

Critère principal : Réponse clinique à la semaine 6

- Diminution ≥ 100 points du score CDAI* à la semaine 6

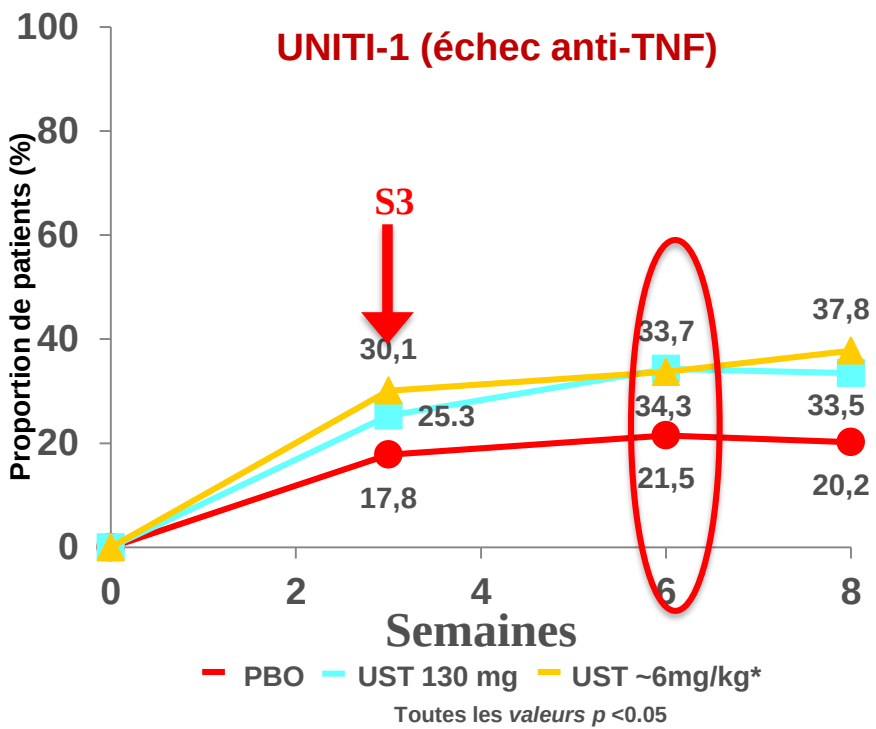




Sandborn WJ, et al. Inflamm Bowel Dis. 2016;22(Suppl 1):S1 ; Feagan B, et al. UEGW 2015 #OP054-LB4

UNITI-1

Quelle proportion de patients répondeurs après une seule injection IV à S6?

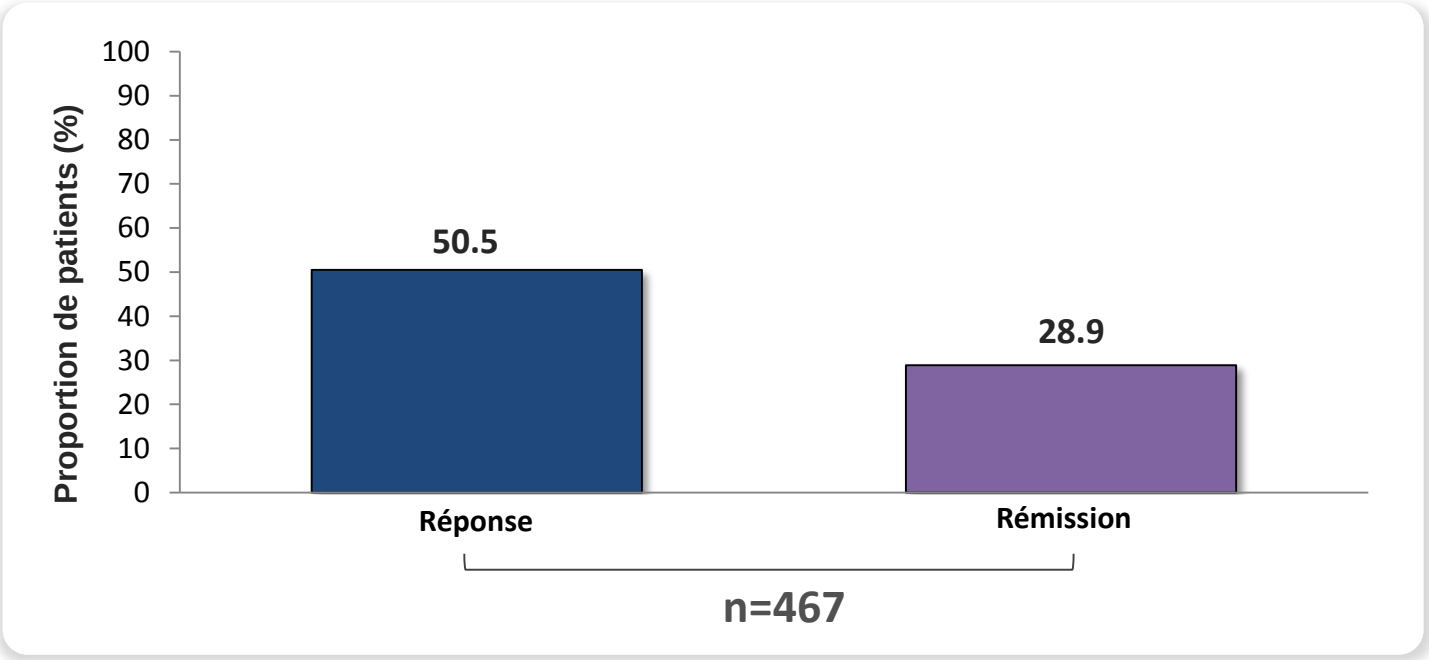


Critère principal

Réponse clinique = diminution du score CDAI d'au moins 100 points

Répondeurs tardifs
Réponse clinique et rémission à la semaine 16
(8 semaines après 1ère dose SC)

- Non répondeurs après induction IV (130 mg ou 6 mg/kg)



Sands B. E., et al. UEGW 2016. Presentation 5.

Programme de développement clinique de l'ustekinumab dans la maladie de Crohn

Programme UNITI – Phase 3 - 2 études d'induction

UNITI-1 : Echec sous anti-TNF

- Placebo IV (N=247)*
- Stelara® 130 mg IV (N=245)*
- Stelara® ~6 mg/kg IV (N=249)*

UNITI-2 : Echec à traitement conventionnel

- Stelara® 130 mg IV (N=209)*
- Stelara® ~6 mg/kg IV (N=209)*
- Placebo IV (N=209)*

Une étude de maintenance

IM-UNITI (n=397)
Etude de maintenance randomisée

Répondeurs

- 90 mg SC / 8 sem
- 90 mg SC / 12 sem
- Placebo SC

Répondeurs

Etude de maintenance sur 44 semaines : suivie par une phase d'extension à long terme (jusqu'à 4 ans)

*** Subjects randomised to placebo and subjects who are non-responders to Stelara are eligible for non-randomised maintenance dosing after completion of the induction study.**

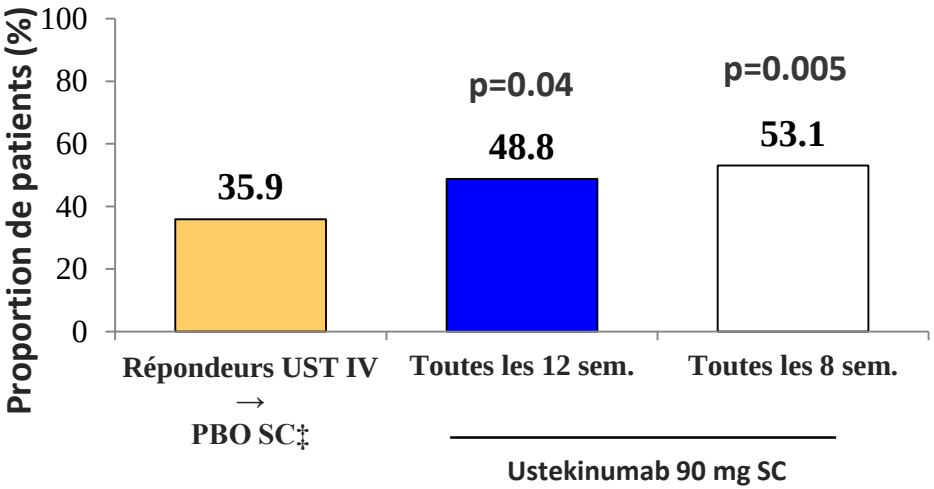
IV: intravenous; SC: subcutaneous; TNF: tumour necrosis factor

