Les biothérapies en Gastroentérologie

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UPEC
Connaissance - Action
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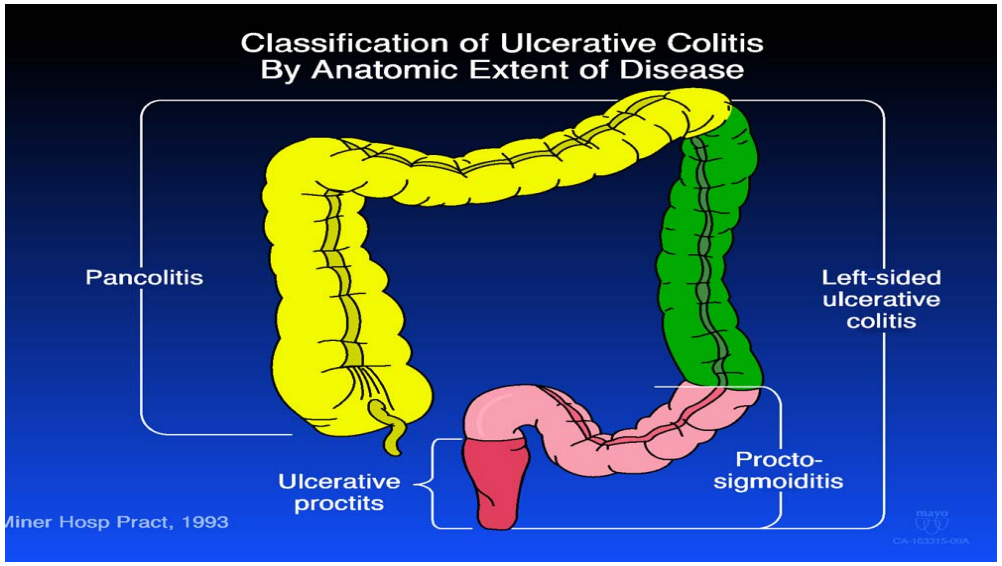
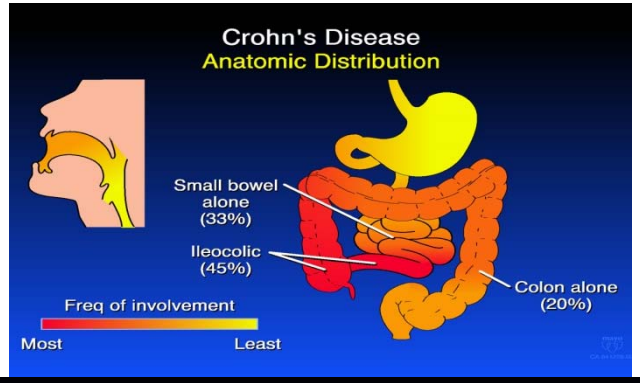
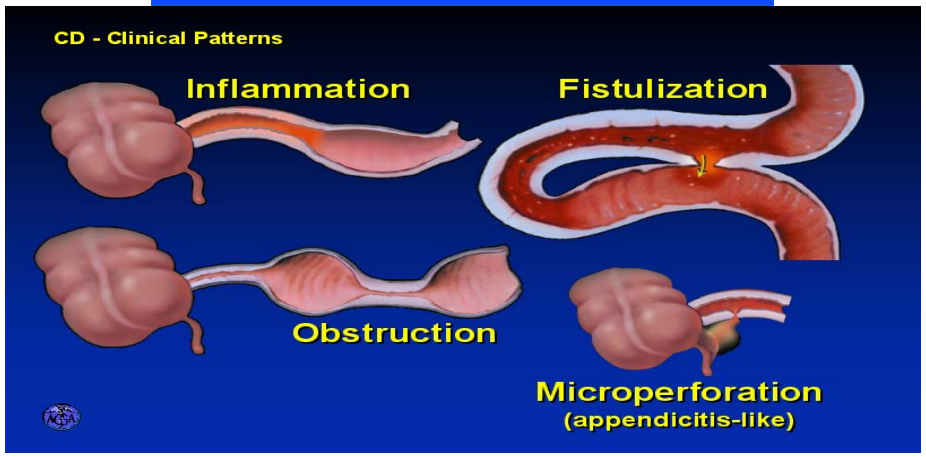
MICIs


Classification of Ulcerative Colitis
By Anatomic Extent of Disease
Pancolitis
Left-sided
ulcerative
colitis
Ulcerative
proctits
Procto-
sigmoiditis
Miner Hosp Pract, 1993


Crohn's Disease
Anatomic Distribution
Small bowel
alone
(33%)
Ileocolic
(45%)
Colon alone
(20%)
Freq of involvement
Most
Least


CD - Clinical Patterns
Inflammation
Fistulization
Obstruction
Microperforation
(appendicitis-like)

Epidémiologie des MICI

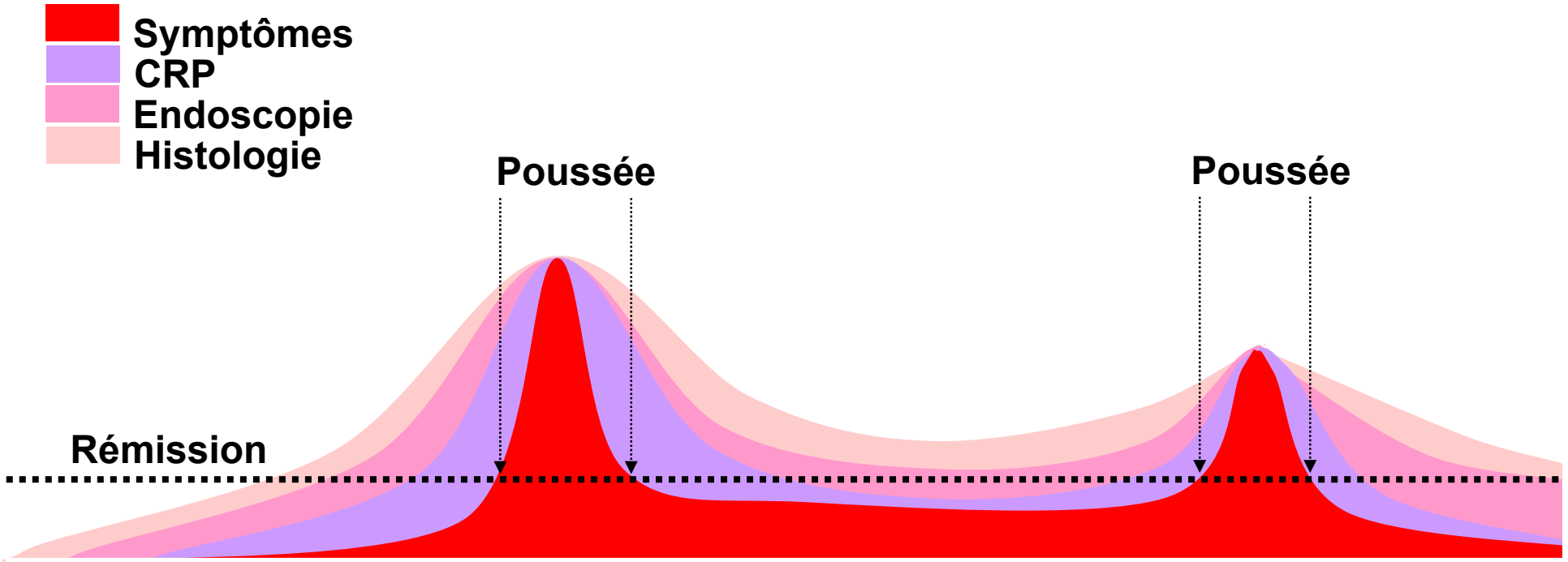
Prévalence 1/1000
1.5 million patients

	Maladie de Crohn n=100 112 (47.7)	RCH n=109 889 (52.3)
Age au diagnostic	32 (23-45)	41 (29-54)
Sexe masculin	42 234 (42)	54 658 (50)
Patients incidents	34 739 (35)	34 986 (32)
Hospitalisation liée à la MICI	11 299 (11.3)	18 531(16.9)

