Les nouvelles biothérapies

Au-delà des anti-TNF

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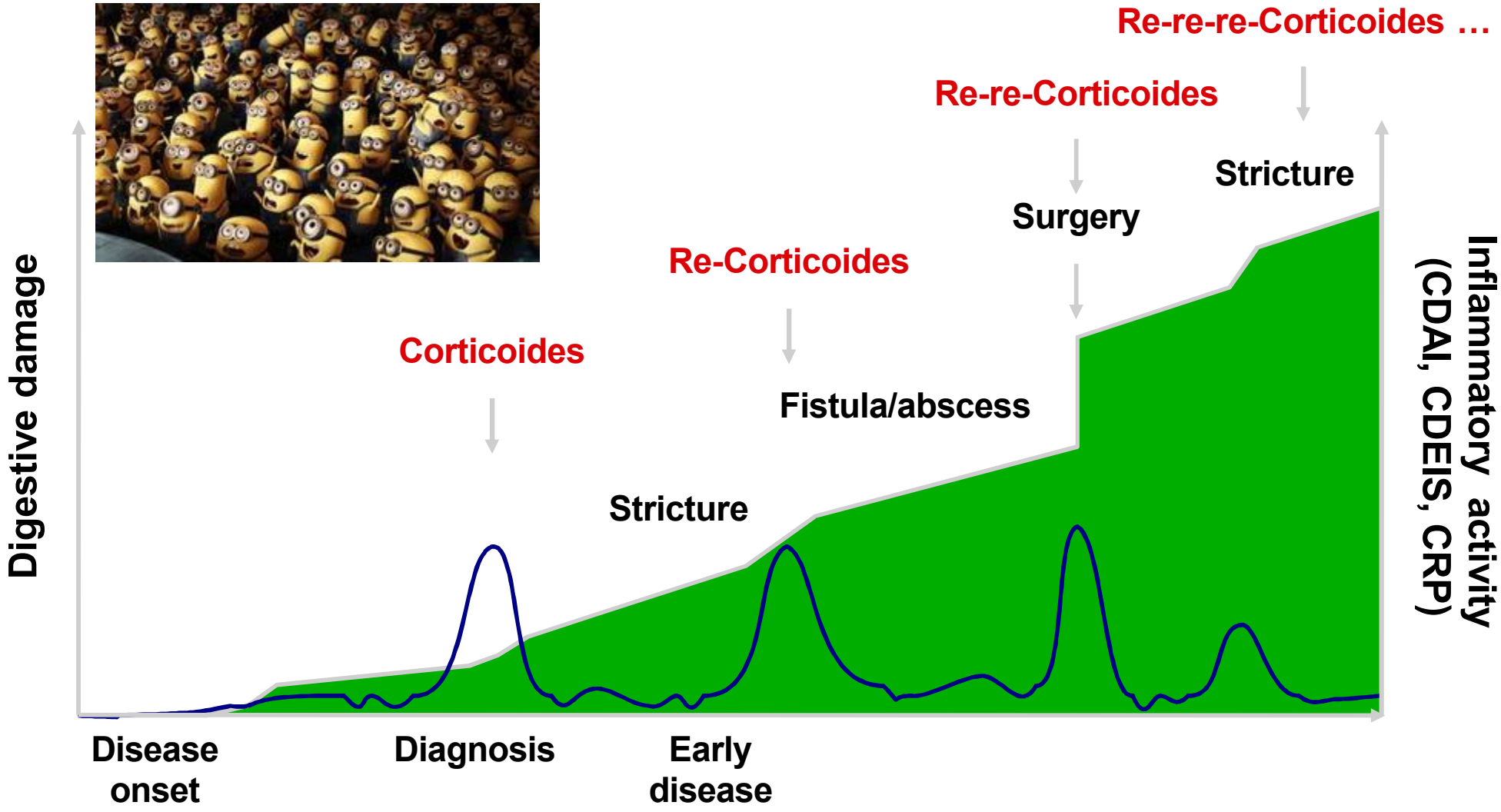
UPEC UNIVERSITÉ PARIS-EST CRÉTEIL VAL DE MARNE Connaissance - Action

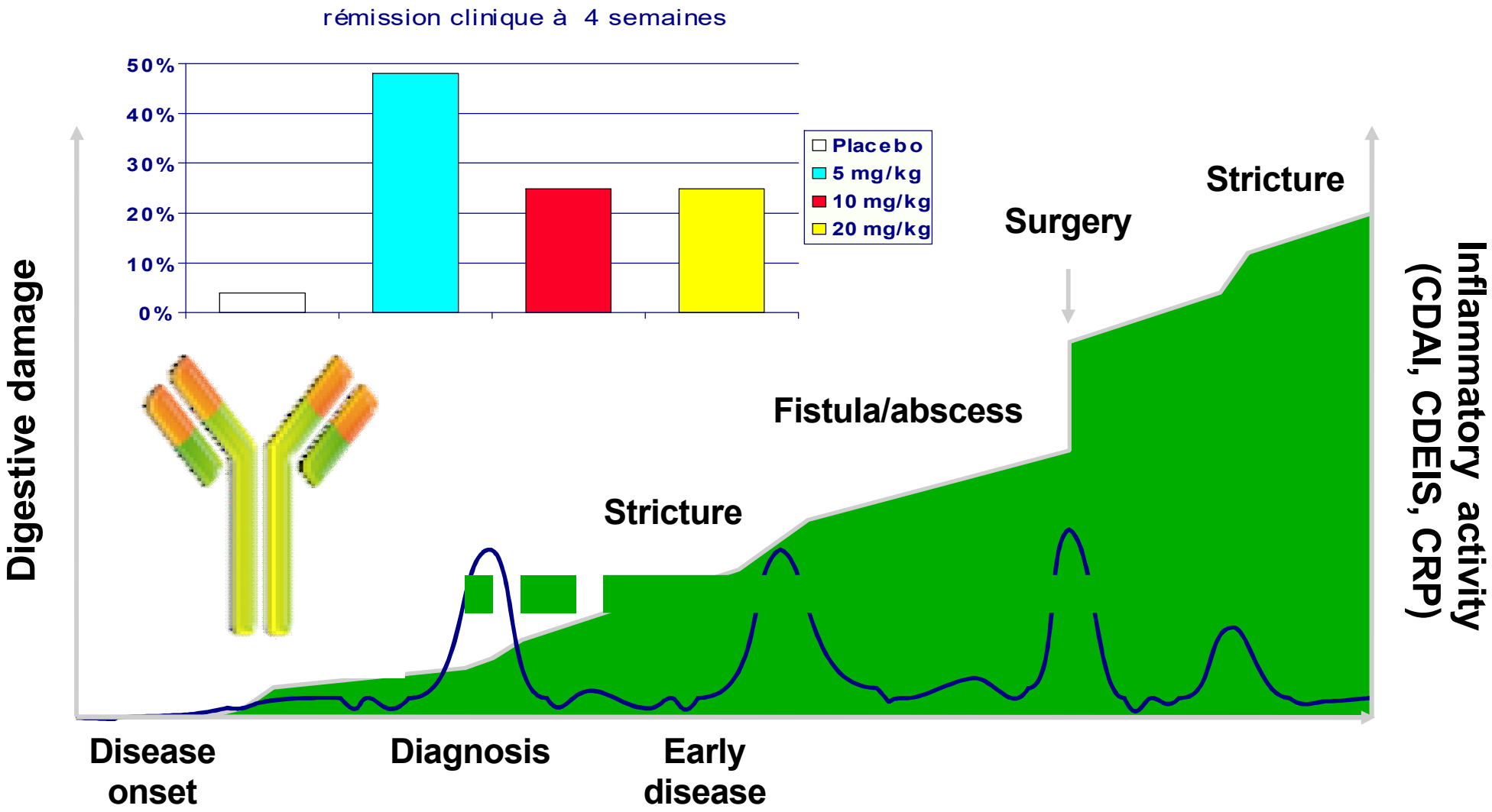
HÔPITAUX UNIVERSITAIRES HENRI MONDOR ALBERT CHENEVIER - JOFFRE-DUPUYTREN EMILE ROUX - GEORGES CLEMENCEAU

Avant l'ère des biothérapies



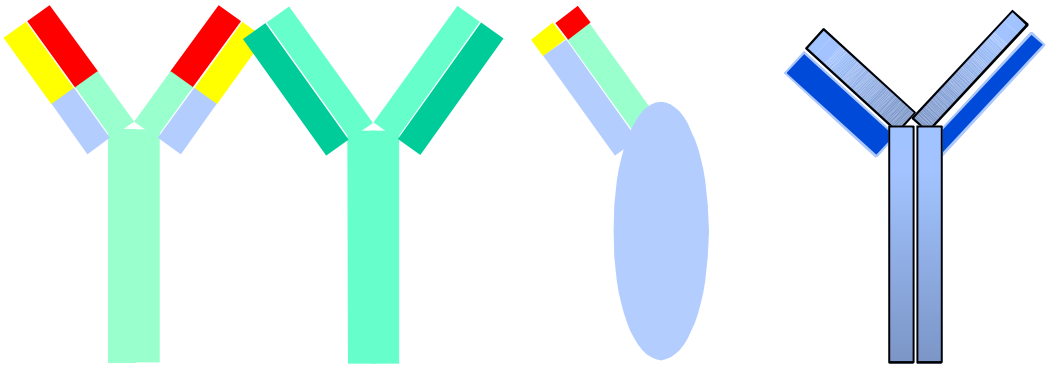
Pariente B, et al. *Inflammatory Bowel Diseases* 2011; 17:1415-22

L'avènement des anti-TNF dans les MICI



Targan et al. N Engl J Med 1997. Pariente B et al. Inflammatory Bowel Diseases 2011