Adapted from Rutgeerts P, et al. ECCO 2016.Abstract no. OP014

Réponse clinique et rémission à la semaine 44

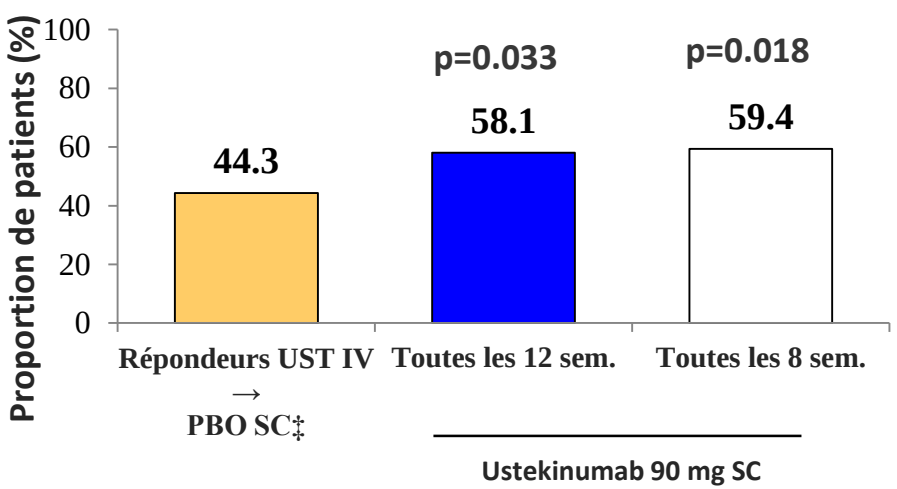
IM-UNITI critère principal :

Score CDAI score <150 à la semaine 44



IM-UNITI critère secondaire majeur :

réponse clinique à la semaine 44

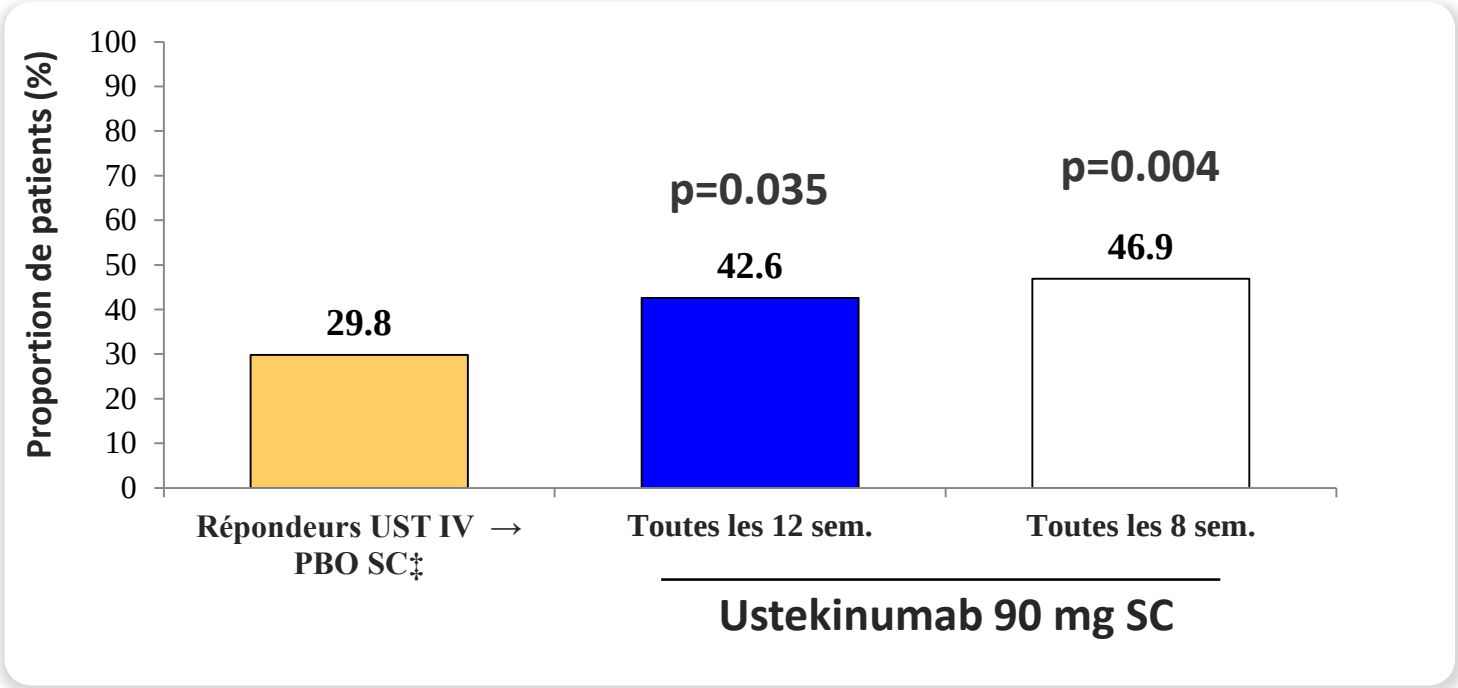


Sandborn W.J., et al. DDW 2016. Presentation 768

Rémission clinique sans corticoïdes à la semaine 44

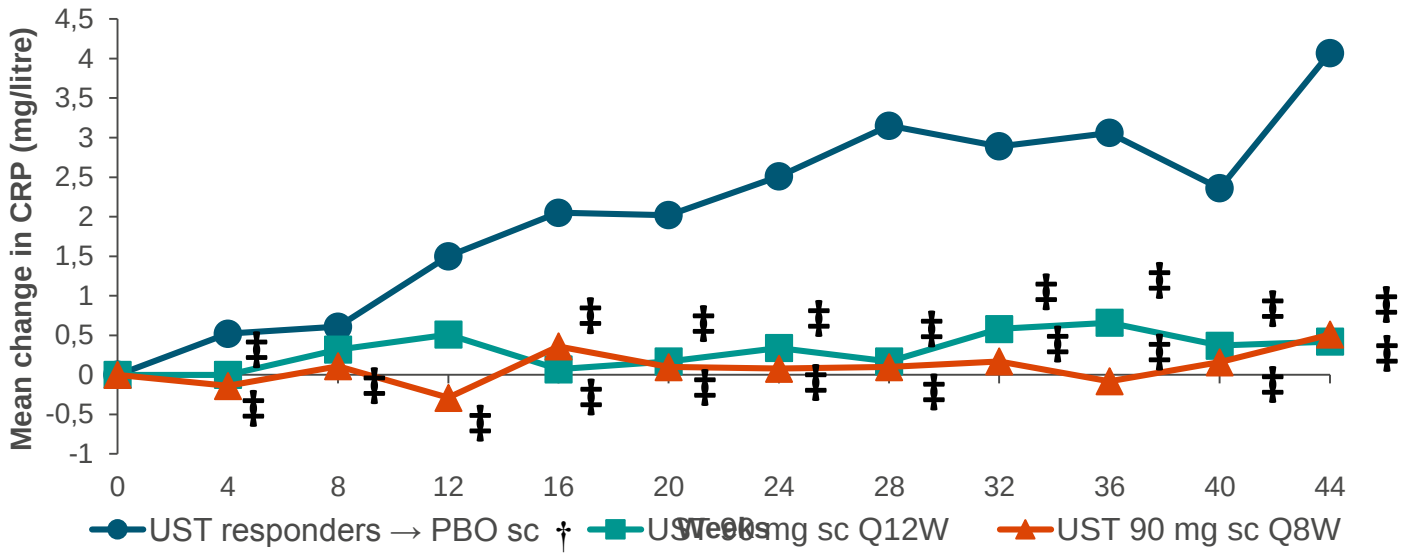
IM-UNITI critère secondaire majeur

Nombre de patients en rémission clinique à la semaine 44 (S44) chez les patients sans corticoïdes à S44