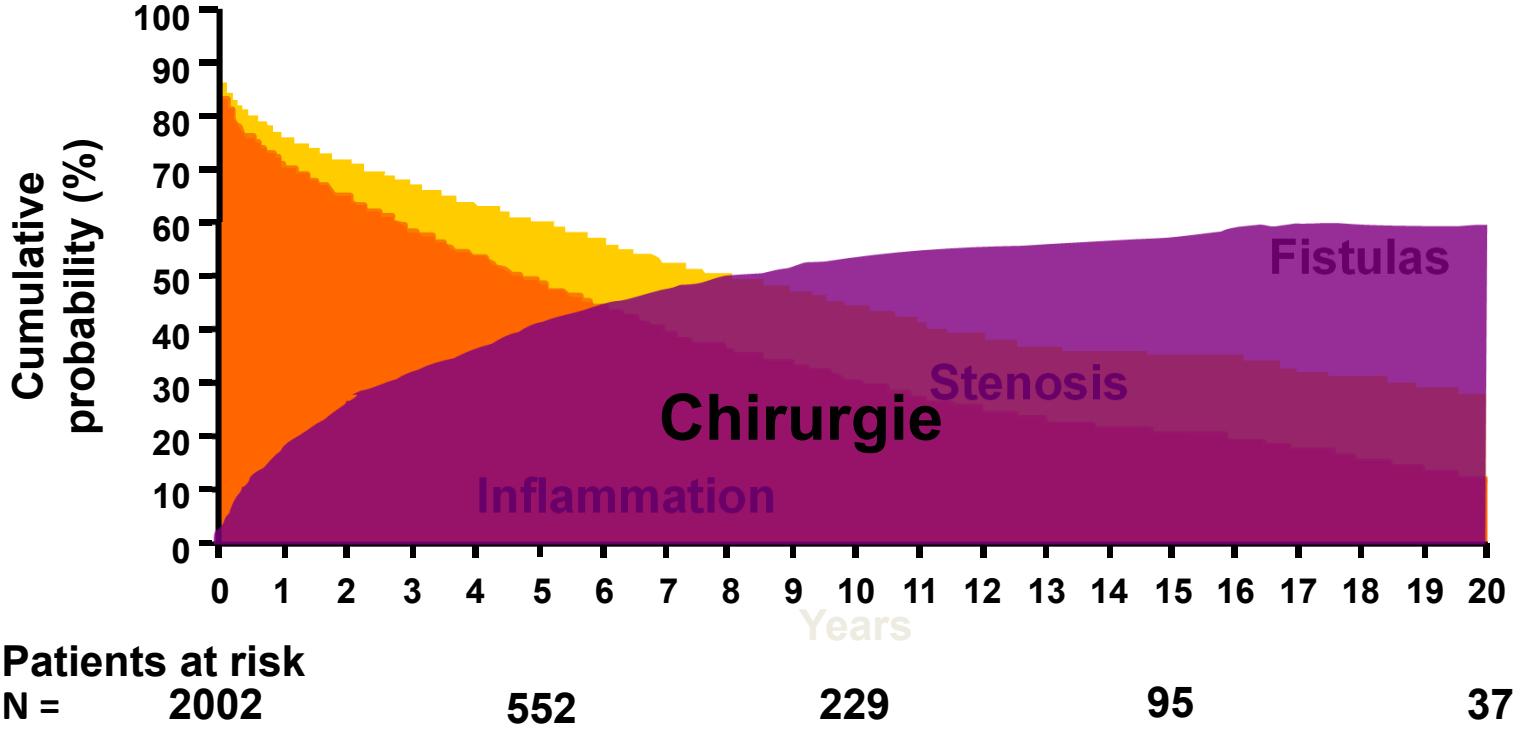
Resultats exprimés en terme de médiane (IQR) ou de nombre (%)

Kirchgesner et al. Aliment Pharmacol Ther 2016

Histoire naturelle des MICI



Histoire naturelle des MICI



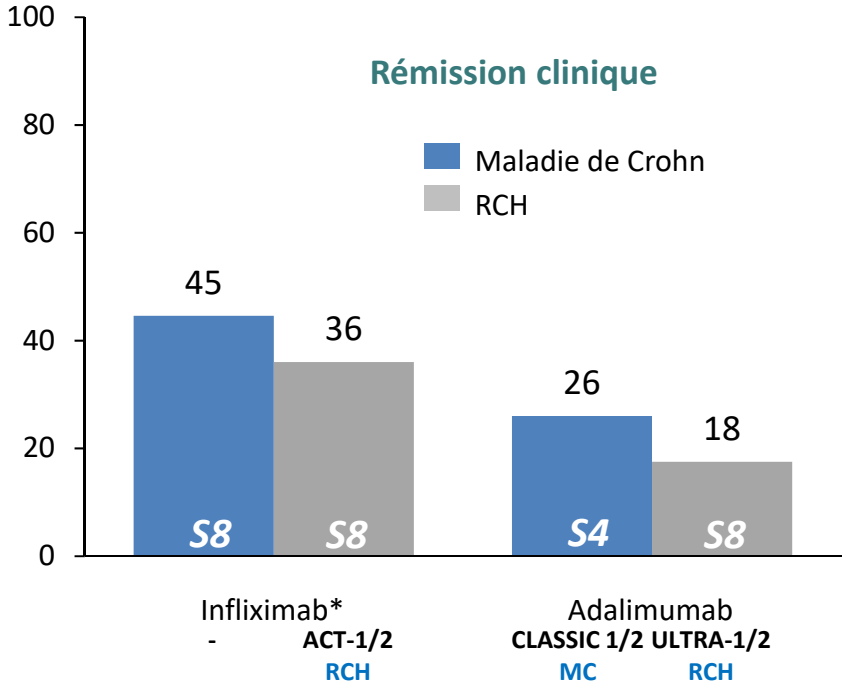
Cosnes J et al. Inflamm Bowel Dis 2002

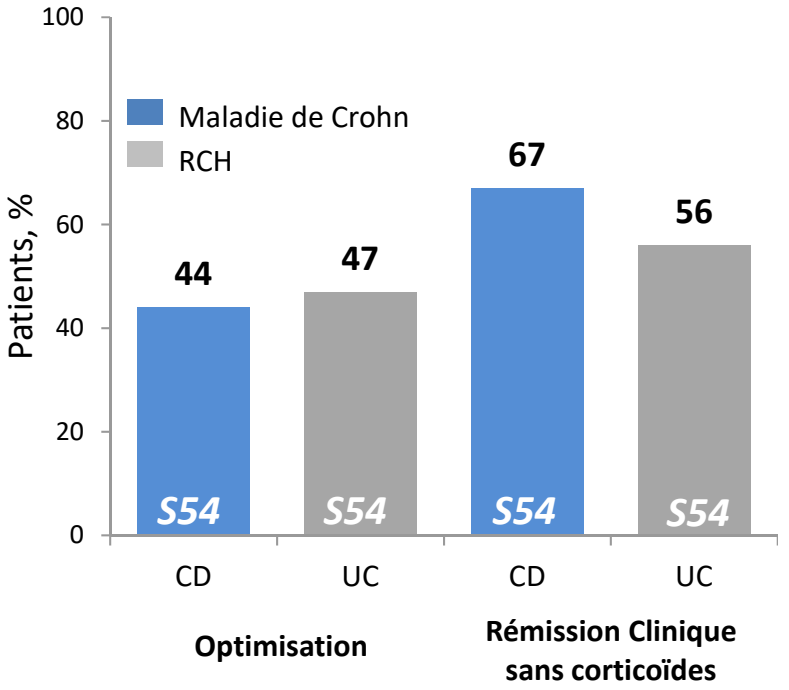
Biothérapies et MICI: Anti-TNF



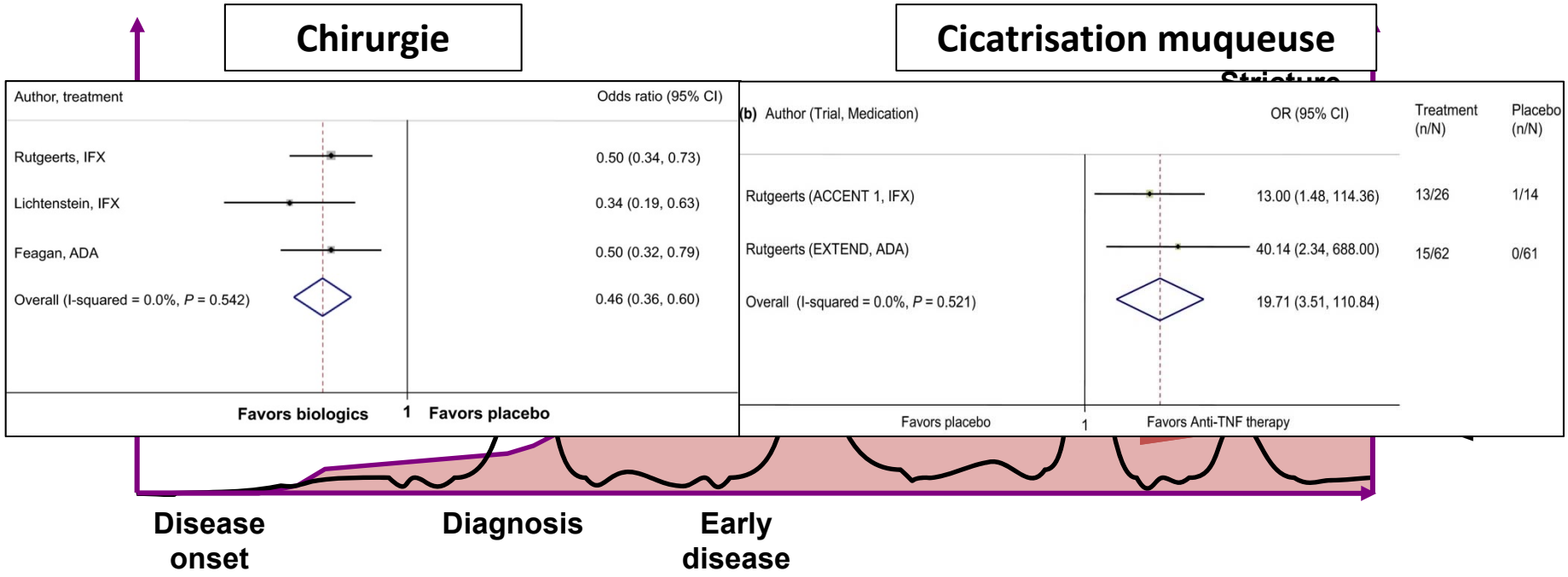
	Infliximab	**Adalimumab**	**Golimumab**
Type	IgG1κ chimérique (75%)	IgG1 Humanisé (100%)	Fab' PEG humanisé (95%)
Demi-vie	8-10 jours	14-19 jours	14 jours
Voie d'admin.	IV	SC	SC
Induction	S0, S2, S6 5mg/kg	S0, S2 40mg	S0, S2, S4 200mg
Maintenance	/8 semaines	/2 semaines	4 semaines
Indication	Crohn / RCH 1999 / 2005	Crohn / RCH 2007 / 2013	RCH 2014