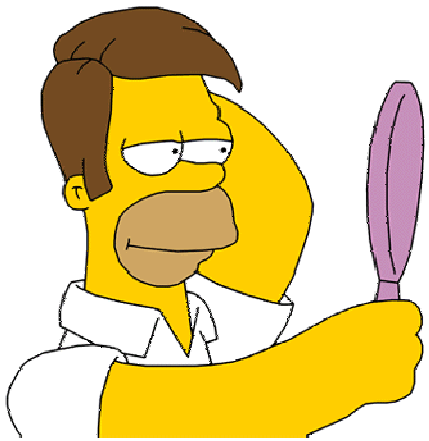
L'avènement des biothérapies dans les MICI



Chimeric	Humanized	Humanized + Peg	Humanized
Infliximab	Adalimumab	Certolizumab	Golimumab
Remicade®	*Humira®*	*Cimzia ®*	*Simponi®*

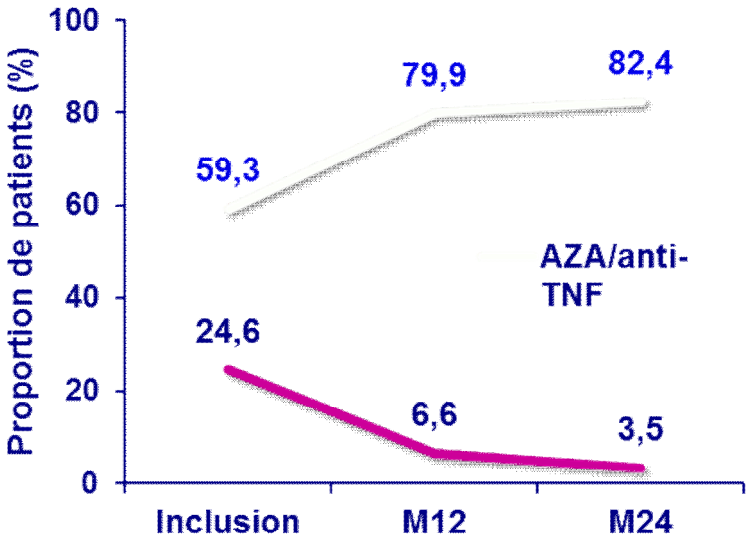
- Traiter les symptômes
- … et uniquement les symptômes
- S'adapter à l'histoire naturelle
- Chirurgie au fil des complciations
- Accépter la maladie

- Maintien en rémission
- Cicatrisation muqueuse
- Prévenir les complications
- Prévenir la chirurgie
- Qualité de vie et productivité normales



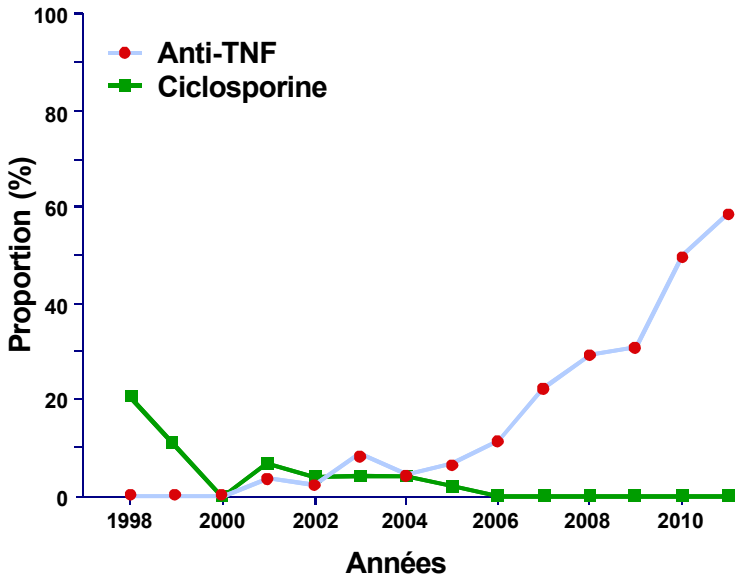
Place des ani-TNF dans les MICI

Cohorte prospective allemande (n = 677)



Maladie de Crohn

Données 1998-2011 Hôpitaux d'Edmonton (n = 657)

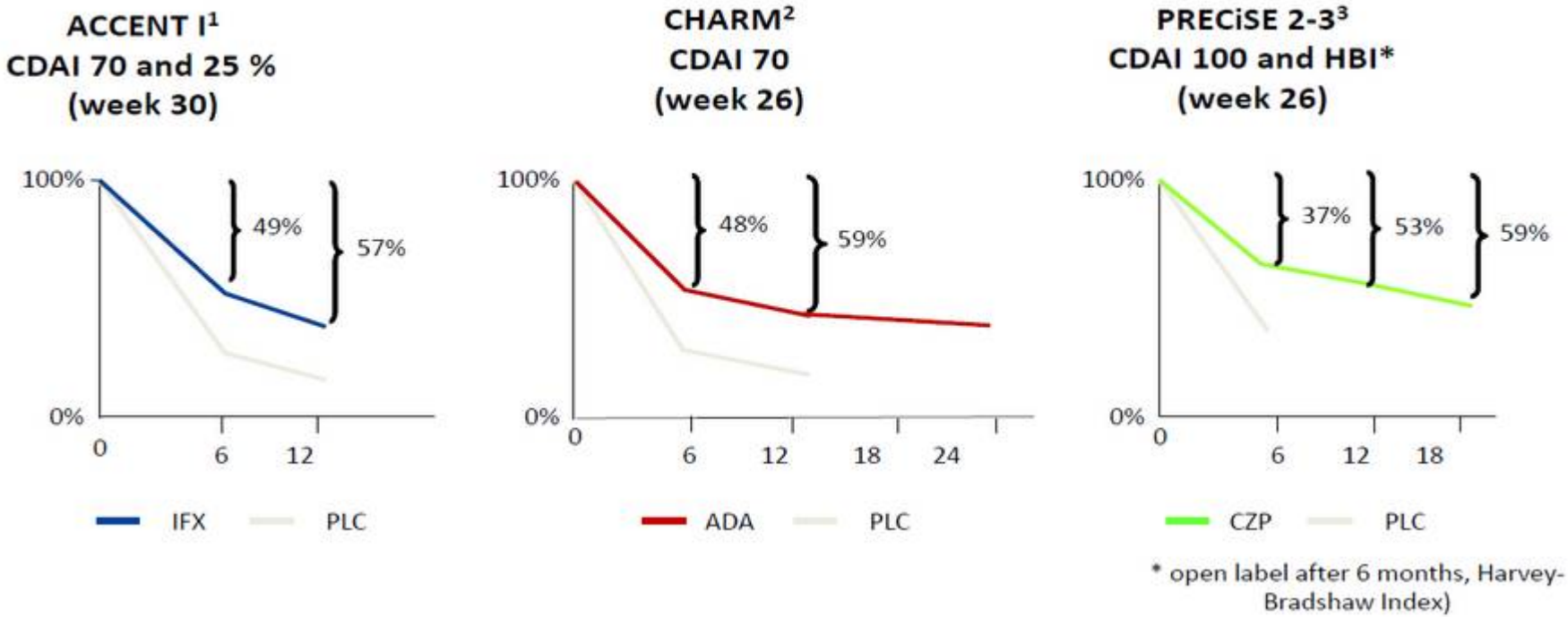


Rectocolite hémorragique

Bokemeyer H et al, ECCO 2013 Reich KM et al, APT 2014

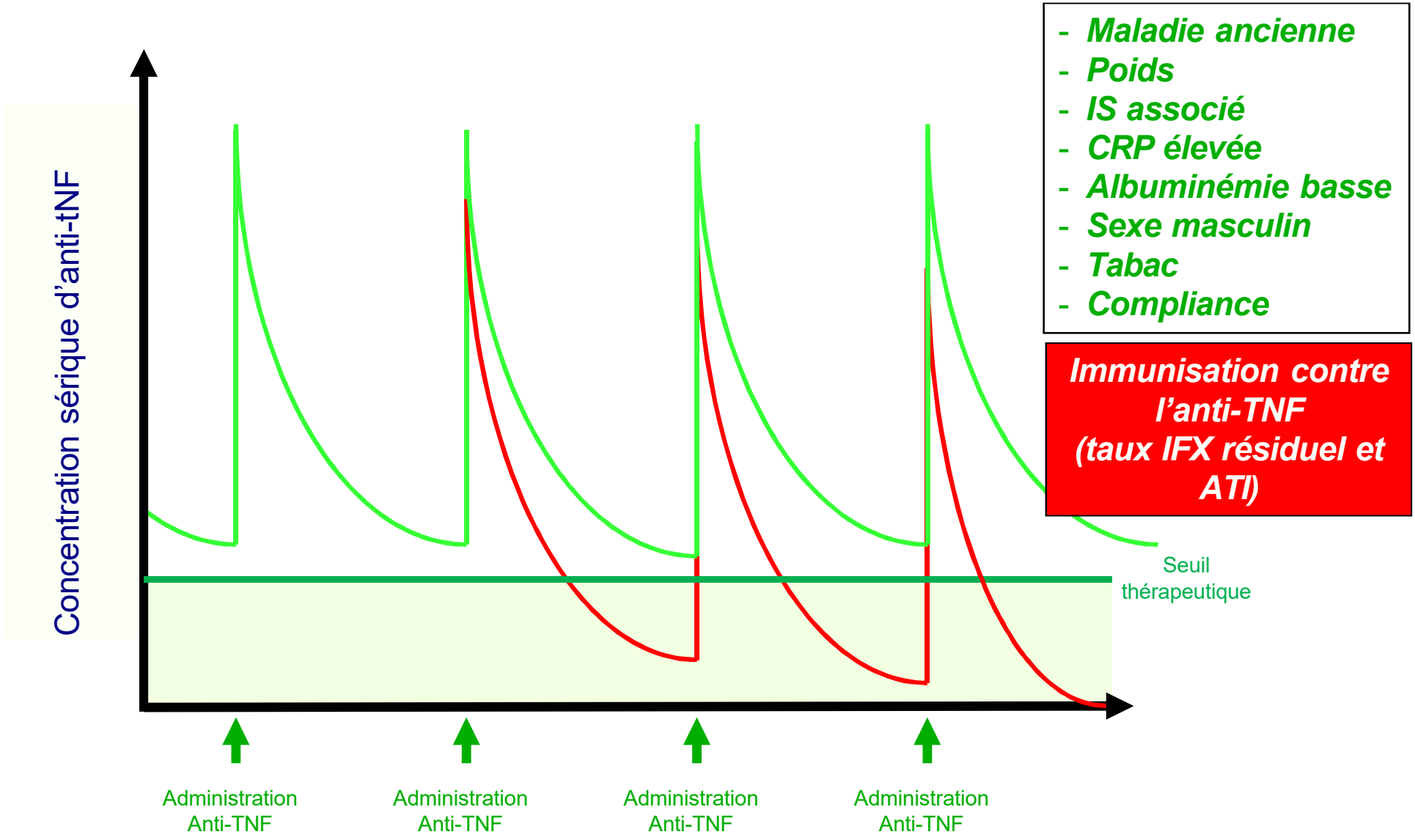
La face cachée des anti-TNF

- **Intolérance – contre-indication**
- **Non-répondeurs primaires # 20-30%**
- **Perte de réponse # 10-20% par an**