Sandborn W.J., et al. DDW 2016. Presentation 768

Change from baseline in CRP concentration through Week 44*†

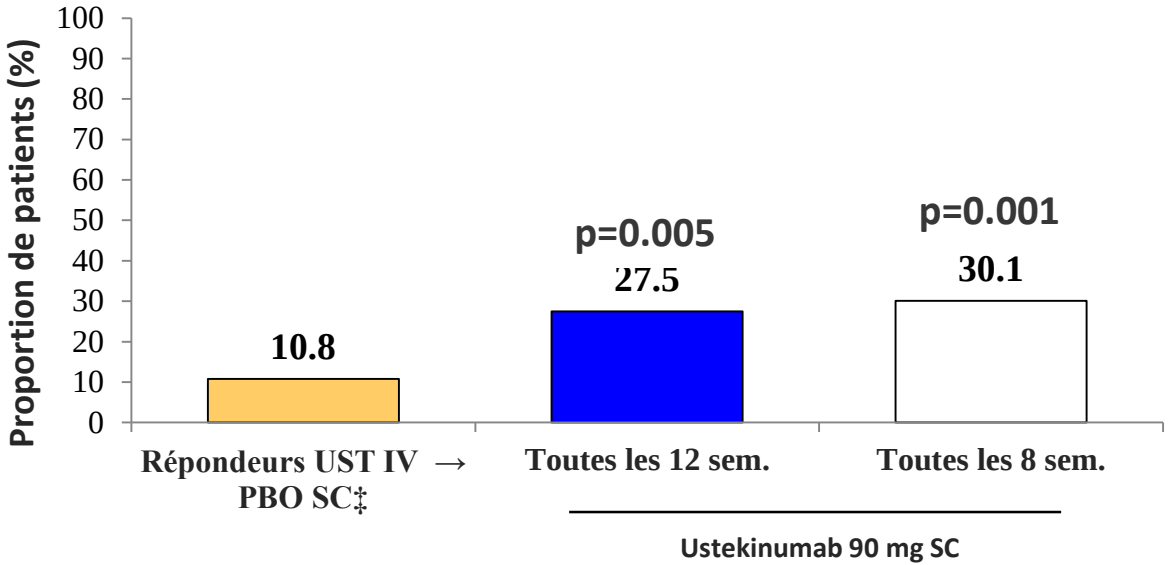


*Subjects who had a prohibited Crohn's disease–related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an AE indicated to be of worsening Crohn's disease prior to the designated analysis time point had their induction baseline value carried forward. †Subjects who had insufficient data at the designated analysis time point had their last value carried forward. ‡$p<0.05$ compared with placebo. ‡Subjects were in clinical response to ustekinumab iv induction dosing and were randomised to placebo sc on entry to this maintenance study.

CRP: C-reactive protein; Q8W: every 8 weeks; Q12W: every 12 weeks; sc, subcutaneously. Feagan BG, et al. *N Engl J Med* 2016;375(20):1946–60.

Taux de calprotectine fécale à la semaine 44

- Calprotectine fécale ≤ 250 mg/kg à la semaine 44



Sandborn W.J., et al. DDW 2016. Presentation 768

Ustekinumab et psoriasis induit par les anti-TNF

- Ustekinumab très efficace dans le traitement des lésions cutanées paradoxales psoriasis-like des anti-TNF[1,2,3]

1. Sanso Sureda A et al. Gastroenterol Hepatol 2011;34(8):546-550
2. Andrisani G et al. 2013;17(20):2831-2836
3. Tillack C et al. Gut 2014;63(4):567-577

Répondeurs à UST IV →	PBO SC induction	UST 90 mg SC q12w	UST 90 mg SC q8w	UST Total
Patients traités randomisés – n	133	132	131	263
Durée moyenne de suivi (semaines)	32.0	36.6	35.2	35.9
Patients avec EI – %	83.5	80.3	81.7	81
Arthralgie	14.3	16.7	13.7	15.2
Maladie de Crohn	14.3	12.1	12.2	12.2
Maux de tête	11.3	11.4	12.2	11.8
Rhinopharyngite	7.5	12.9	10.7	11.8
Douleurs abdominales	12.0	9.8	8.4	9.1
Infection des voies respiratoires sup.	15.8	6.8	9.9	8.4
Pyrexie	7.5	8.3	6.1	7.2
Diarrhée	5.3	8.3	3.8	6.1
Fatigue	4.5	6.1	4.6	5.3
Nausée	6.8	7.6	3.1	5.3
Influenza	3.8	6.1	3.8	4.9
Infection urinaire	2.3	6.1	3.1	4.6
Toux	2.3	3	5.3	4.2
Irritation	3.8	3	5.3	4.2
Vomissement	6.8	3.8	3.1	3.4
Erythème au site d'injection	0	0.8	5.3	3

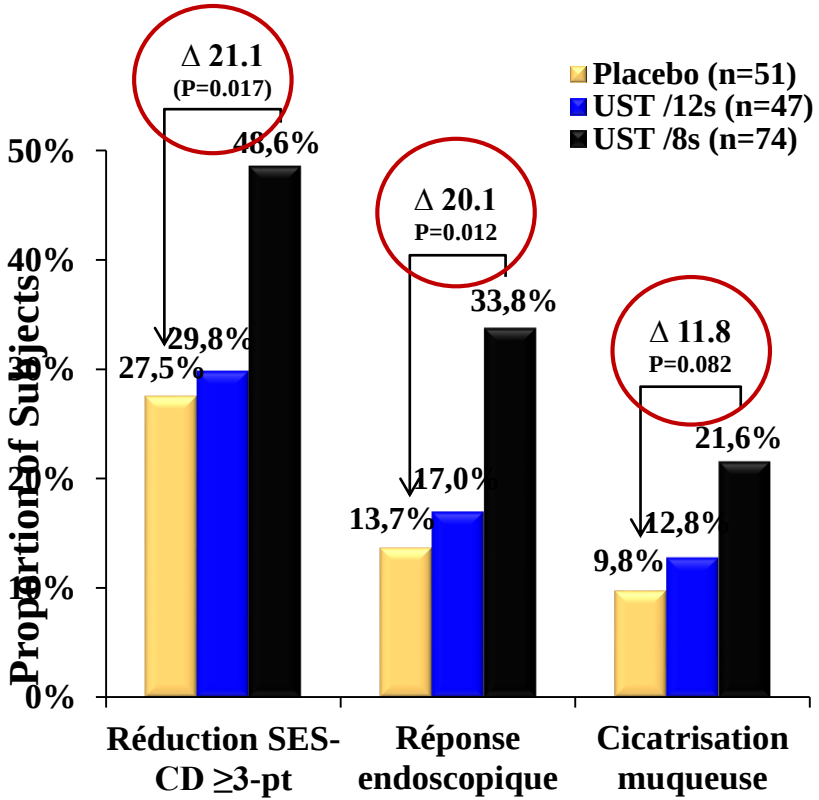
Feagan et al. N Engl J Med 2016;375:1946-60

Quel taux d'immunogénécité à 2 ans ?

- 4.2% (10/237) des patients randomisés et qui entrent dans la phase d'extension à long terme ont développé des anticorps
  - 2.4% (2/82) des patients randomisés à /8s

Feagan et al. ECCO 2017 OP010

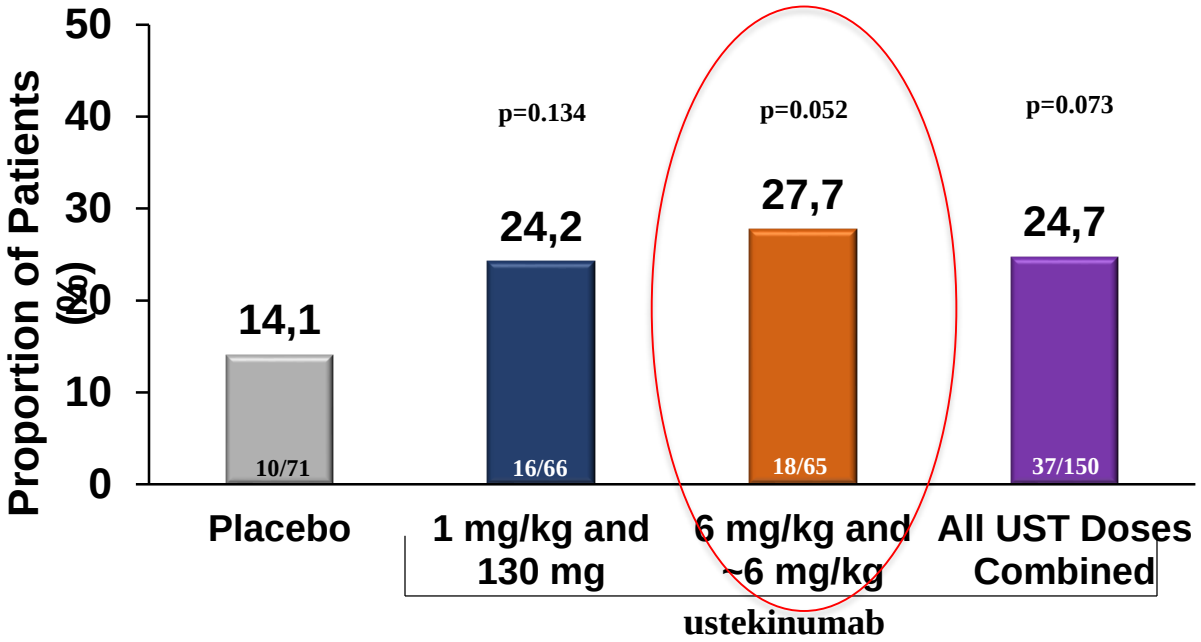
Quels résultats endoscopiques à S44 pour la population poolée IM-UNITI ?