Anti-TNF et MICI



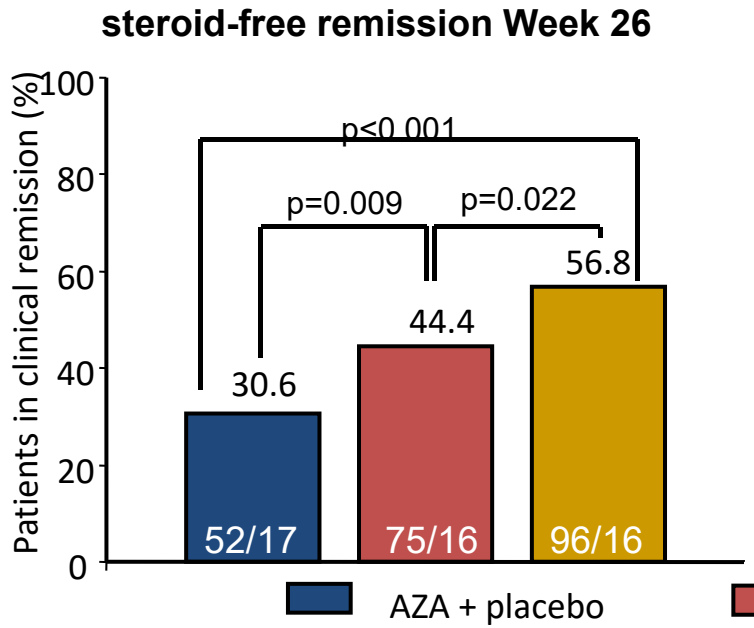


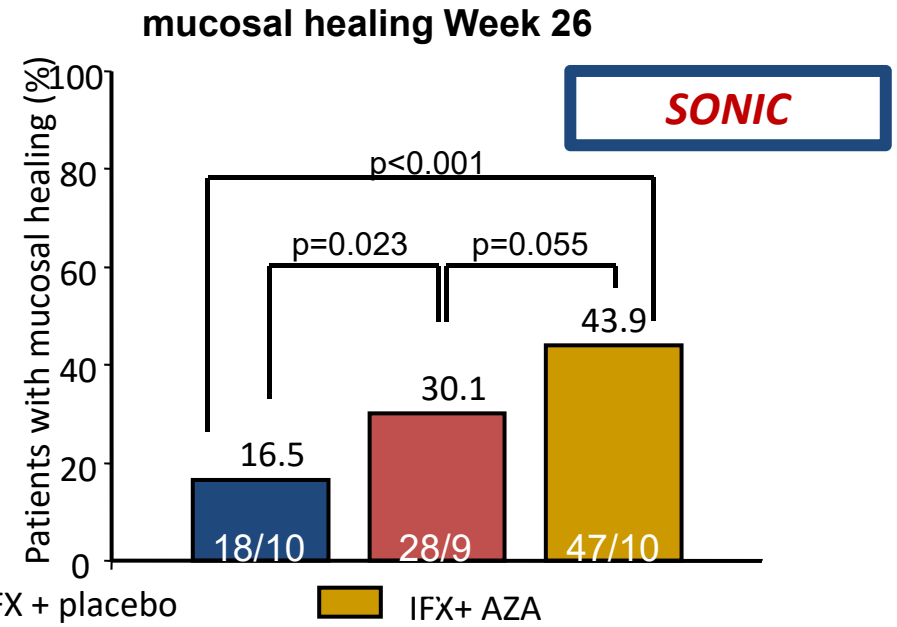
Anti-TNF: au-delà des symtpômes



Mao et al. Aliment Pharmacol Ther 2017; 45(1): 3-13
Cholapranee et al. Aliment Pharmacol Ther 2017; 45(10): 1291-302

Anti-TNF: utilisation précoce



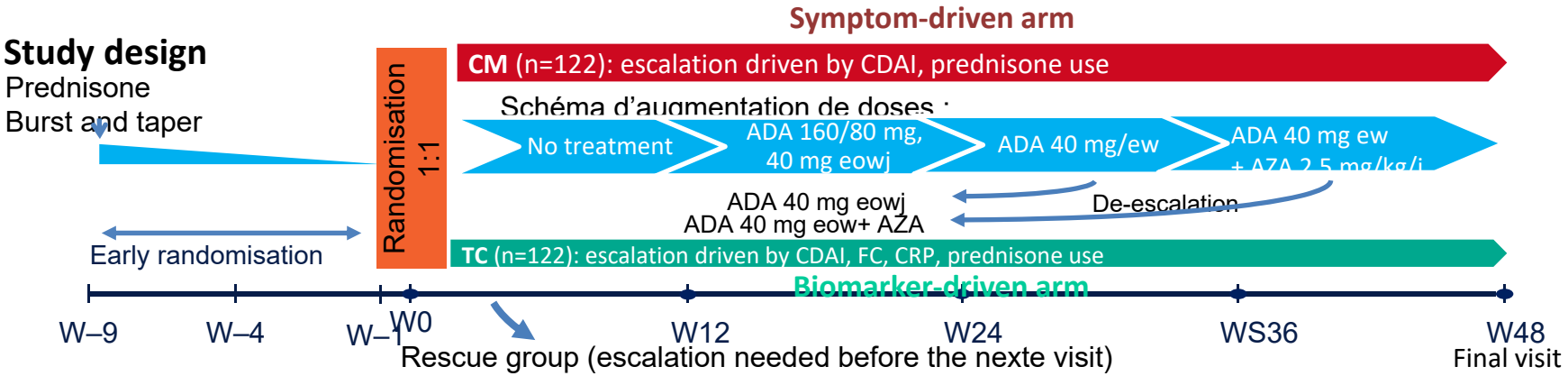


Colombel JF, et al. New Engl J Med 2010;362:1383–95

Critères d'inclusion (durée MC #2 ans)

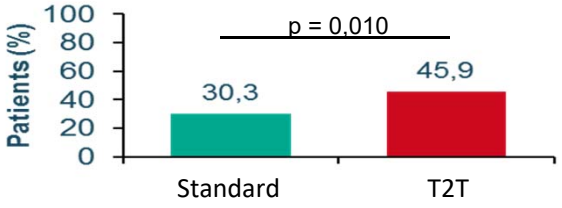
- ***CDAI entre 220 et 450***
- ***Corticodépendant, ou échec 5-ASA ou budésonide***
- ***Naïf de thiopurine et d'anti-TNF***

Monitoring au-delà des symptômes

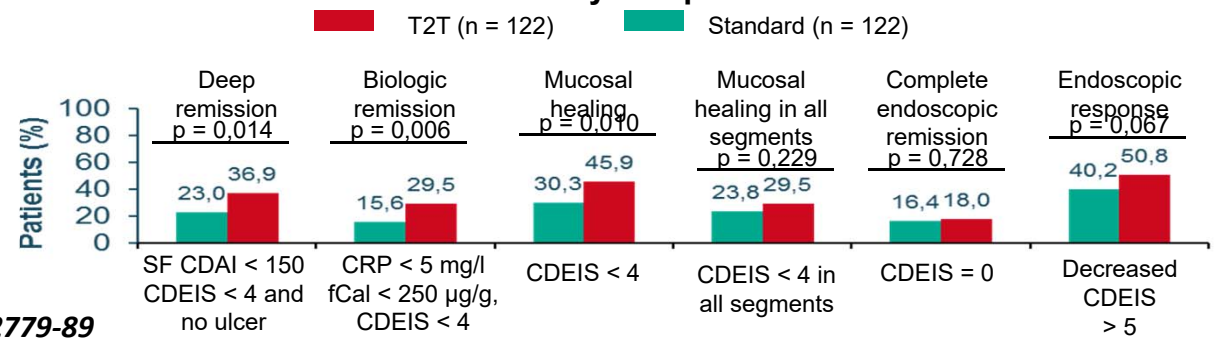


CDEIS < 4 without any ulcer at W48

(Primary end-point)