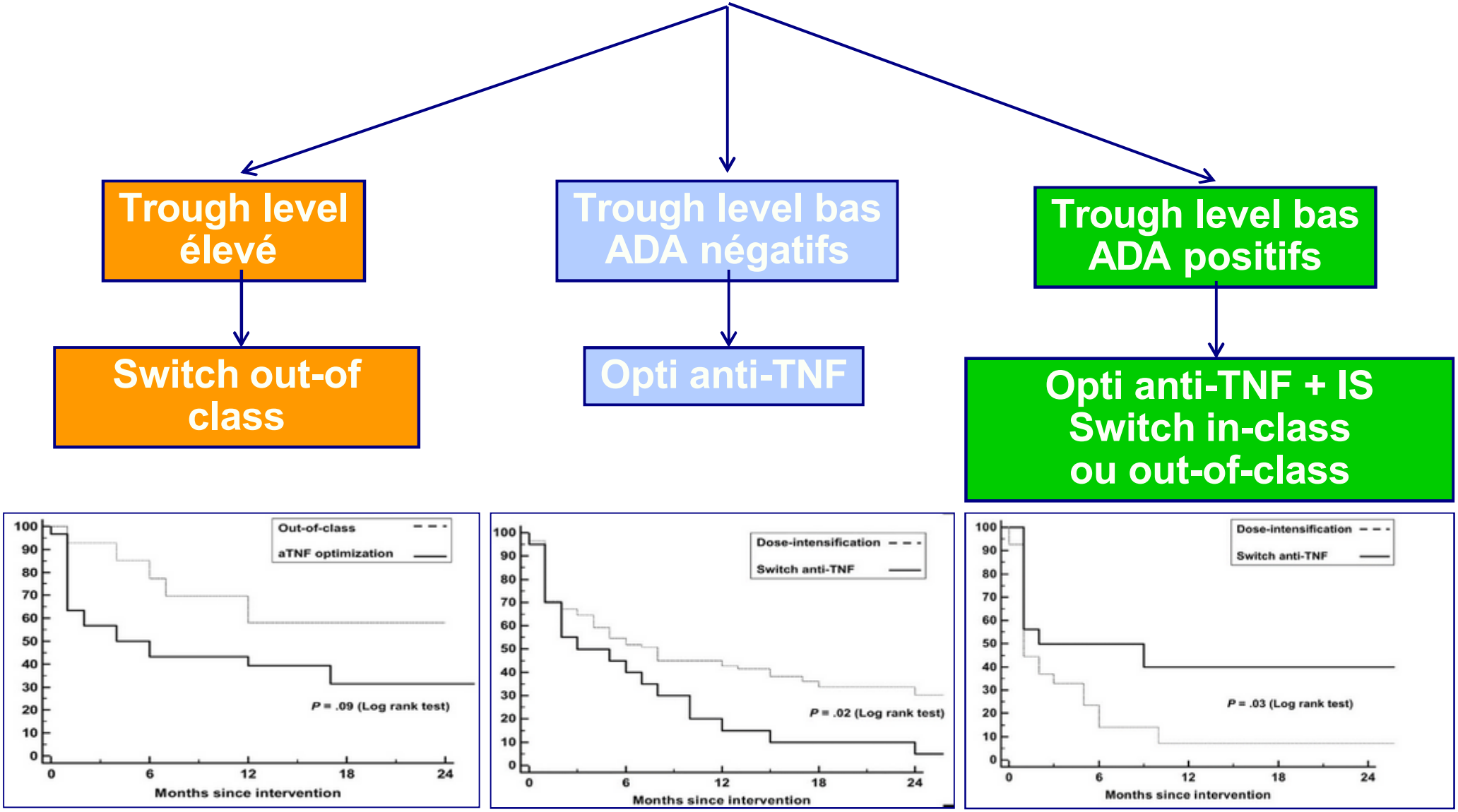


Allez et al. J Crohns Colitis. 2010; 4: 355-66

Mécanisme de résistance aux anti-TNF

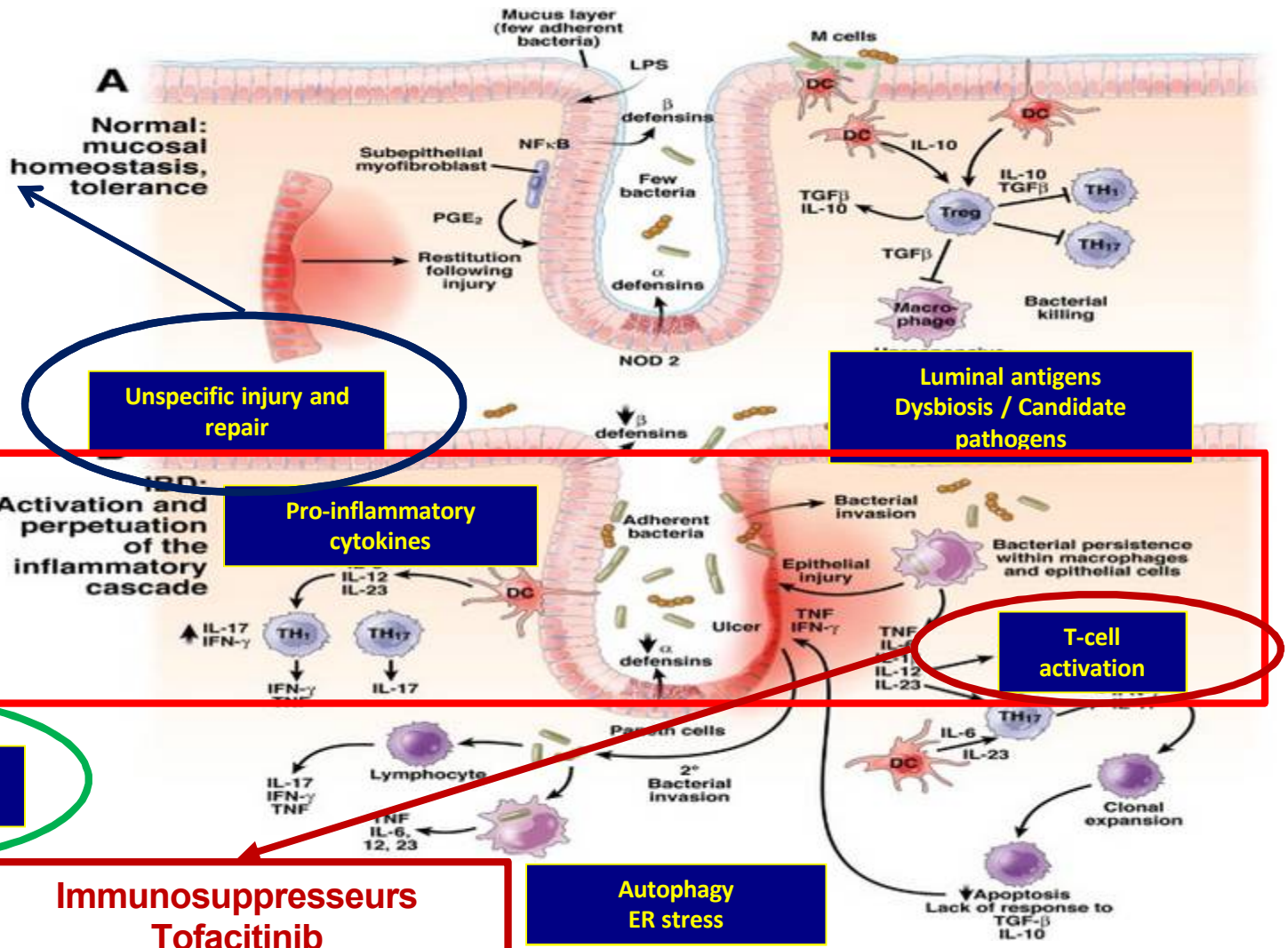


Algorithme en fonction des dosages thérapeutiques en cas de perte de réponse à un anti-TNF



Roblin et al. Am J Gastroenterol 2014 Yanai et al. Clin Gastro and Hepatol 2015

Nouvelles biothérapies au cours des MICI



Immunosuppresseurs
Biothérapie
-anti TNFα (IFX, ADA, GOL)
-anti-IL12/23 (ustekinumab)