Rutgeerts et al. UEGW 2016. Presentation 104

Données poolées

Pourcentage de résolution des fistules à S8 parmi les patients ayant des fistules drainées à l'inclusion dans CERTIFI, UNITI-1 et UNITI-2

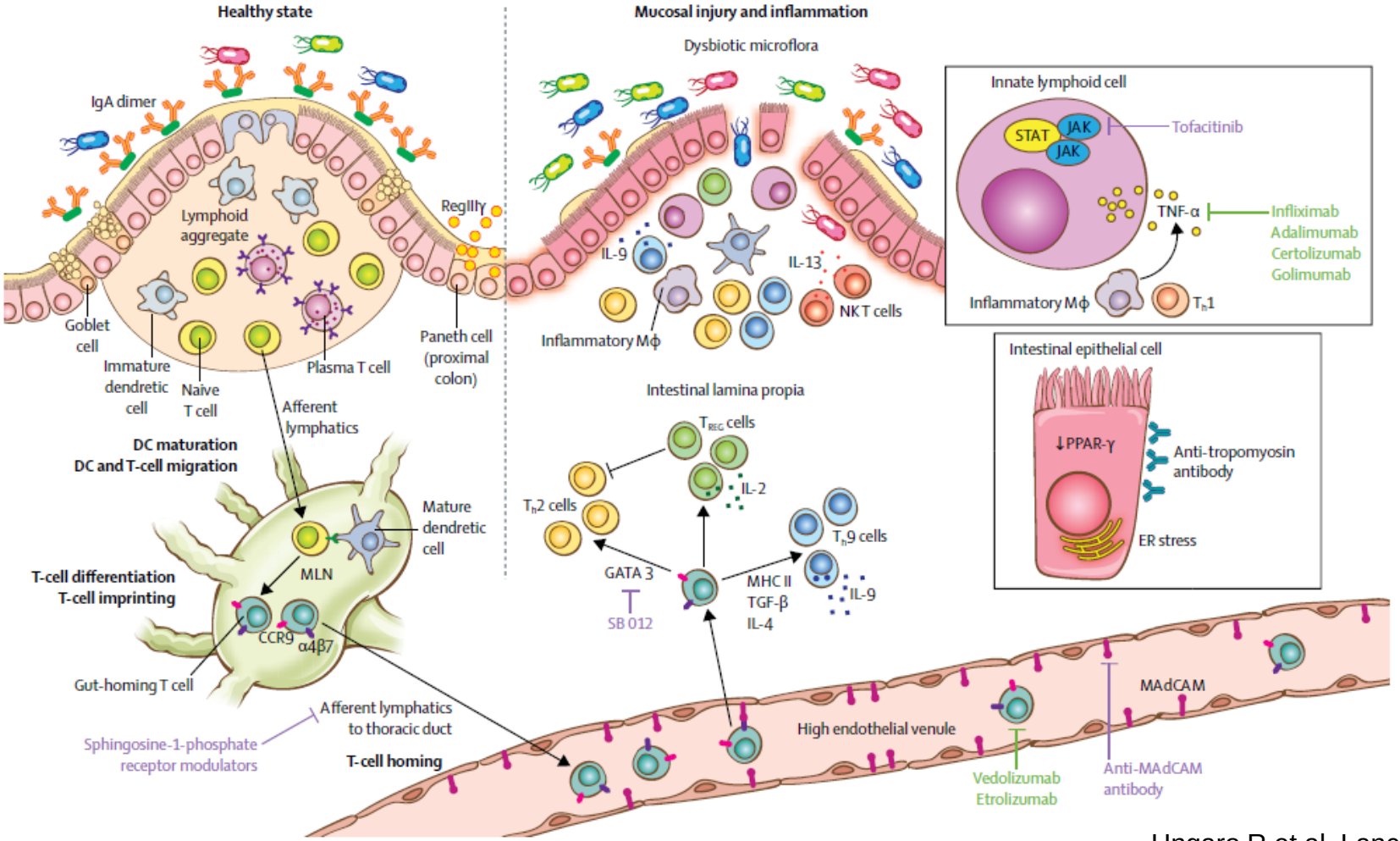


Sands, BE et al., DDW 2017

Ordre d’utilisation des nouveaux biologiques dans la prise en charge des MICI

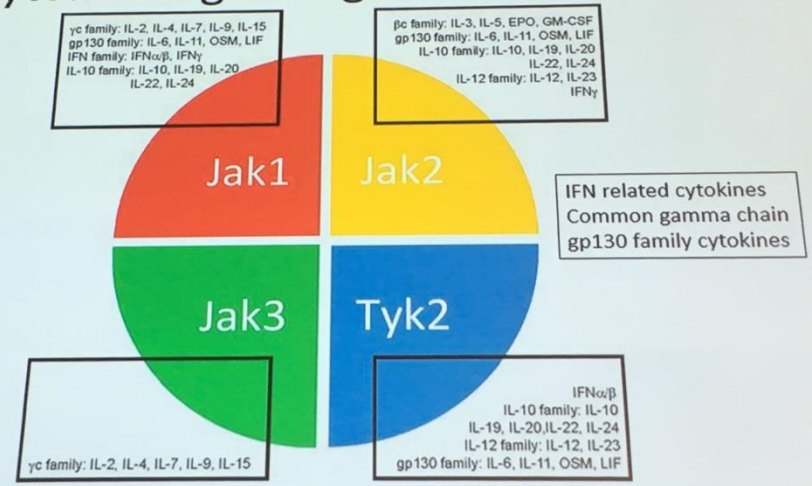
1. Anti-TNF
2. Vedolizumab (RCH)
3. Ustekinumab