Secondary end-points at W48

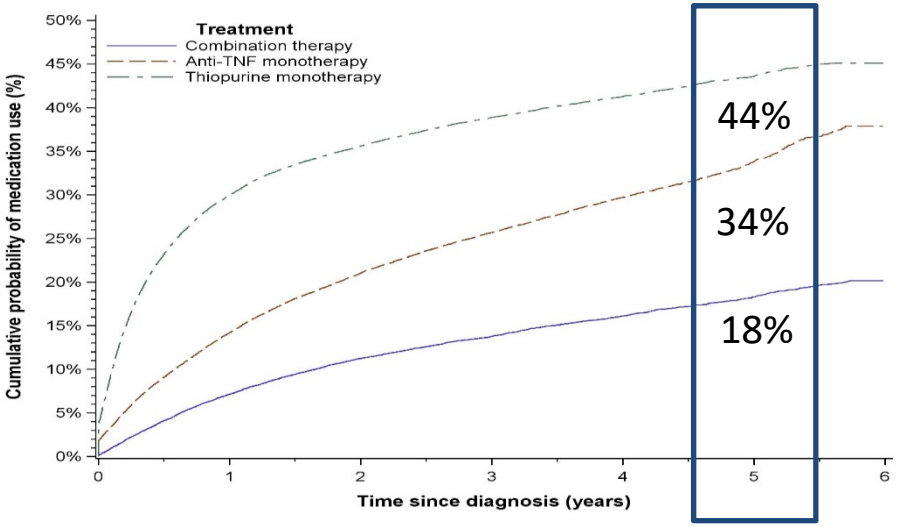


Colombel et al. Lancet 2018; 390(10114): 2779-89

Changement de paradigme

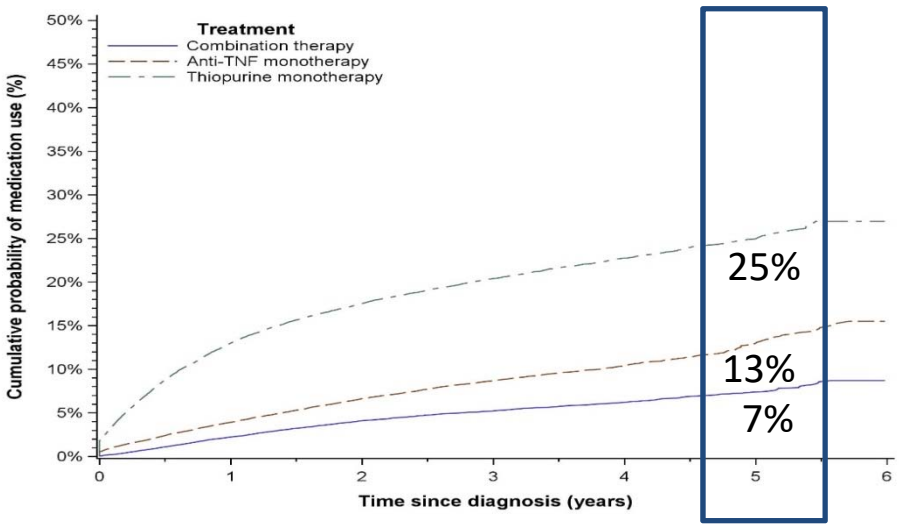
Maladie de Crohn incidentes (2009-2013)

n=34 739



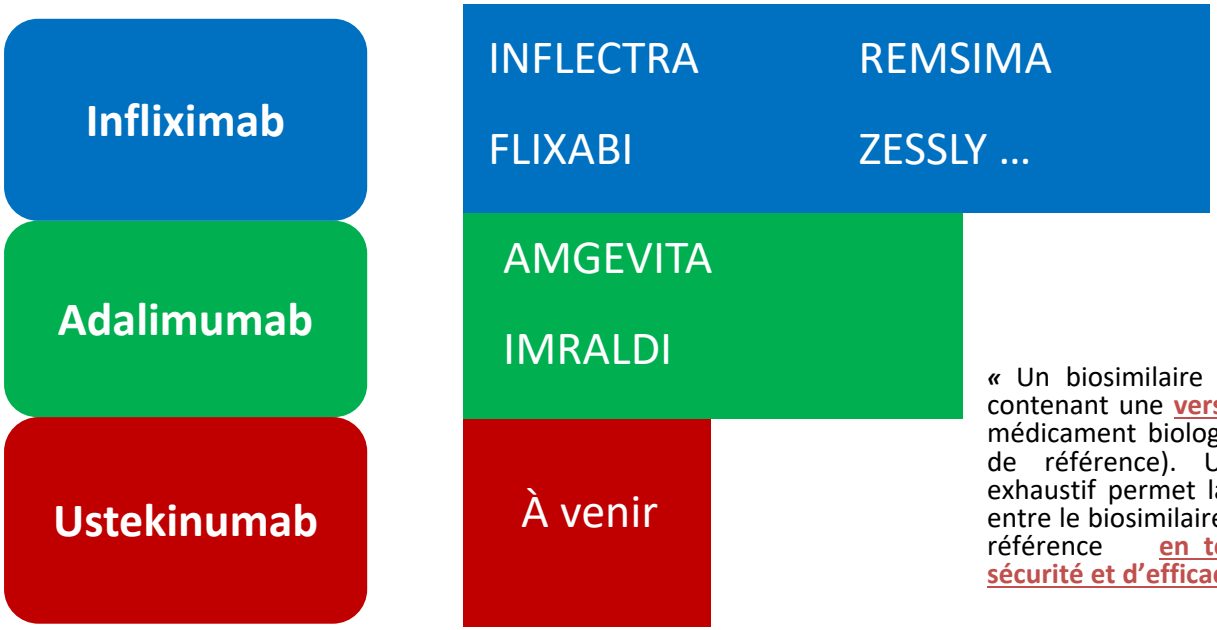
RCH incidentes (2009-2013)

n=34 986



Kirchegesner et al. Aliment Pharmacol Ther. 2017 Jan;45(1):37-49

L’ère des biosimilaires



« Un biosimilaire est un produit médicamenteux contenant une **version de la substance active** d’un médicament biologique déjà autorisé (médicament de référence). Un exercice de comparabilité exhaustif permet la démonstration de la similarité entre le biosimilaire et le médicament biologique de référence **en termes d’activité biologique, de sécurité et d’efficacité**.”

Interchangeabilité des biosimilaires

	IFX (N= 202)	CT-P13 (N=206)	Adjusted rate difference (95% CI)
Aggravation de la maladie inflammatoire	53 (26.2%)	61 (29.6%)	-4.4 (-12.7–3.9)

	IFX	CT-P13	Adjusted rate difference* (95% CI)
Maladie de Crohn	14 (21.2%)	23 (36.5%)	-29.3–10.0%
HBI	0,26 (2,35)	0,49 (3,15)	-1,14-0,33
RCH	3 (9.1%)	5 (11.9%)	-15.2–10.0%
UCDAI partiel	0,09 (1,28)	-0,17 (1,68)	-0,30-0,59
Calprotectine fécale (log10)	0,035 (0,506)	0,096 (0,477)	-0,086-0,177