Unspecific injury and repair

Luminal antigens
Dysbiosis / Candidate pathogens

Pro-inflammatory cytokines

T-cell activation

Anti-α4 intégrine

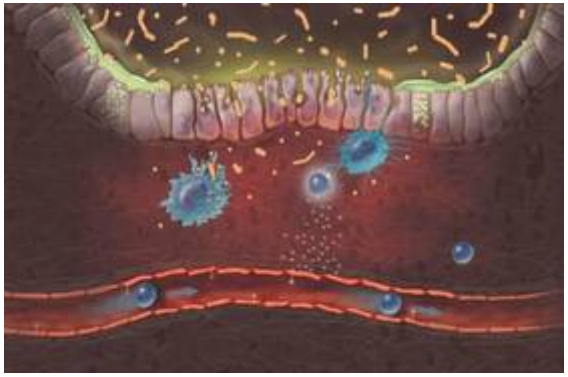
Adhesion and cell infiltration

Immunosuppresseurs
Tofacitinib

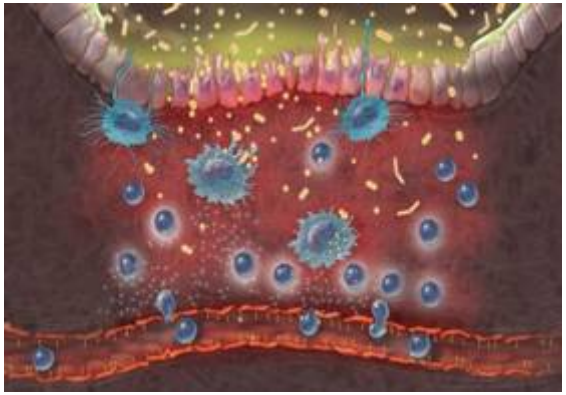
Autophagy
ER stress

Anti-SMAD7
Mongersen

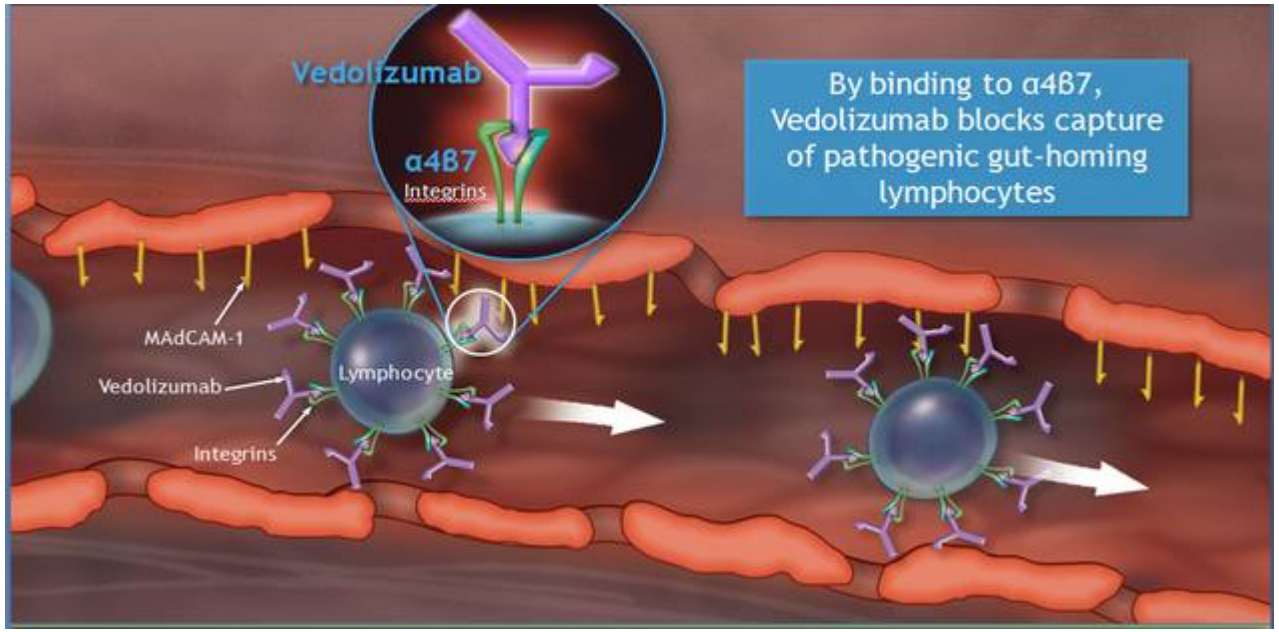
Vedolizumab



Rupture de la barrière Intestinale + activation immunité locale

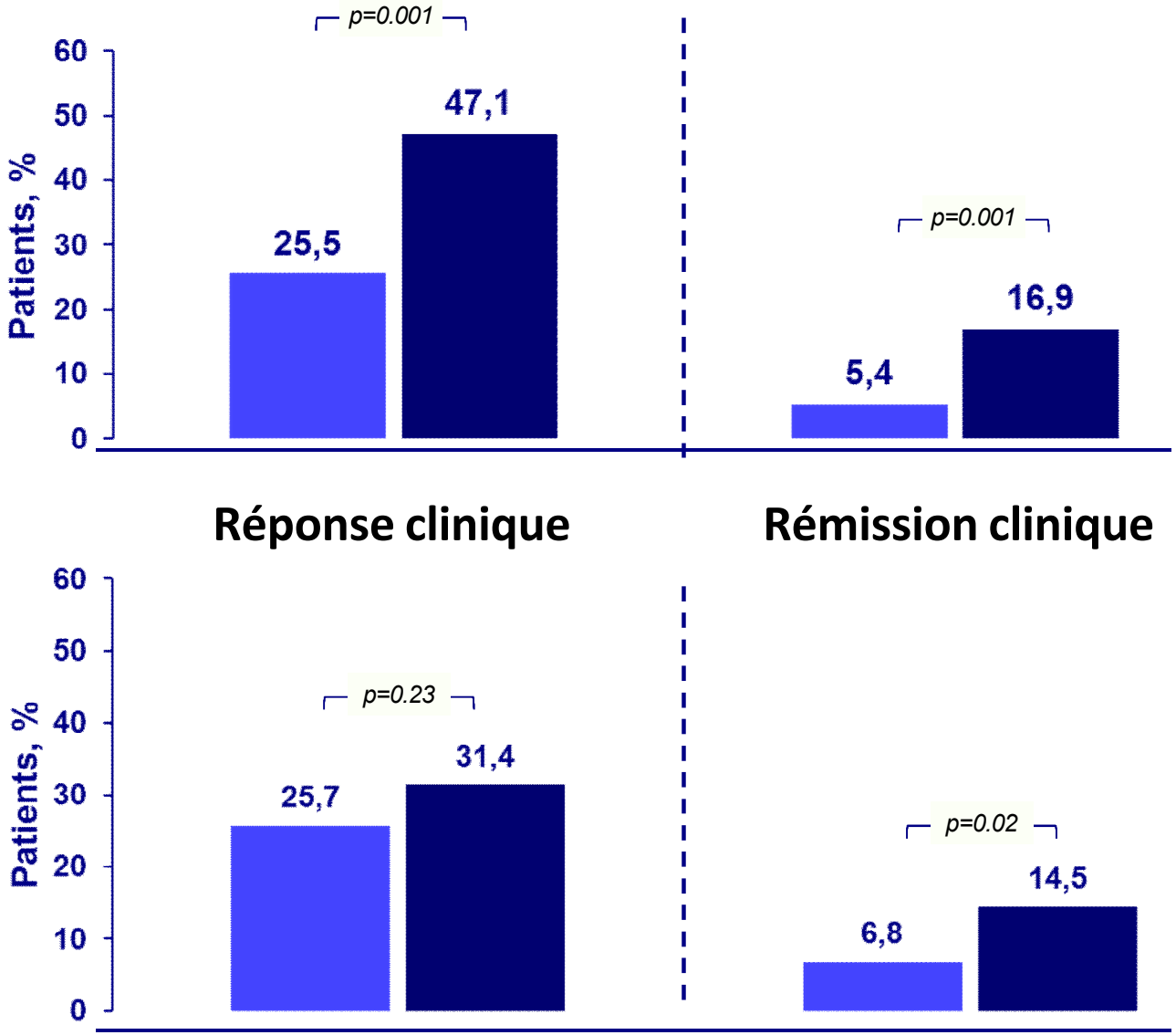


Recrutement et amplification de l'inflammation



Xavier et al. Nature 2007. Soler et al. J Pharmacol Exp Ther 2009. Sandborn W, et al. N Engl J Med 2013

Vedolizumab: GEMINI trials – Induction (S6)