Saut de ligne = contre-indication (SEP et anti-TNF) ou situations particulières



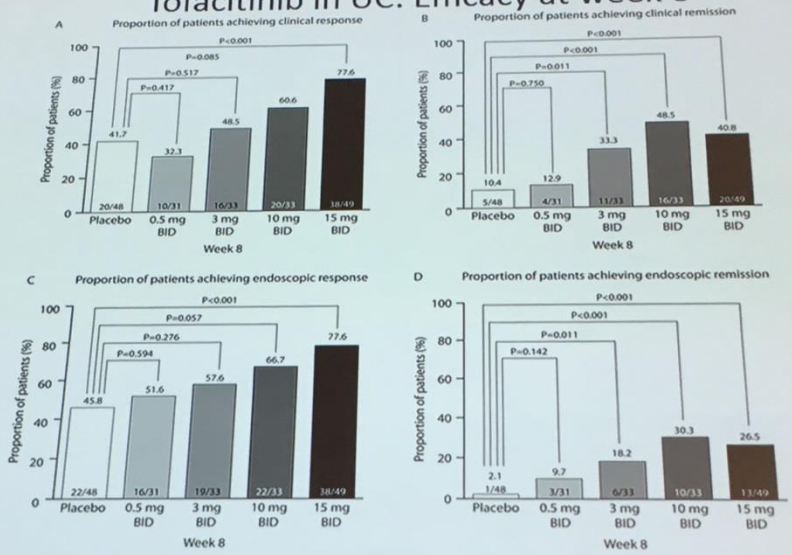
Ungaro R et al. Lancet 2017

Cytokine signalling via Janus kinases



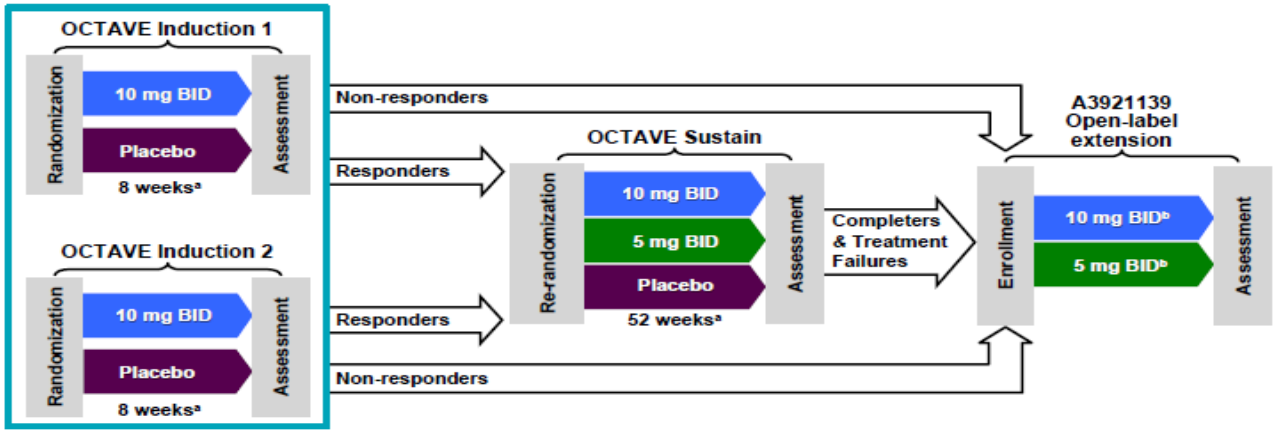
O'Shea JJ et al. Ann Rheum Dis 2013

Tofacitinib in UC: Efficacy at week 8



Sandborn, Ghosh, Panes et al N Eng J Med 2012

Phase 3 Program Design

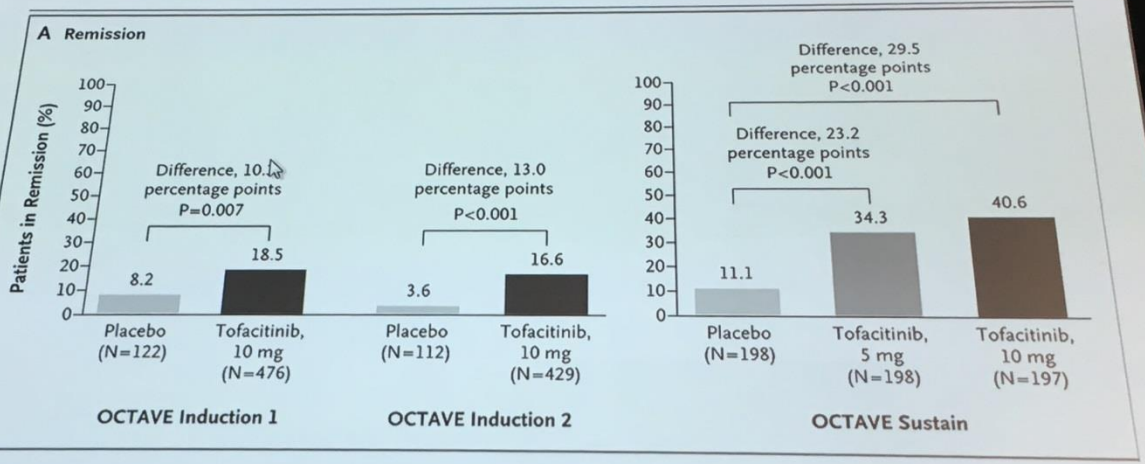


Patients

- ≥18 years old, moderately to severely active ulcerative colitis (Mayo score ≥6; rectal bleeding subscore ≥1; centrally read endoscopic subscore ≥2 (colonoscopy or flexible sigmoidoscopy)
- Prior failure or intolerance to ≥1 of: corticosteroids, azathioprine, 6-MP or TNF inhibitors (TNFi)
- Washout: TNFi, 8 weeks; immunosuppressants, 2 weeks
- Concomitant corticosteroids: max dose 25 mg/day; stable during the study

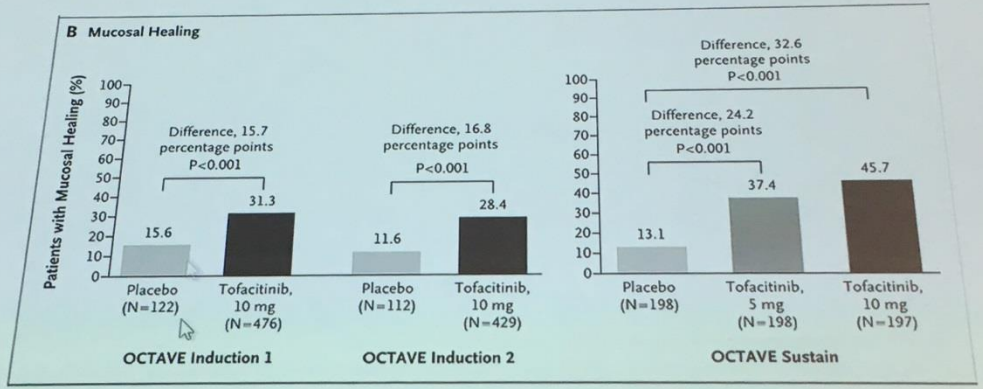
[a]Final complete efficacy assessment at week 8/52. Treatment continued up to week 9/53; [b]Patients in remission at OLE baseline: 5 mg BID; all others:10 mg BID
6-MP, 6-mercaptopurine; BID, twice daily; TNF, tumor necrosis factor

OCTAVE Induction 1 and Induction 2 and OCTAVE Sustain: Remission



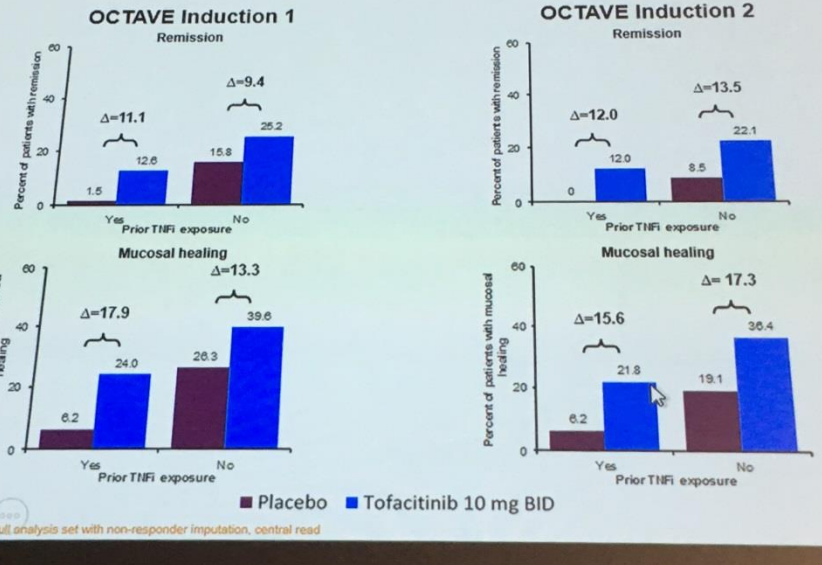
Sandborn WJ et al N Engl J Med 2017;376:1723-36.