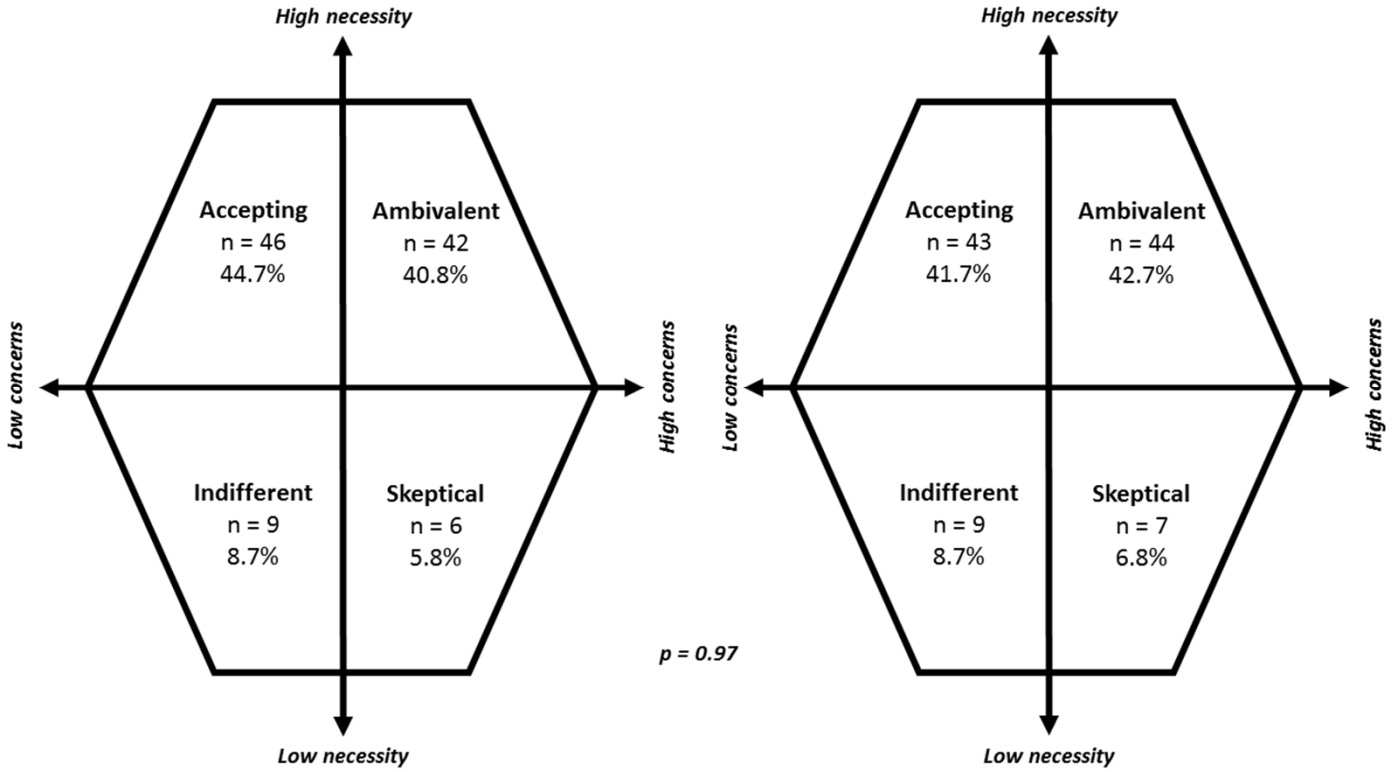
NOR SWITCH

	IFX (N= 241)	CT-P13 (N=240)
Incidence of ADAb	17 (7.1%)	19 (7.9%)

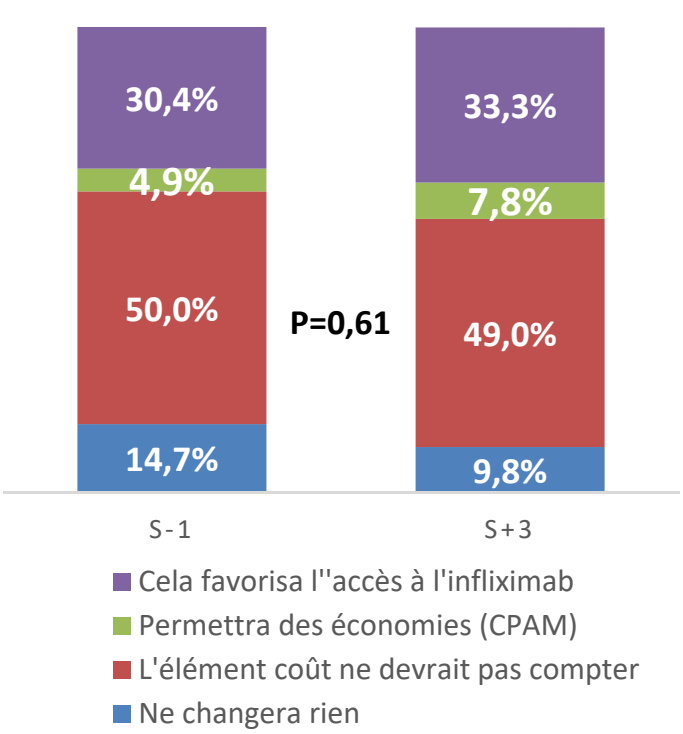
EudraCT Number: 2014-002056-40[1]

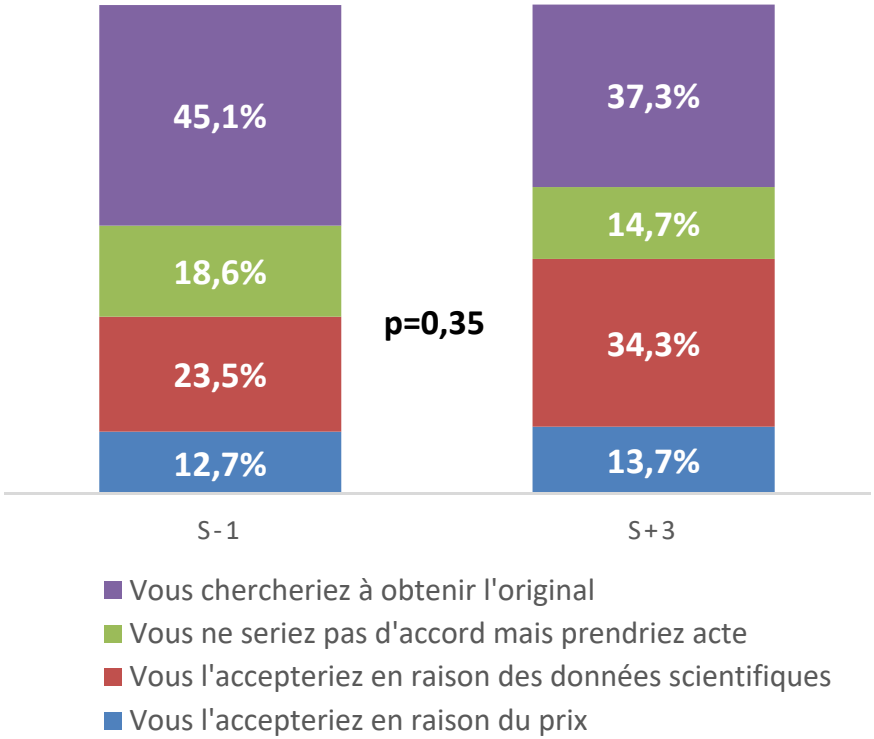
Jørgensen K, et al. Lancet 2017; 389: 2304-16

Biosimilaires: acceptation



Biosimilaires: relation médecin / patient +++

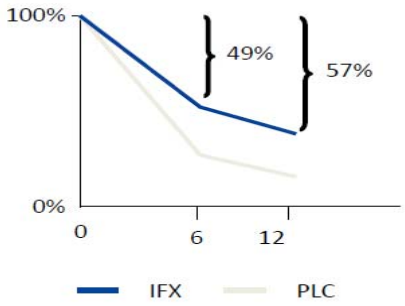




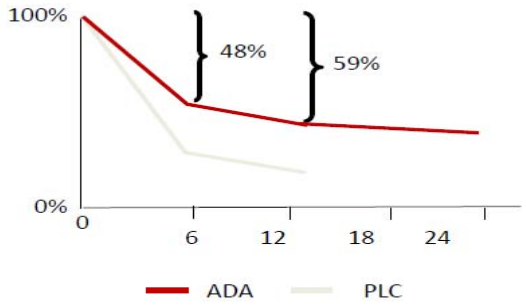
La face cachée des anti-TNF

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

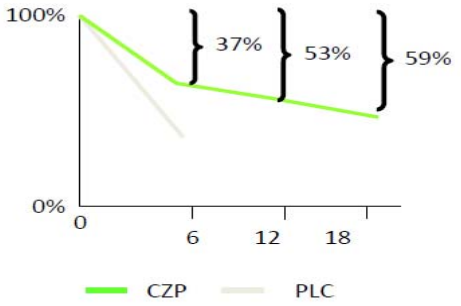
ACCENT I[1]
CDAI 70 and 25 %
(week 30)



CHARM[2]
CDAI 70
(week 26)