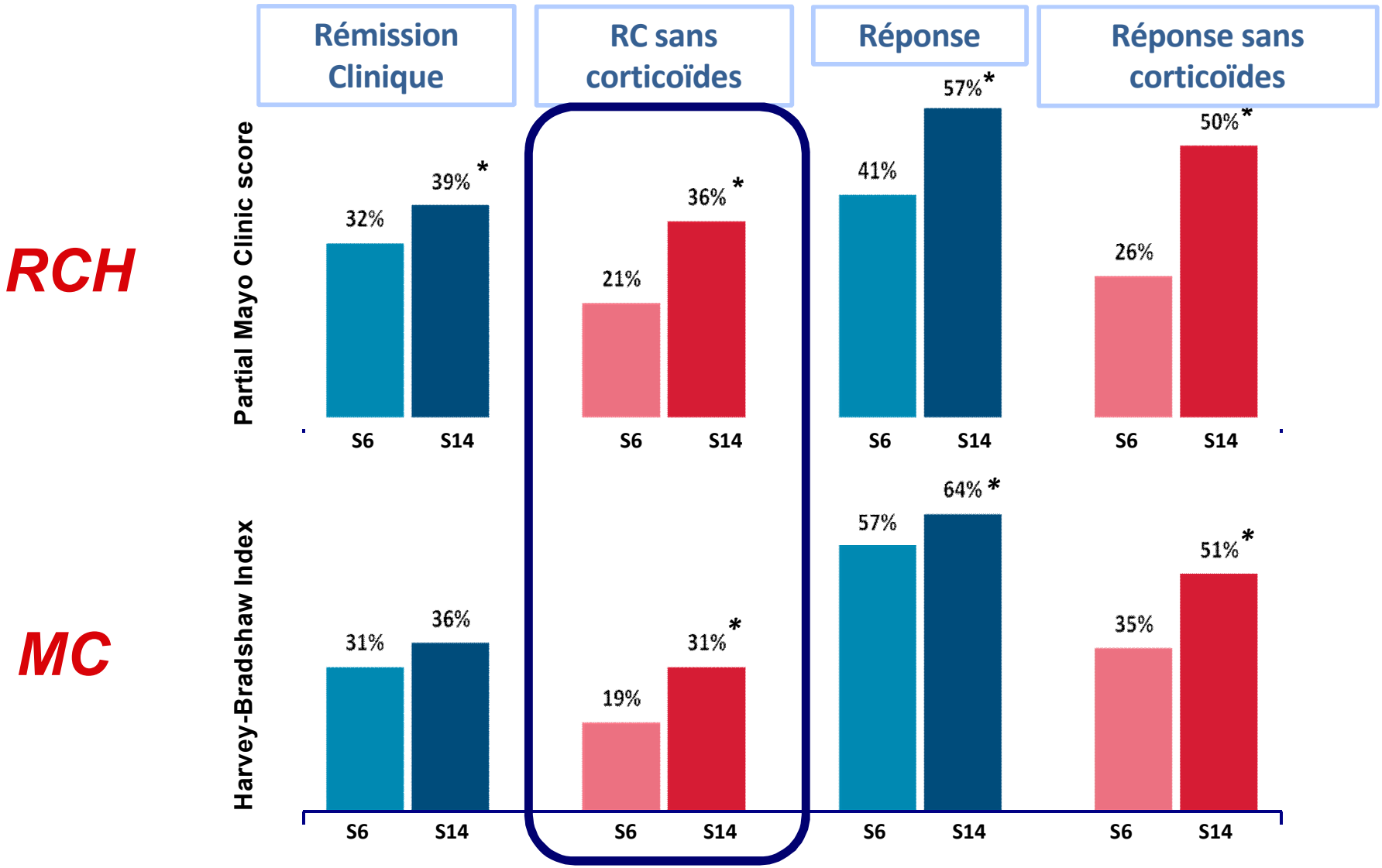


GEMINI I
RCH

GEMINI II
Maladie de Crohn

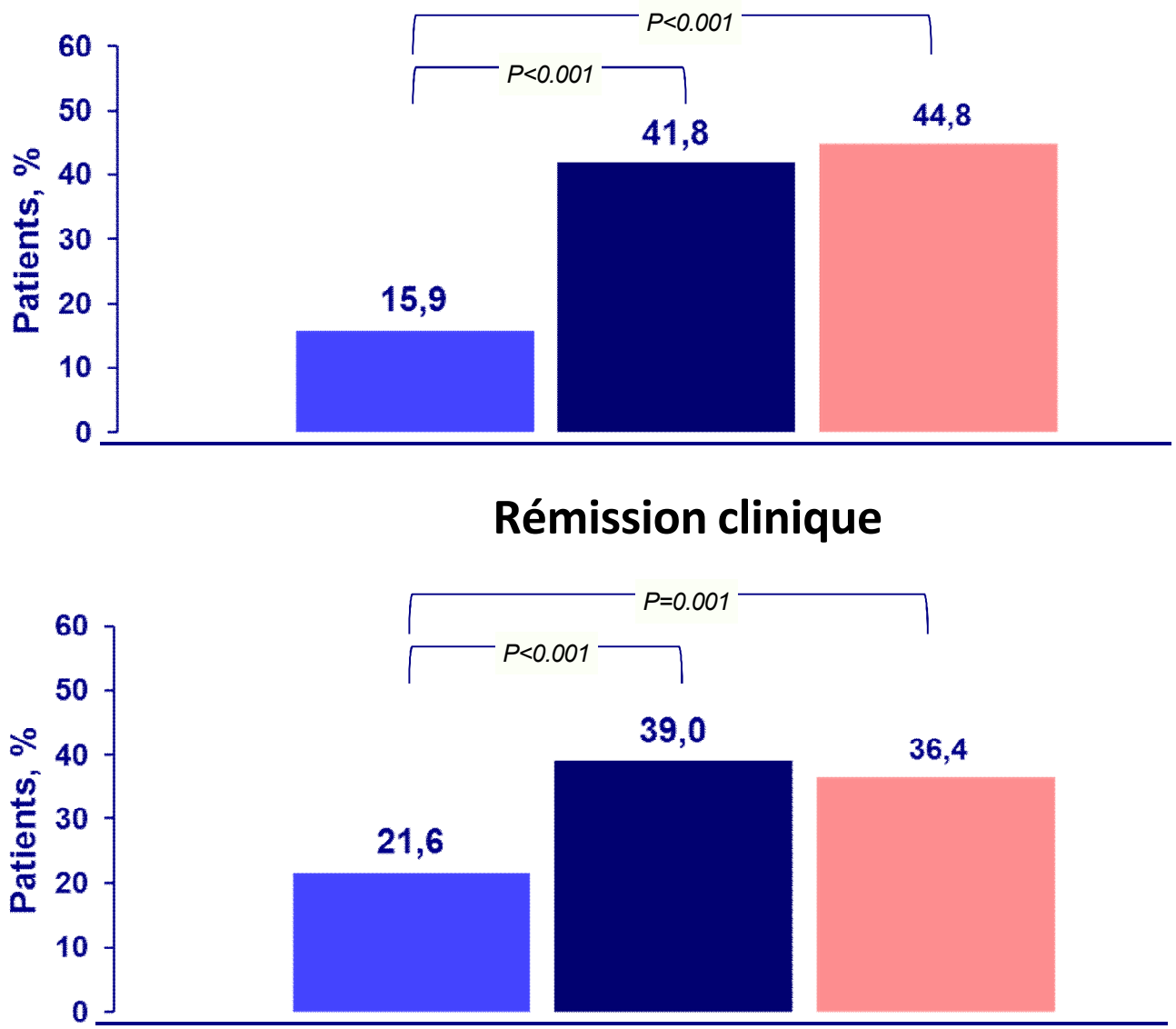
***Feagan BG et al. N Engl J Med* 2013; 369: 699-710. Sandborn WJ et al. N Engl J Med 2013; 369:711-21.**

Vedolizumab dans la vraie vie: OBSERV-MICI



Amiot et al. Clin Gastroenterol Hepatol 2016

Vedolizumab: GEMINI trials - maintenance



GEMINI I
RCH

GEMINI II
laladie de Crohn

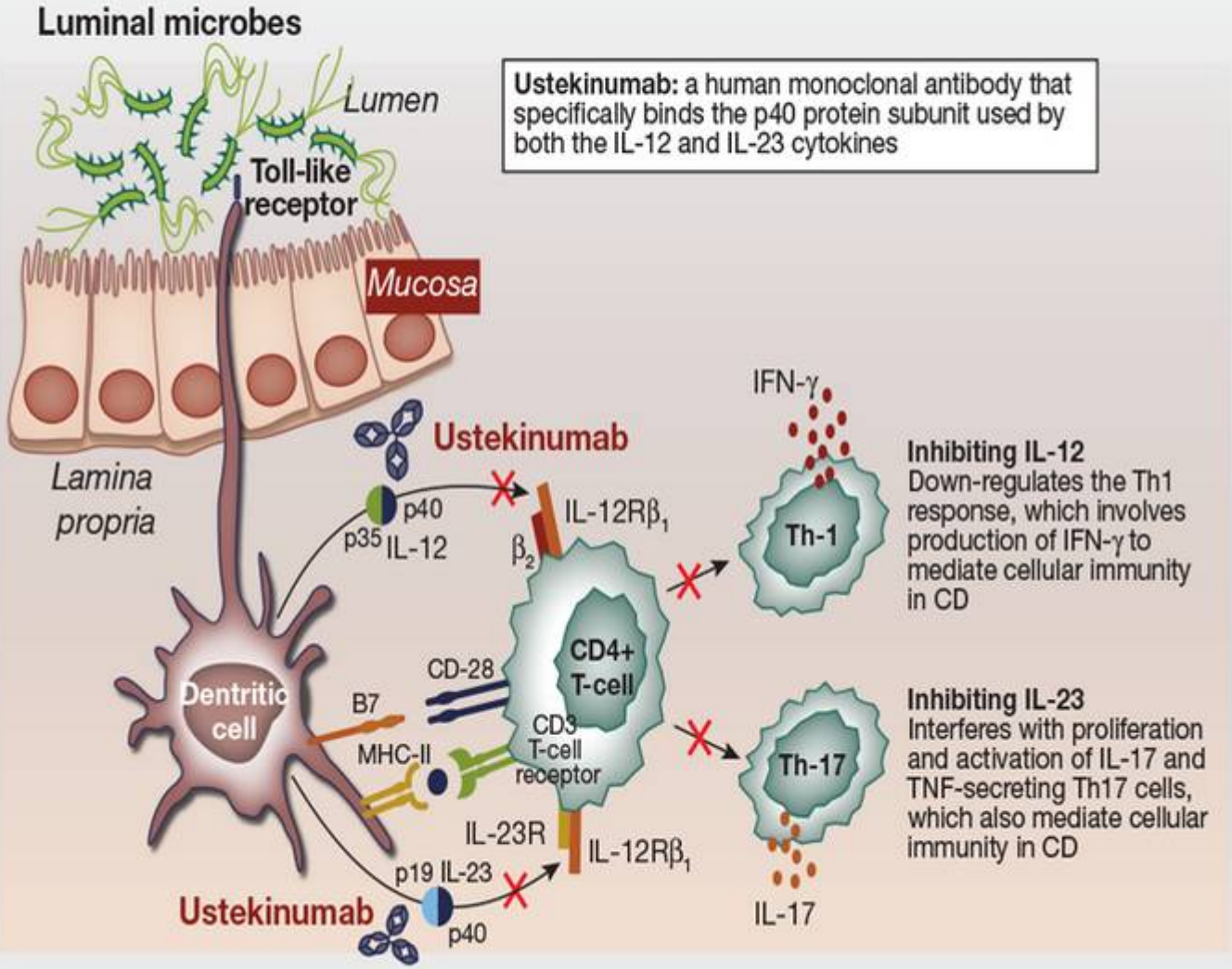
Feagan BG et al. N Engl J Med 2013; 369: 699-710. Sandborn WJ et al. N Engl J Med 2013; 369:711-21.