Tofacitinib Key Secondary Endpoint: Mucosal Healing



Sandborn WJ et al N Engl J Med 2017;376:1723-36

Efficacy by TNF inhibitor exposure

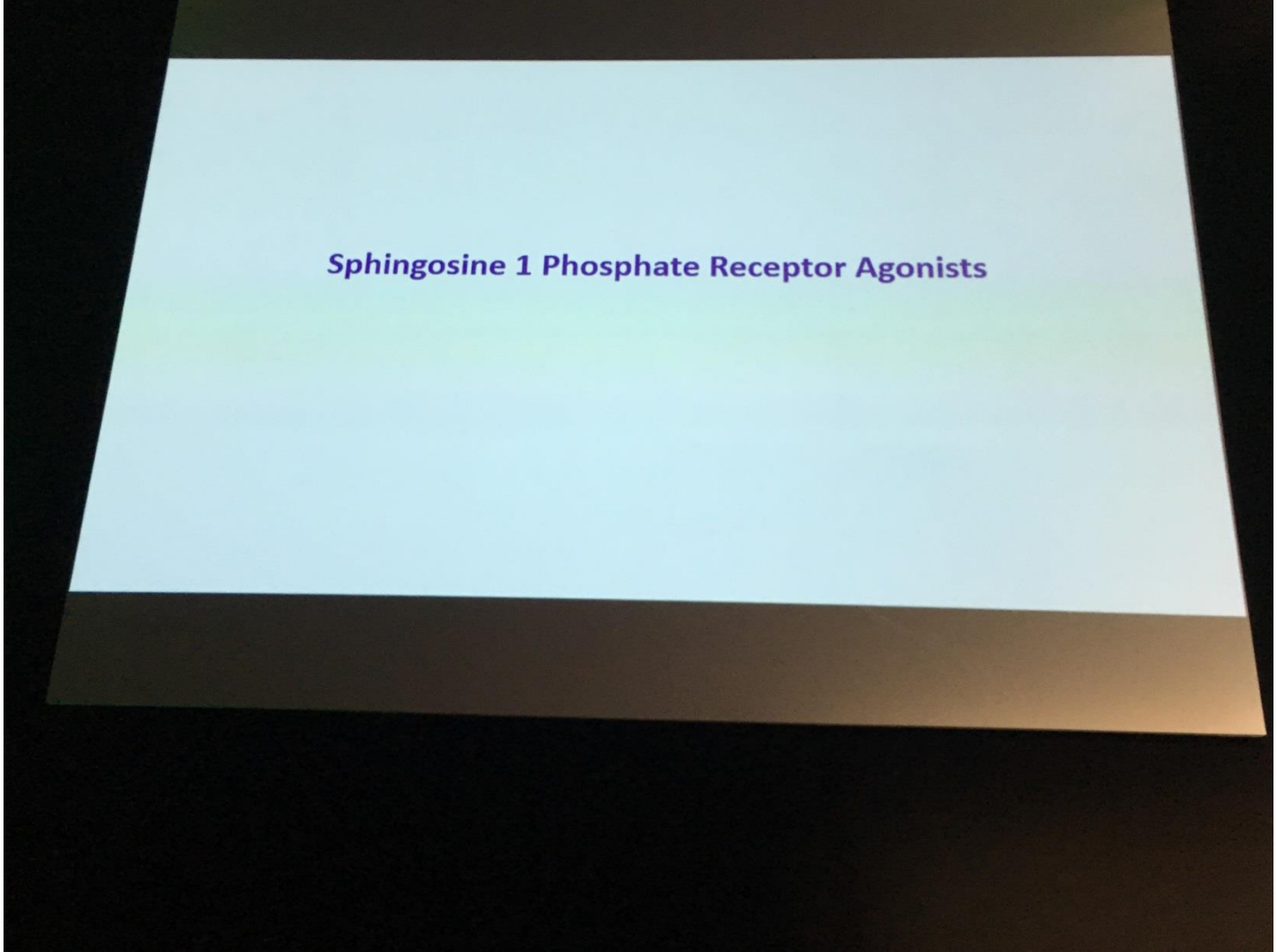


Data are full analysis set with non-responder imputation, central read

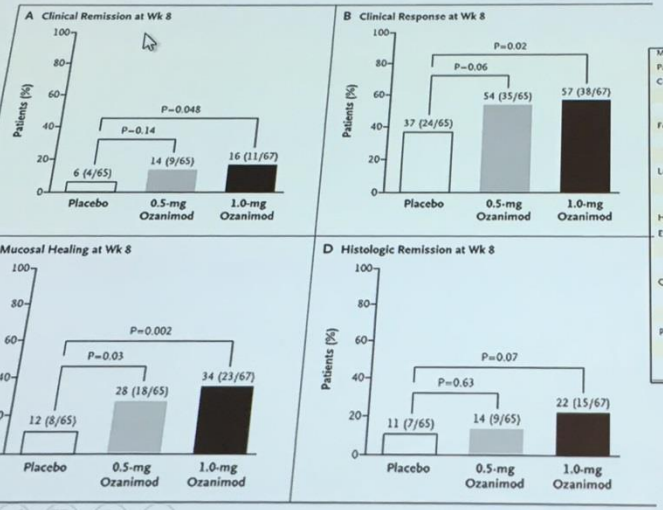
Safety events of special interest

	OCTAVE Induction 1		OCTAVE Induction 2	
	Placebo N=122	Tofacitinib 10 mg BID N=475	Placebo N=112	Tofacitinib 10 mg BID N=429
Infections, n (%)[a]	19 (15.6%)	111 (23.3%)	17 (15.2%)	78 (18.2%)
Herpes zoster[b]	1 (0.8%)	3 (0.6%)	0 (0.0%)	2 (0.5%)
Serious infections, n (%)[c]	0 (0.0%)	6 (1.3%)	0 (0.0%)	1 (0.2%)
Cardiovascular events, n (%)[d]	0 (0.0%)	2 (0.4%)	0 (0.0%)	1 (0.2%)
Intestinal perforations, n (%)[e]	0 (0.0%)	1 (0.2%)	1 (0.9%)	0 (0.0%)
Malignancies, n (%)[d]	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Non-melanoma skin cancer	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)

[a]There were no cases of tuberculosis in either study; [b]None were reported as serious adverse events; [c]Serious infections were: anal abscess, cellulitis, *clostridium difficile* infection, febrile infection, otitis externa, pneumonia, furuncle, all n=1; [d]Per an external independent adjudication committee based on pre-defined adjudication criteria; [e]Preferred term


Sphingosine 1 Phosphate Receptor Agonists

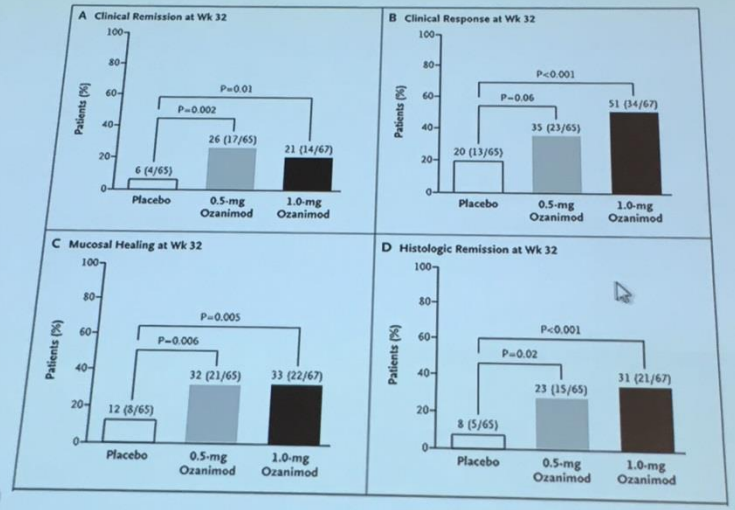
Ozanimod efficacy results at week 8. The TOUCHSTONE STUDY



Mayo Clinic score‡	8.6±1.5	8.3±1.5	8.5±1.6
Partial Mayo Clinic score‡	6.1±1.3	5.8±1.3	6.0±1.3
C-reactive protein — mg/liter			
Median	4.9	3.9	4.3
Range	0.20–141.4	0.10–131.2	0.10–82.5
Fecal calprotectin — μg/g			
Median	1272	1477	1238
Range	30–8380	66–11,108	10–10,511
Lactoferrin — μg/g			
Median	29.0	30.6	29.9
Range	1.4–1049	1.4–483	1.4–586
Hemoglobin — g/liter	123.7±20.1	119.7±20.5	126.0±20.7
Extent of disease — no. (%)			
Left side of colon	41 (63)	41 (63)	41 (61)
Extensive	24 (37)	24 (37)	26 (39)
Concomitant medication use — no. (%)			
Glucocorticoid	24 (37)	22 (34)	27 (40)
Aminosalicylate	57 (88)	53 (82)	53 (79)
Previous medication use — no. (%)			
Immunosuppressive agent§	17 (26)	24 (37)	22 (33)
TNF-antagonist therapy	10 (15)	13 (20)	13 (19)