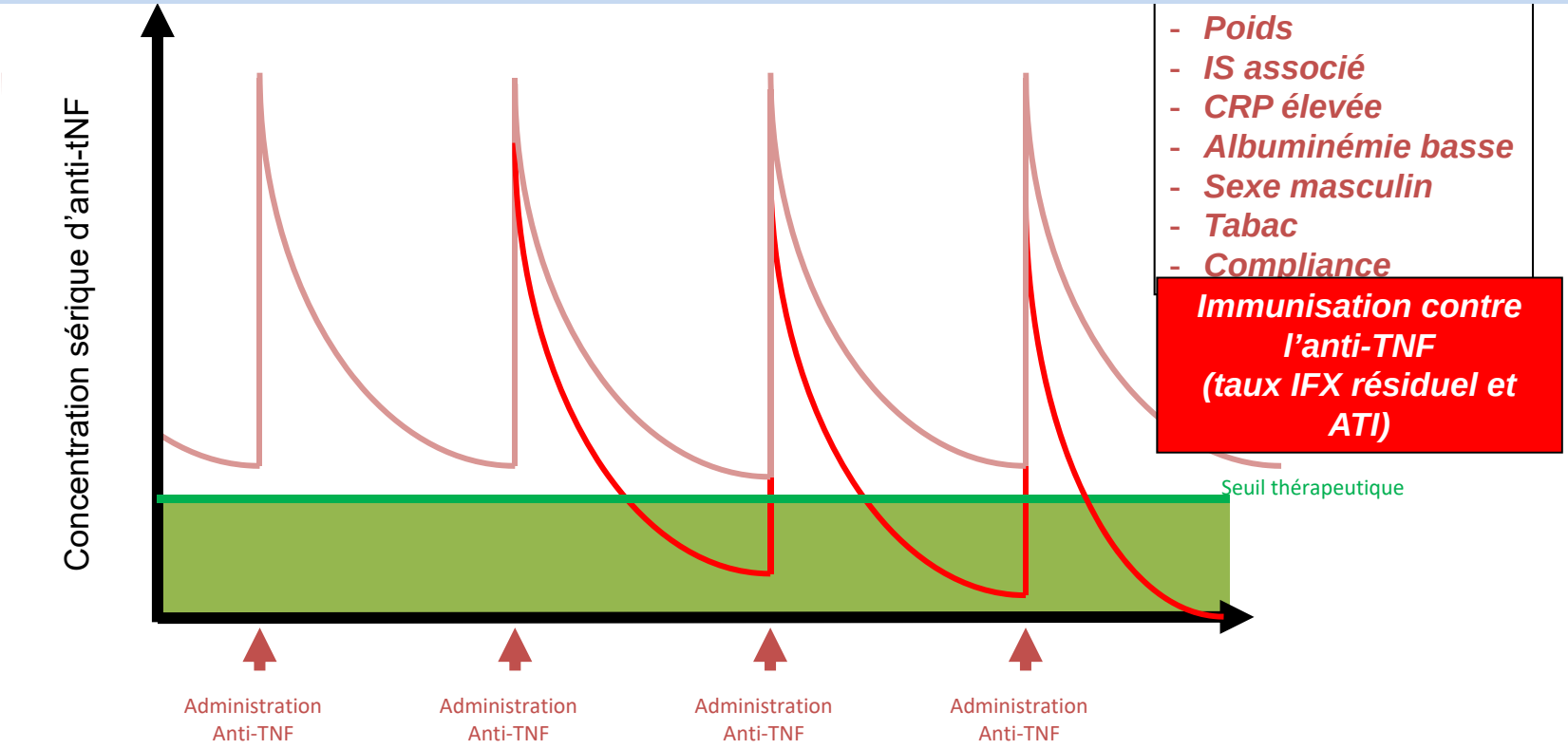
PRECiSE 2-3[3]
CDAI 100 and HBI*
(week 26)



* open label after 6 months, Harvey-Bradshaw Index)

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

Mécanisme de résistance aux anti-TNF

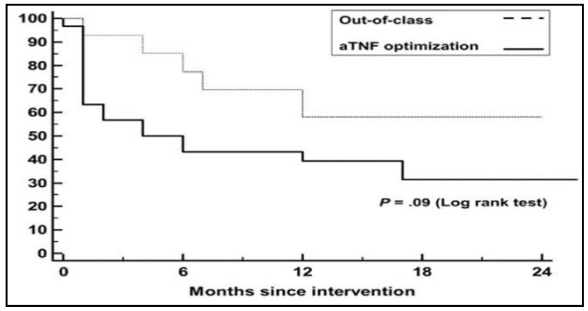


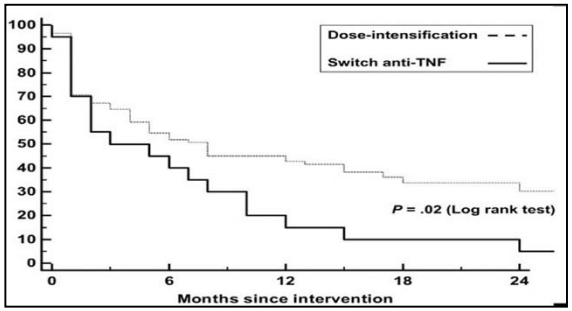
Monitoring pharmacologique des anti-TNF

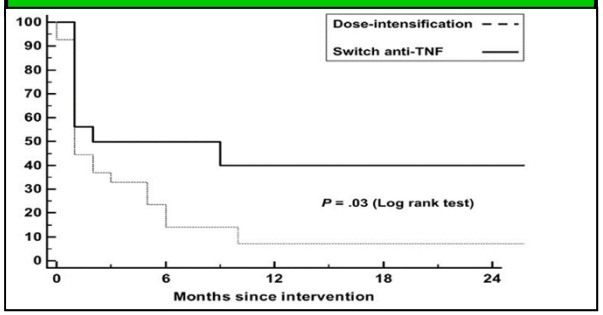
Trough level élevé → **Switch out-of class**

Trough level bas ADA négatifs → **Opti anti-TNF**

Trough level bas ADA positifs → **Opti anti-TNF + IS Switch in-class ou out-of-class**







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

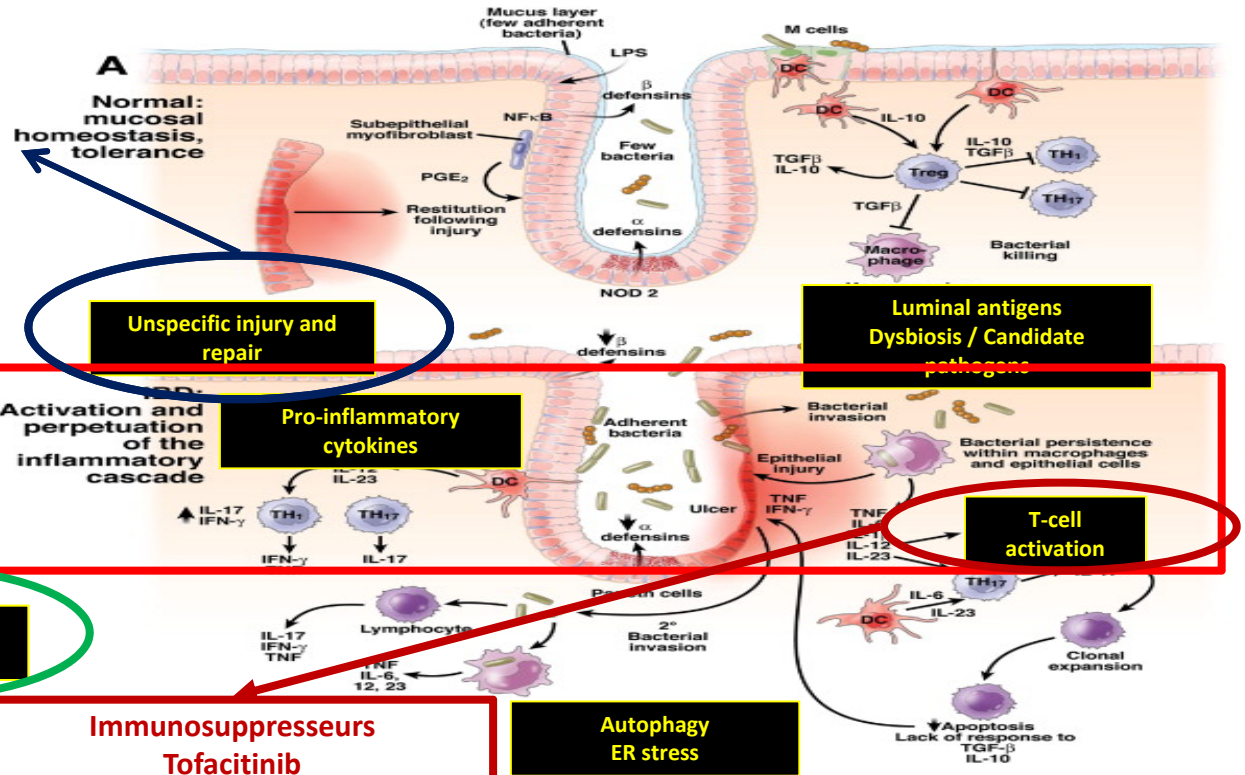
Nouvelles biothérapies au cours des MICI