Vedolizumab dans la vraie vie: OBSERV-MICI - tolérance

	S0-S14 (n = 294)	S14-S52 (n = 237)
Effet indésirable	93 (31.6%)	62 (26,2%)
Céphalées	16 (5.4%)	9 (3,8%)
Paresthésies	13 (4.4%)	3 (1,3%)
Aggravation MICI	12 (4.1%)	9 (3,8%)
Eruptions cutanées “paradoxales”	12 (4.1%)	7 (3%)
Effets indésirables graves	24 (8.2%)	17 (7,2%)
Infections incidentes	37 (12.6%)	37 (15,6%)
Rhinopharyngite	12	12
Infection respiratoire haute	6	8
Infection digestive	5	12
Syndrome grippal	3	2
Sinusite	3	1
Angine	3	2
Divers	11	8
Infection sévère	7 (2.4%)	6 (2,5%)
Cancer incident	1 (0.3%)	1 (0,4%)

Amiot et al. Clin Gastroenterol Hepatol 2016

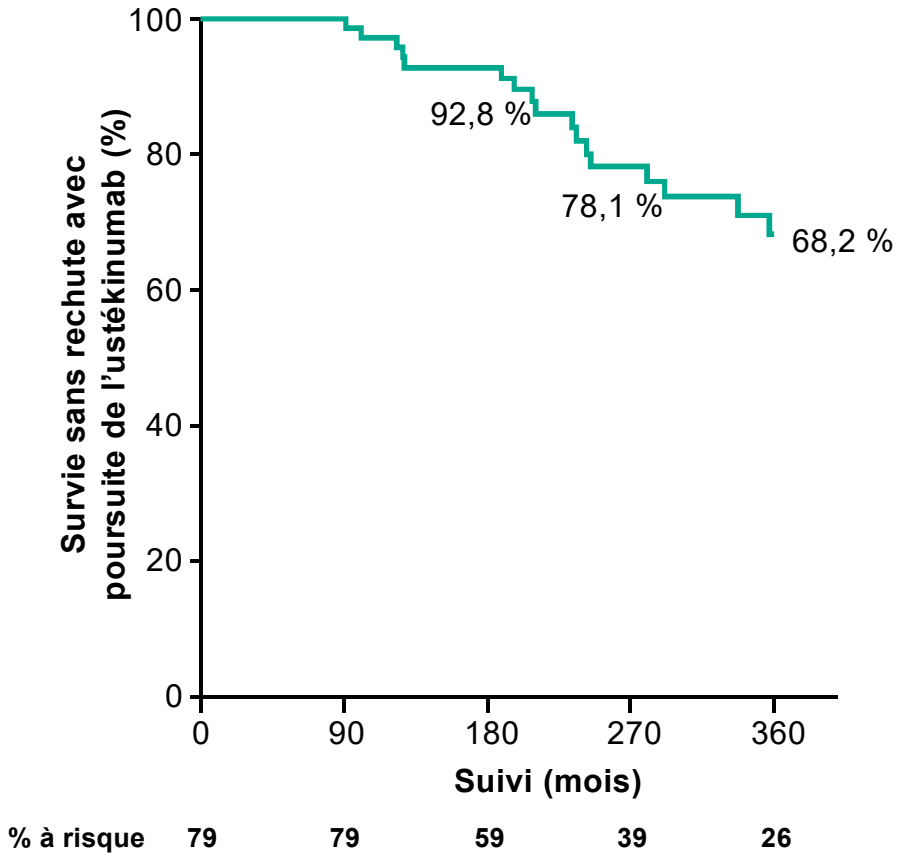
Targeting the IL-12/IL-23 Pathway: Ustekinumab[1]



PeerVoice

Ustekinumab dans la vraie vie: OBSERV-MICI

- **Méthode**
  - Registre rétrospectif du GETAID des patients atteints de MC traités par ustekinumab par voie sous-cutanée
- **Efficacité**
  - 122 patients inclus (110 MC luminales et 12 ano-périnéales) : 79 (65 %) avec bénéfice clinique à 3 mois
  - Facteur prédictif d'une bonne réponse : traitement immunosuppresseur concomitant
- **Tolérance**
  - 20 effets indésirables dont 1 grave (pneumopathie)

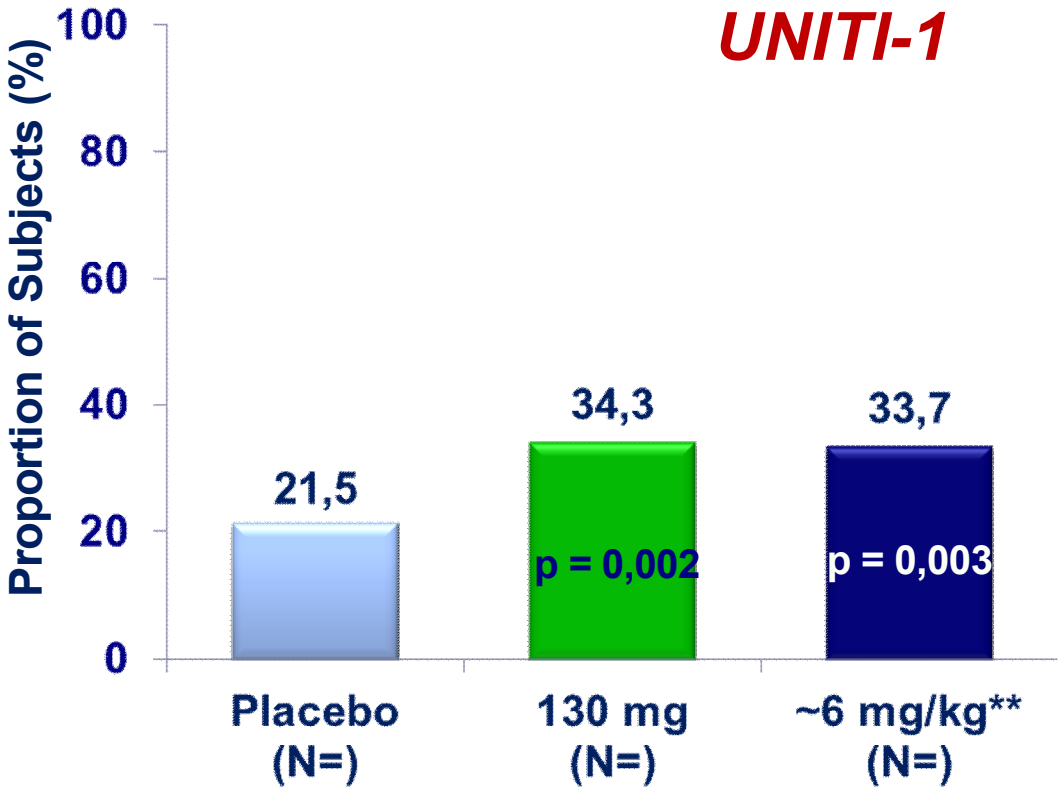


Wils et al. Clin Gastroenterol Hepatol 2015

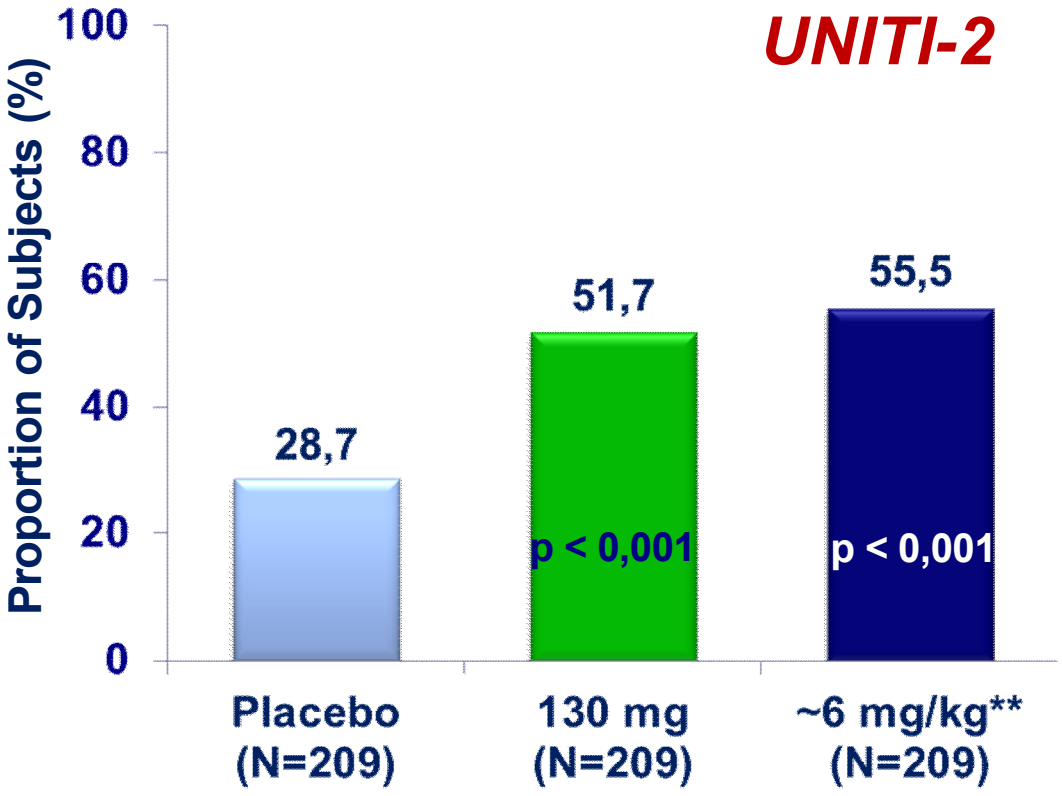
Ustekinumab (anti-IL12/23 p40): *phase III*