NEJM 2016;374:1754-1762

Ozanimod exploratory efficacy outcomes at week 32: TOUCHSTONE study



NEJM 2016;374:1754-1762

Oral targeted therapies: opportunities and challenges

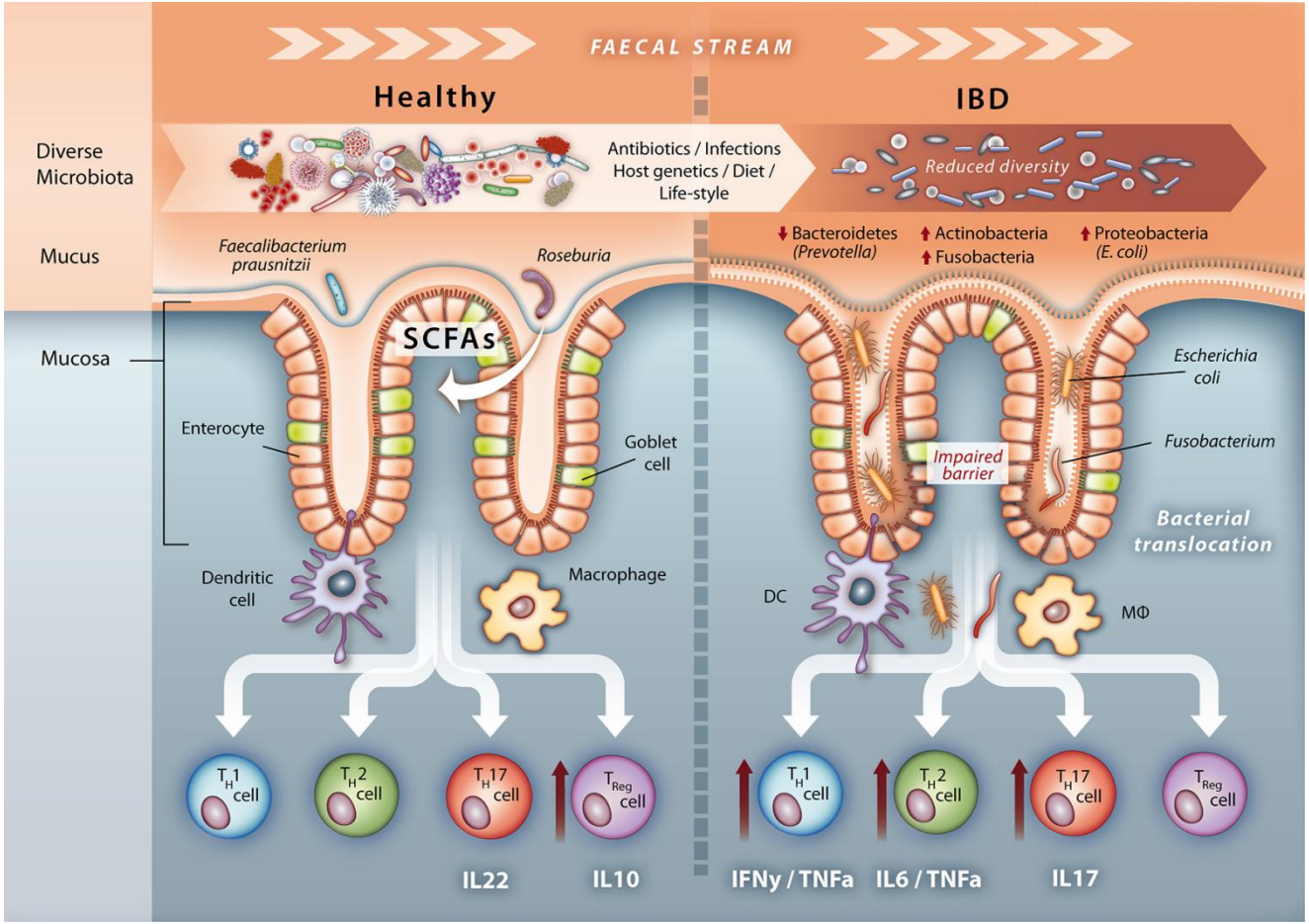
OPPORTUNITIES

- *Oral administration*
- *Stop and Start therapies*
- *Narrow therapeutic window : no TDM generally*
- *Monotherapy opportunity*
- *Possibility of combination with biologics ?*
- *Efficacy in EIMs*

CHALLENGES

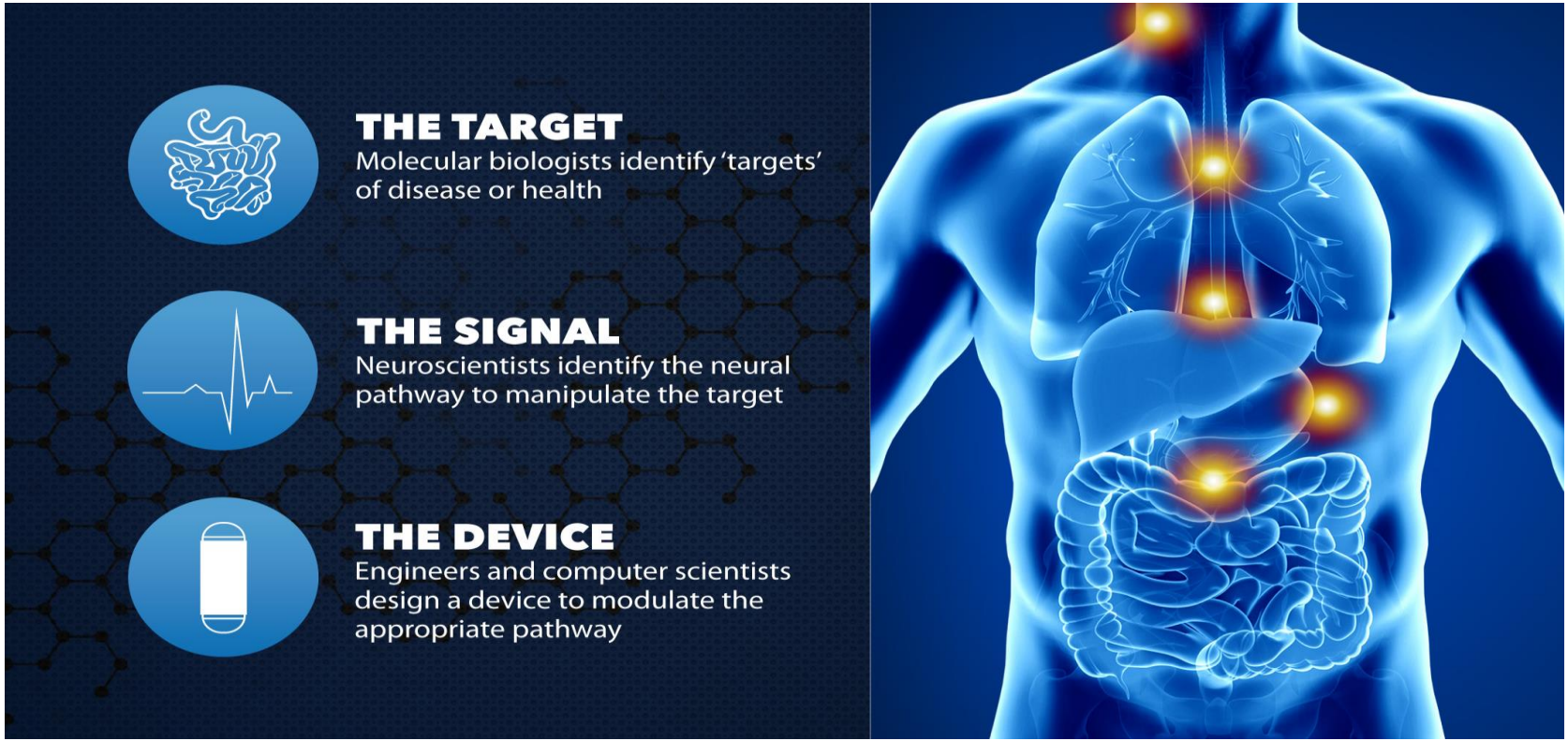
- Off target effects
- Limited dose optimisation
- Adherence issues
- Multiple dosing
- New monitoring issues

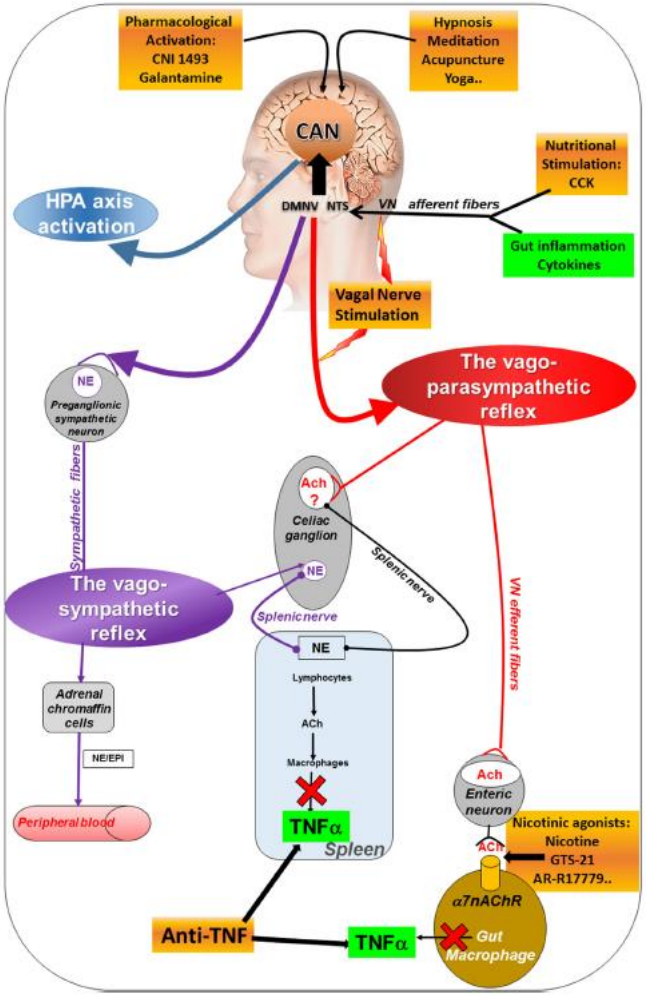
Microbial signatures of a healthy gut and IBD



Gut. 2017;66: 1734-1738

Non-drug therapy of IBD
Bioelectronic Medicine (Electroceuticals)