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

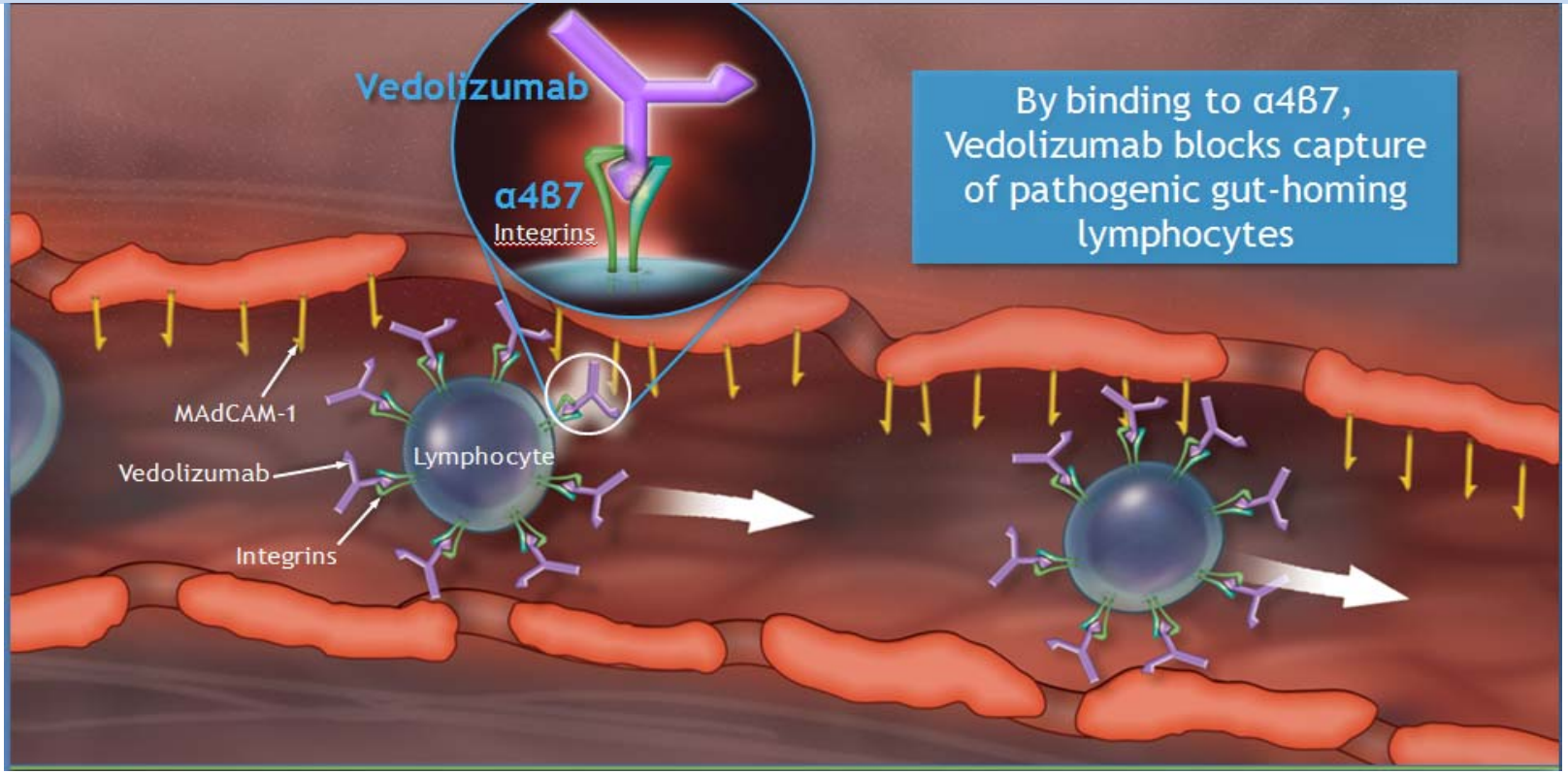
Anti-α4 intégrine

Adhesion and cell infiltration

Anti-SMAD7
Mongersen

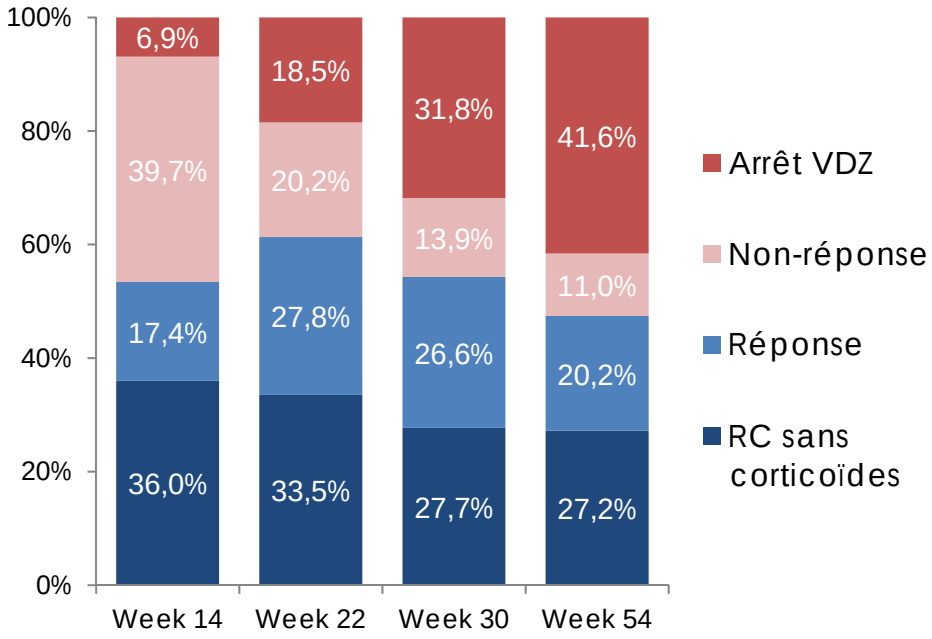


Vedolizumab

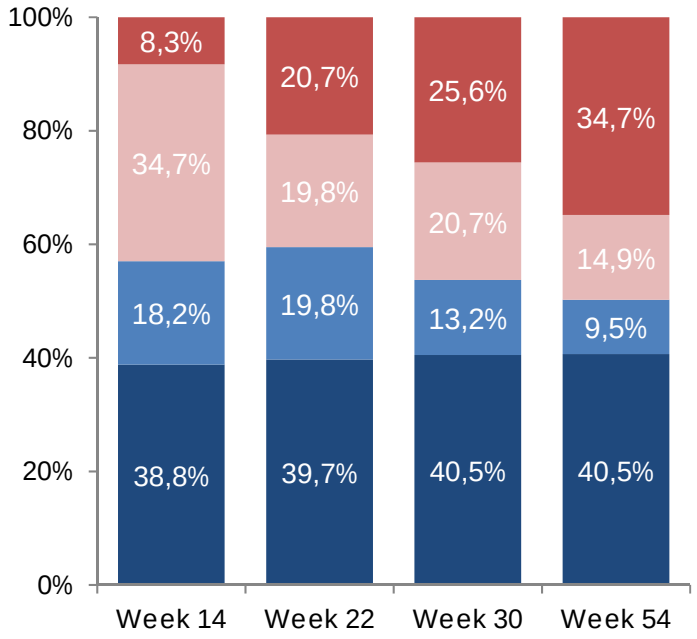


Vedolizumab

Maladie de Crohn
n = 173

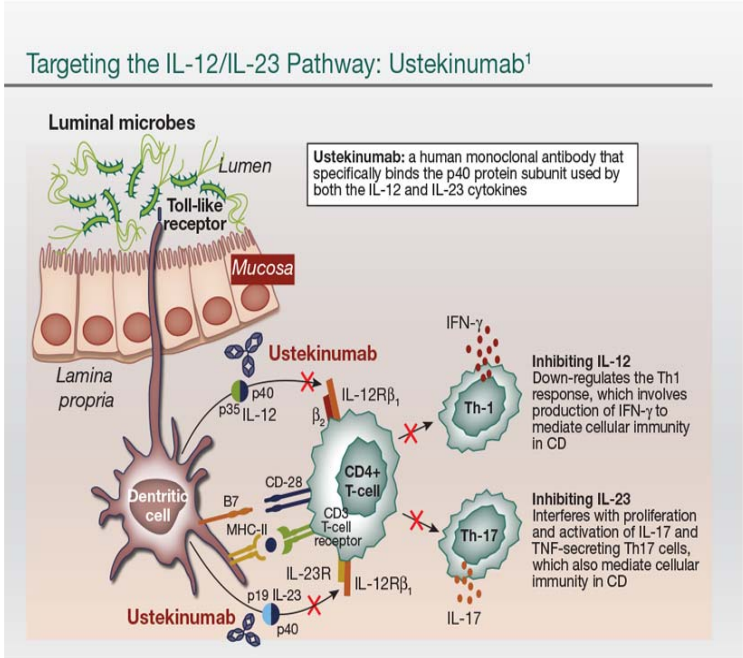


Rectocolite hémorragique
n = 121



Amiot et al. Aliment Pharmacol Ther 2017

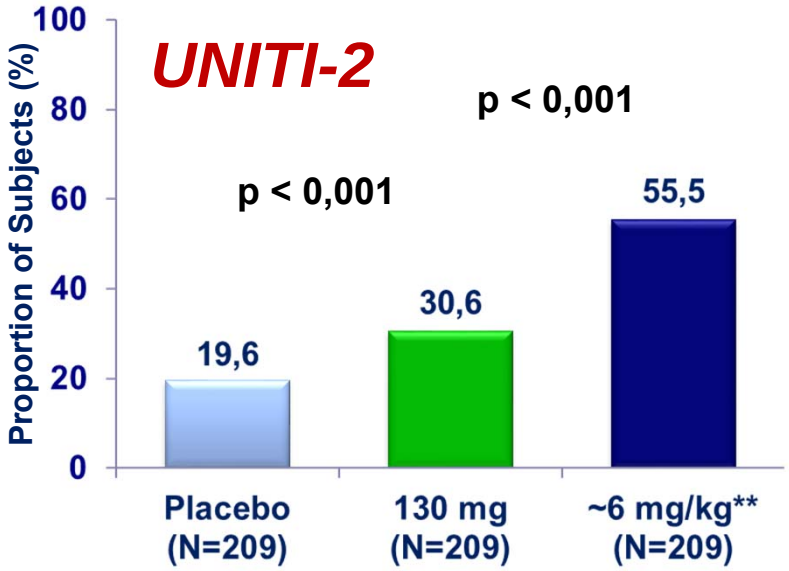
Ustekinumab



http://www.peervoice.com/o1/pvr208

PeerVoice

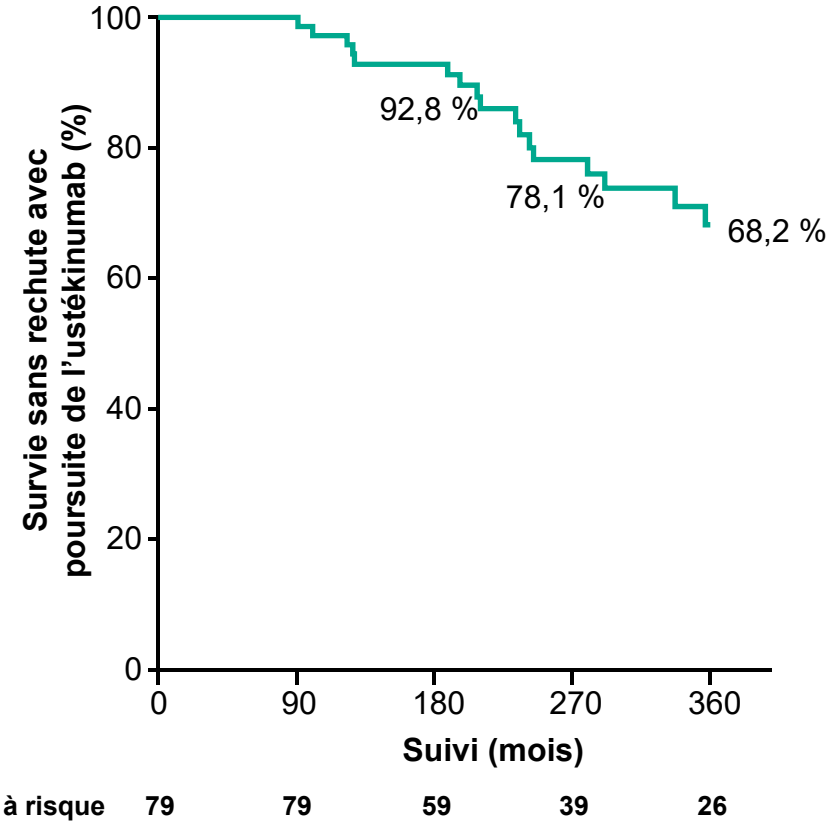
Ustekinumab