Primary Endpoint: clinical response at week 6

Clinical Response at W6: ≥100 Point CDAI Reduction



Patients who previously failed or were intolerant to at least 1 or more TNF-antagonist



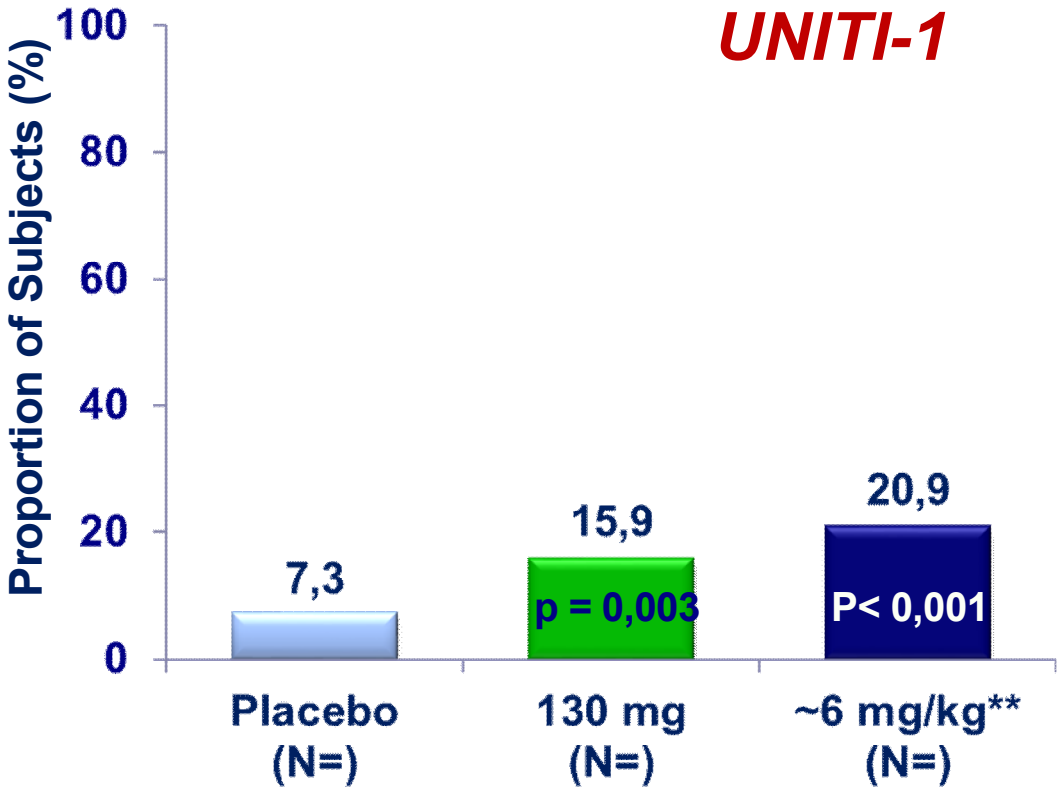
Patients who had **NOT** previously demonstrated inadequate response or intolerance to 1 or more TNF antagonist

Sandborn et al. Inflamm Bowel Dis 2016. Feagan et al. UEGW 2015.

Ustekinumab (anti-IL12/23 p40): *phase III*

clinical remission at week 8

Clinical Remission at W8: CDAI <150



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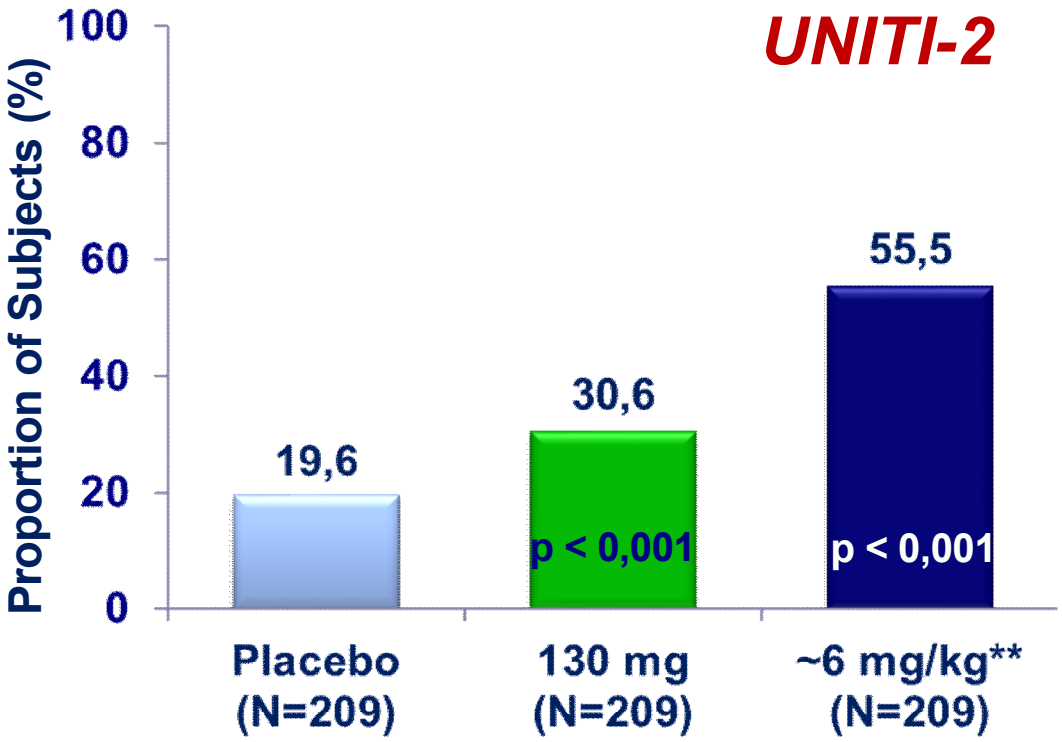
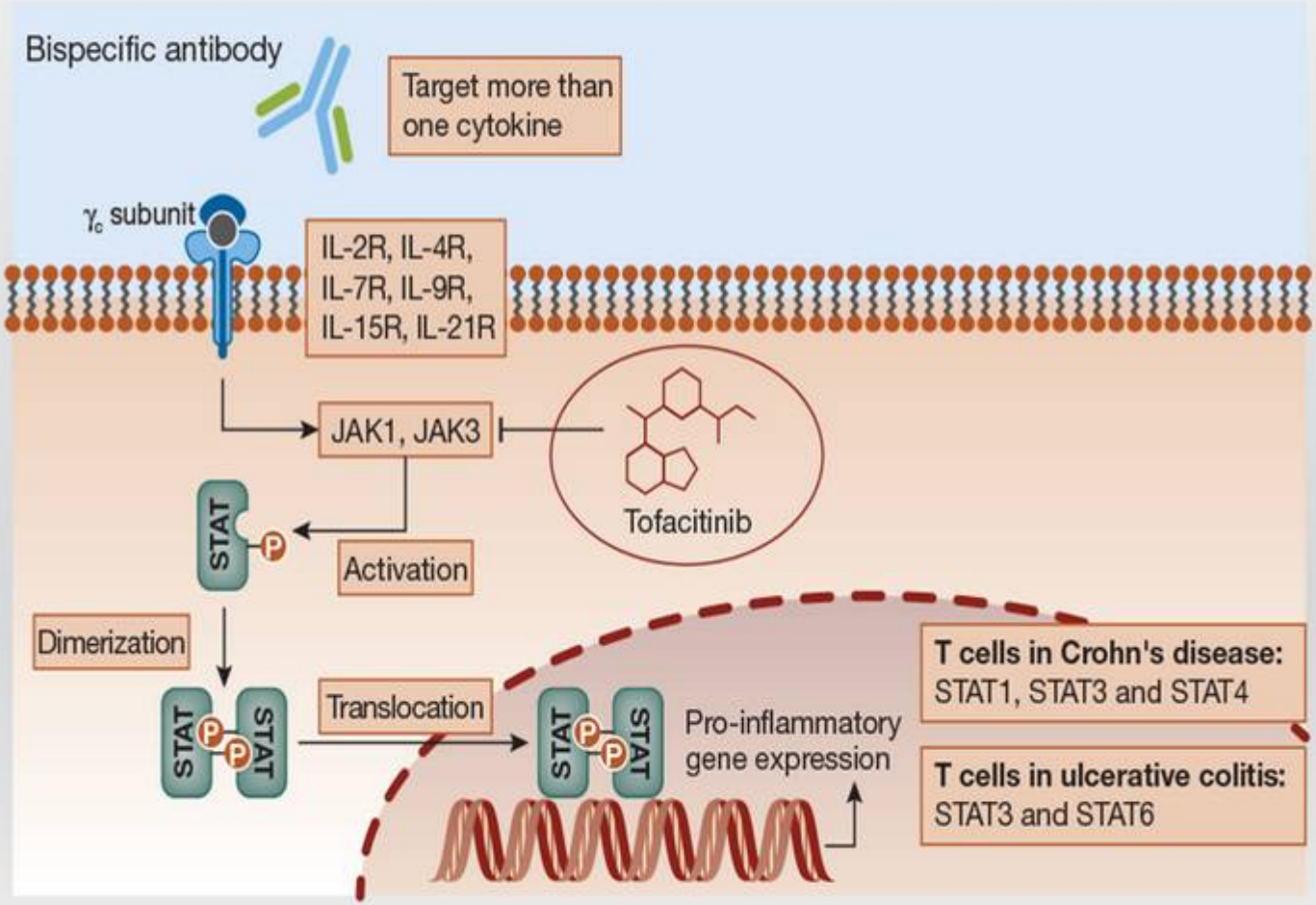


Patients who had **NOT** previously demonstrated inadequate response or intolerance to 1 or more TNF antagonist

Sandborn et al. Inflamm Bowel Dis 2016. Feagan et al. UEGW 2015.