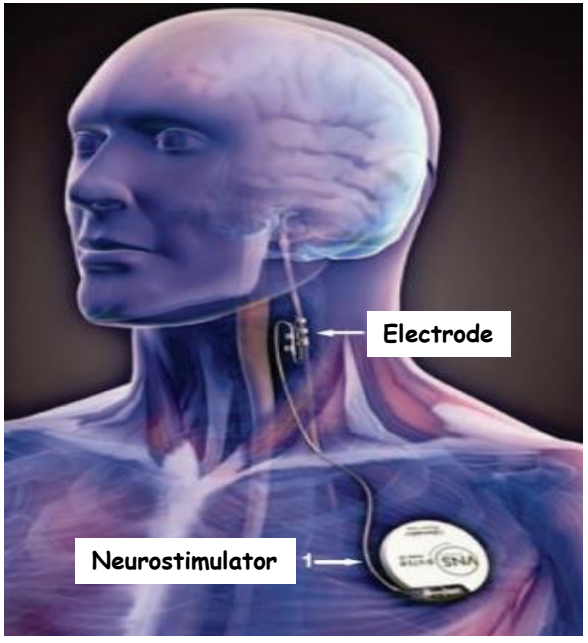




Bonaz B et al. Front Immunol. 2017;8:1452

VNS in Human: From epilepsy to the CAP

- VNS approval
  - 1997: treatment of refractory epilepsy
  - 2005: treatment of refractory depression
- ~ 100,000 patients implanted
- Efficacy
  - ~50 percent of patients attained a clinically significant reduction in seizure frequency greater than 50 percent, with about 12 percent experiencing a 90 percent decrease in seizures (Englot DJ, 2011)
- Side-effects: mild to moderate, usually occur during stimulation and often diminish over time: voice alteration, tickling in the throat, cough and a feeling of shortness of breath (Morris GL, 1999)
- VNS parameters (<u>afferents</u>) in epilepsy and depression: 20-30 Hz; 0.5-1.5mA; 500 μs; 30 sec ON, 5 min OFF
- VNS parameters (<u>efferents</u>) in inflammation: 1-10 Hz



Bonaz B et al. Neurogastroenterol Motil 2013;25: 208-21

Autonomic Neuroscience: Basic and Clinical 160 (2011) 82–89

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

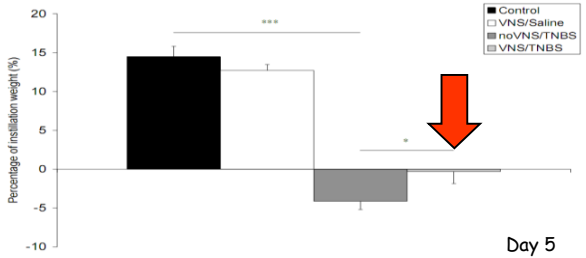
journal homepage: www.elsevier.com/locate/autneu

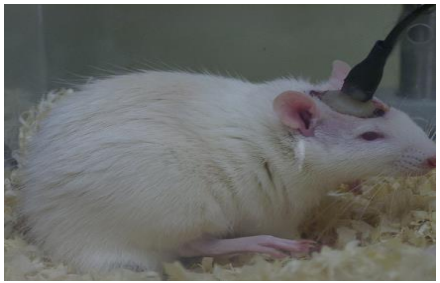
Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease

J. Meregnani [a,1], D. Clarençon [a,b,1], M. Vivier [b], A. Peinnequin [a,b], C. Mouret [b], V. Sinniger [a], C. Picq [a,b], A. Job [b], F. Canini [a,b], M. Jacquier-Sarlin [a], Bruno Bonaz [a,c,*]

I. Integrative effect

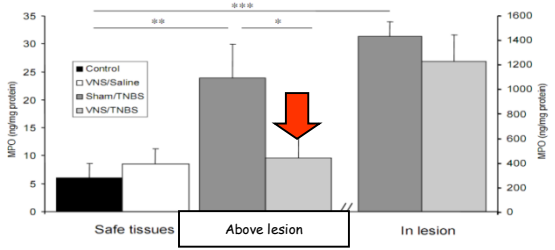
Weight loss



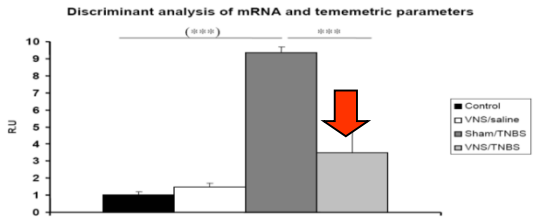


II. Anti-inflammatory effects

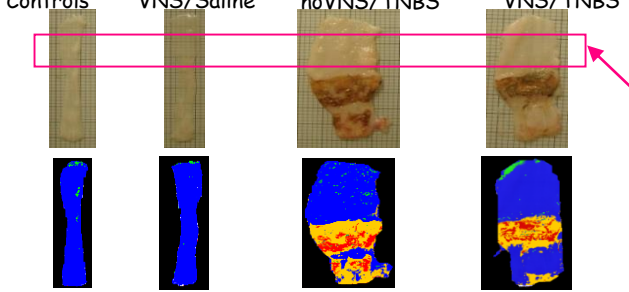
Myeloperoxydase



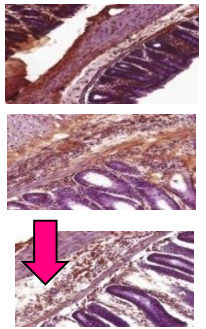
Discriminant analysis



Colorimetric quantification

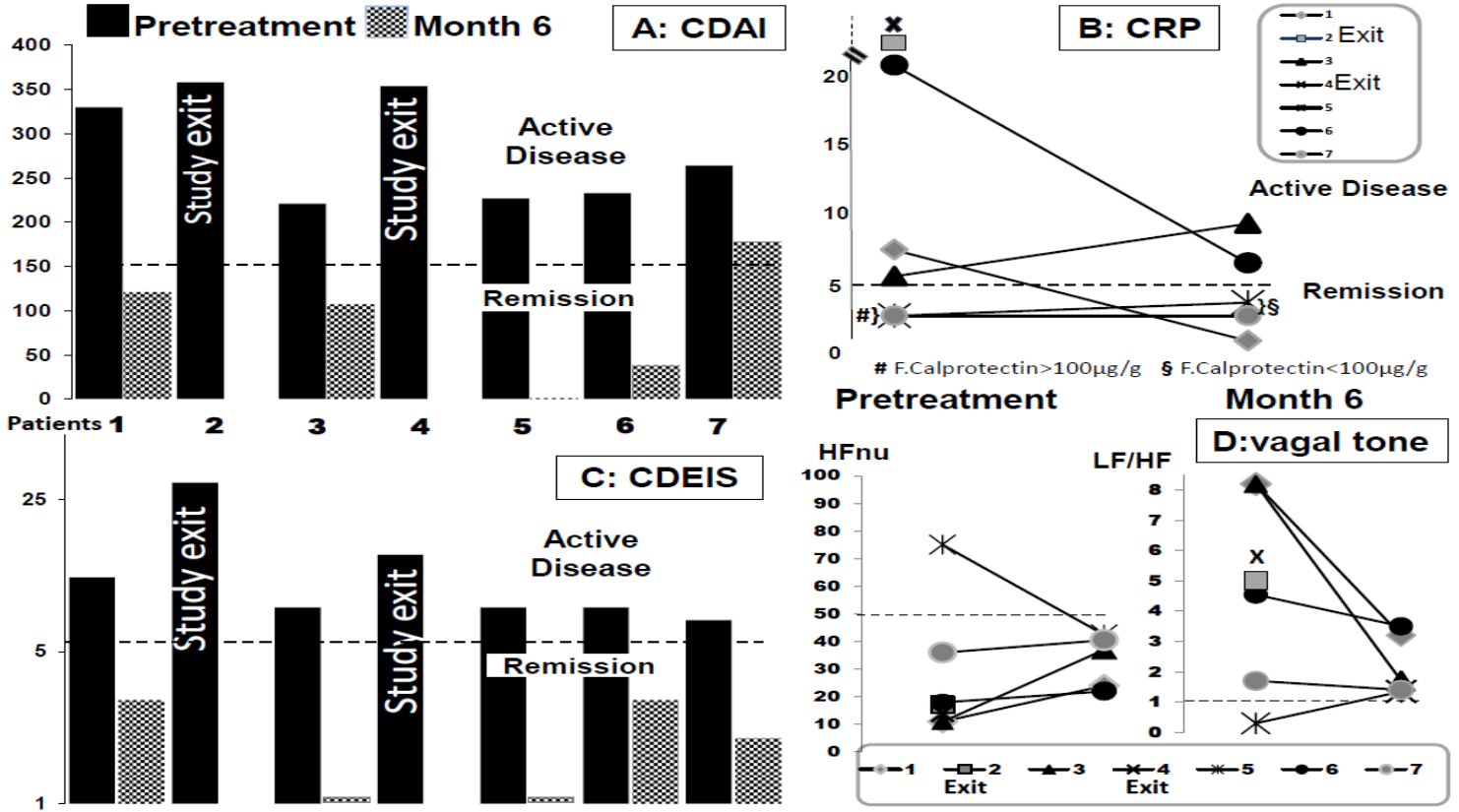


Histology



Auton Neurosci 2011;160:82-9

Effect of VNS over a 6-month follow-up in the seven patients with active Crohn's disease at inclusion



Bonaz B et al. Neurogastroenterol Motil. 2016 Feb 27

Je vous remercie pour votre attention