New Targets of Cytokine Signalling in IBD: Tofacitinib[1]

- Tofacitinib is a JAK1/JAK3 inhibitor approved for rheumatoid arthritis

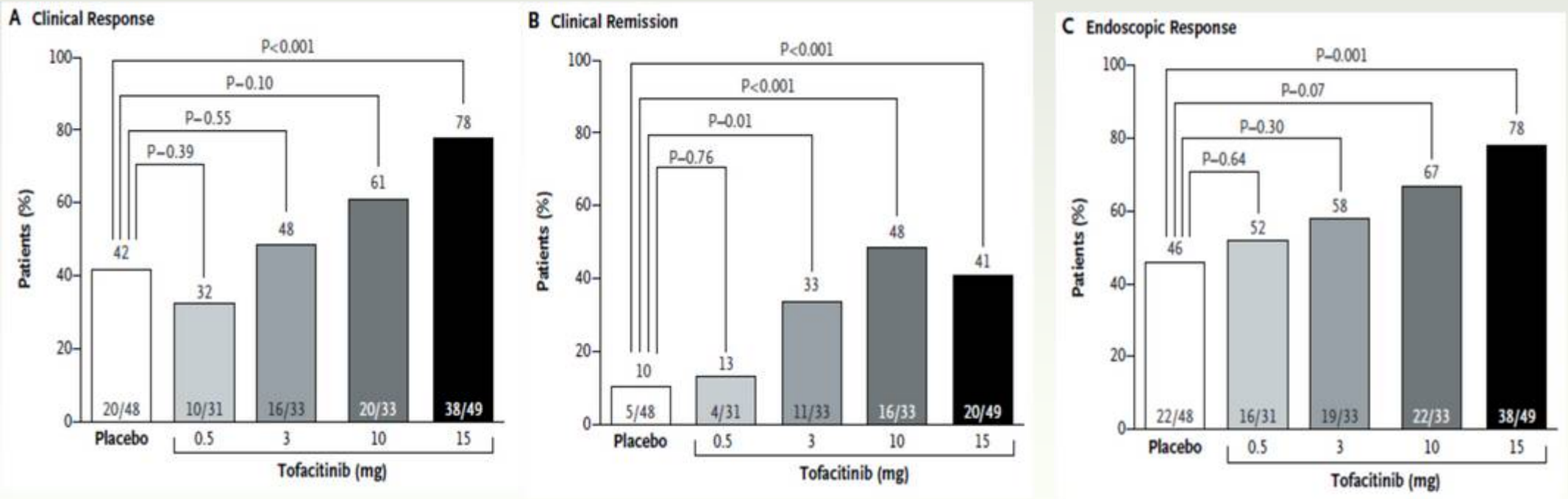


PeerVoice

Tofacitinib

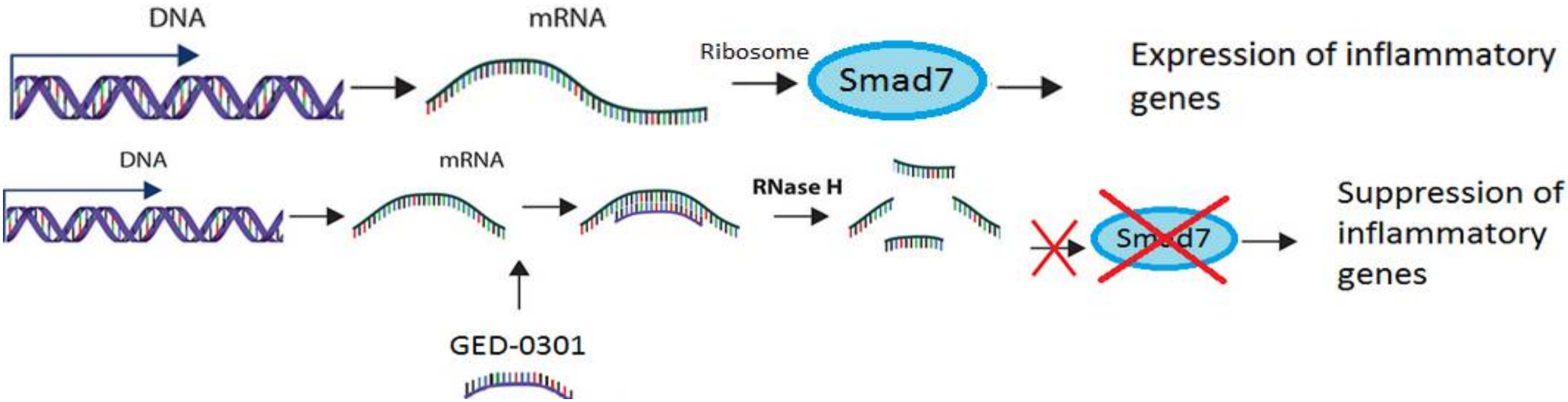
- Essai de phase II (4 doses de CP-690,550) randomisée contre placebo, en double aveugle
- 194 RCH modérées à sévère Mayo > 6 et sous score endoscopique > 2

Objectif principal : réponse clinique (baisse > 30 % score Mayo) à S8



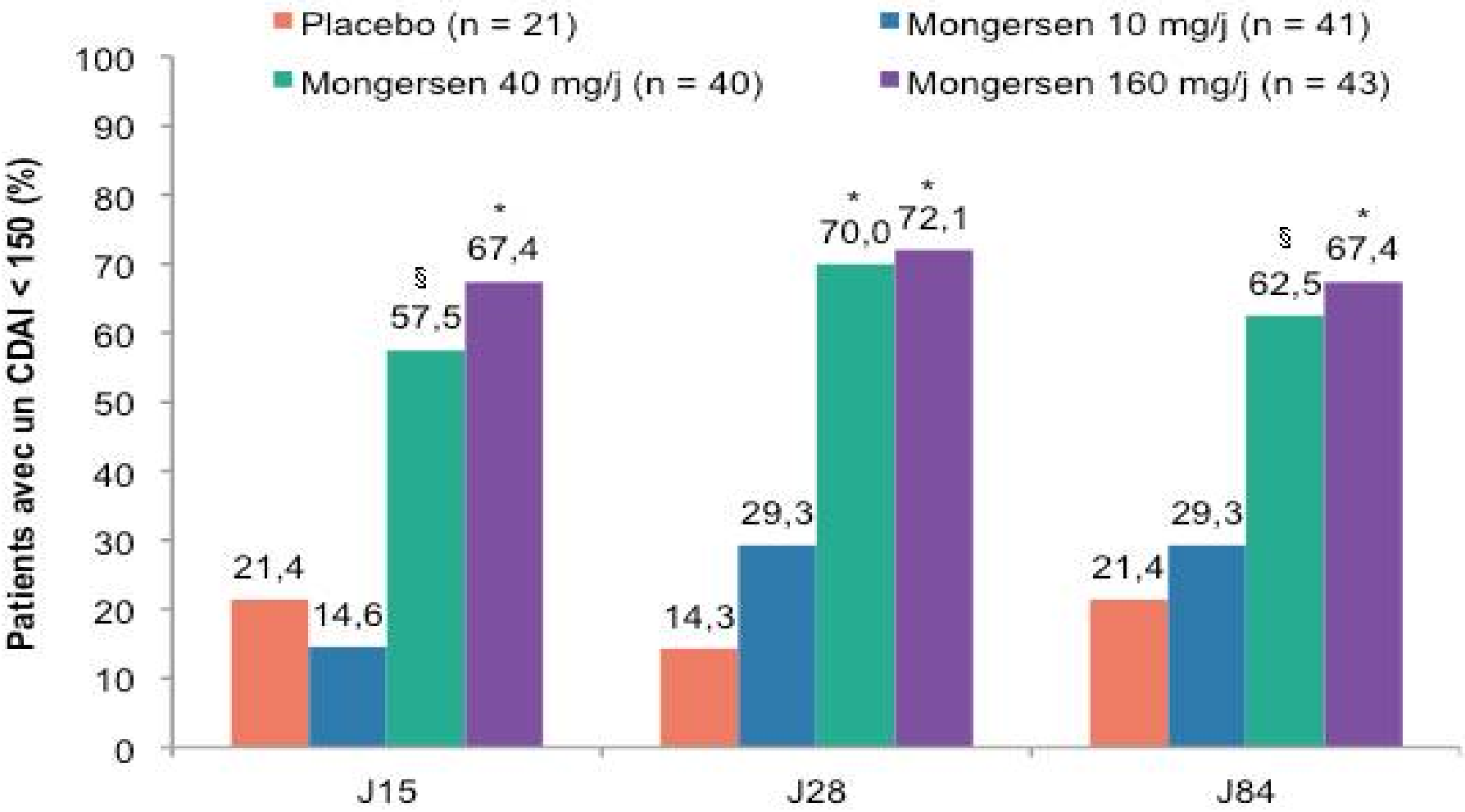
Sandborn et al. N Engl J Med 2012

Mongersen: oligonucléotide antisens anti-Smad7 (TGFβ)



Monteleone et al. N Engl J Med. 2015

Mongersen: oligonucléotide antisens anti-Smad7 (TGFβ)



Monteleone et al. N Engl J Med. 2015

Conclusion

Arguments socio-économiques → OM vs. PSG