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

Wils et al. Clin Gastroenterol Hepatol 2015

Sandborn et al N Engl J Med 2017

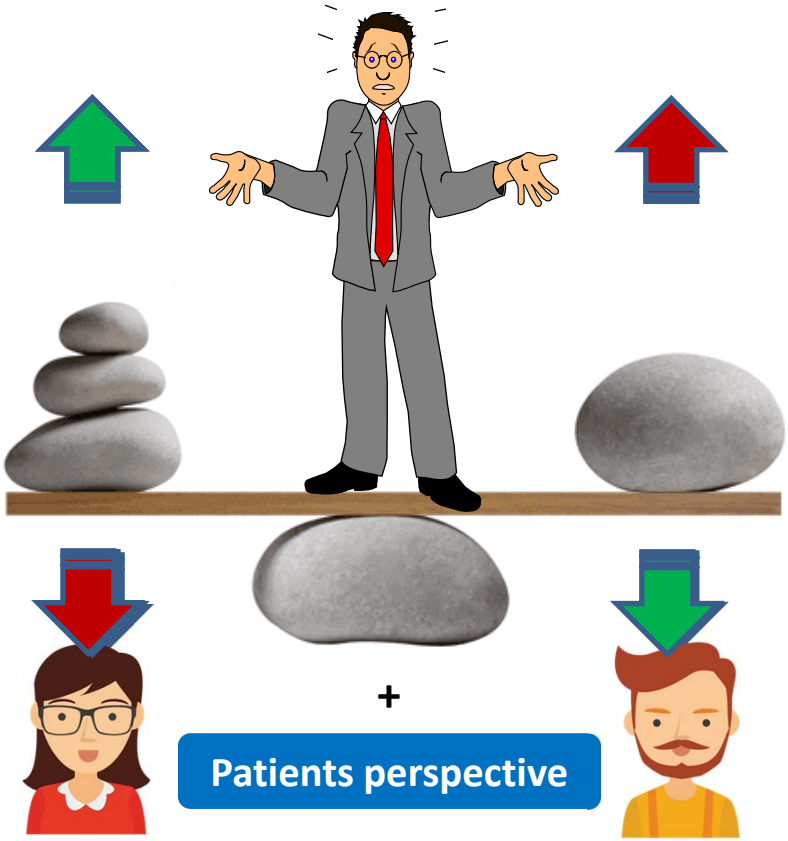


Rapport bénéfice/risque des anti-TNF

Rémission prolongée

Cicatrisation muqueuse

PRO / QoL



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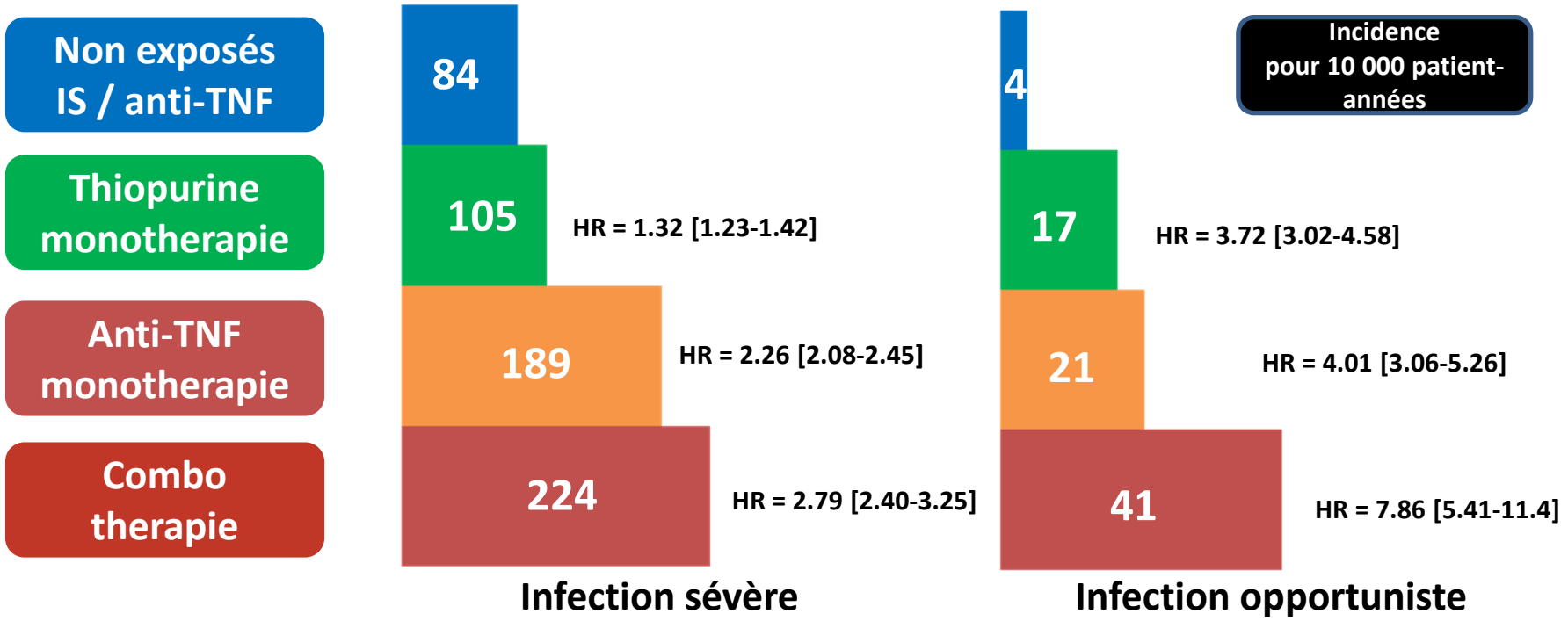
Patients perspective

Infection Effets secondaires

Cancer - Lymphome

Aspect médicoéconomique

Risque infectieux et anti-TNF



Kirchgesner et al. Gastroenterology 2018; 155(2): 337-46.

Risque néoplasique et MICI

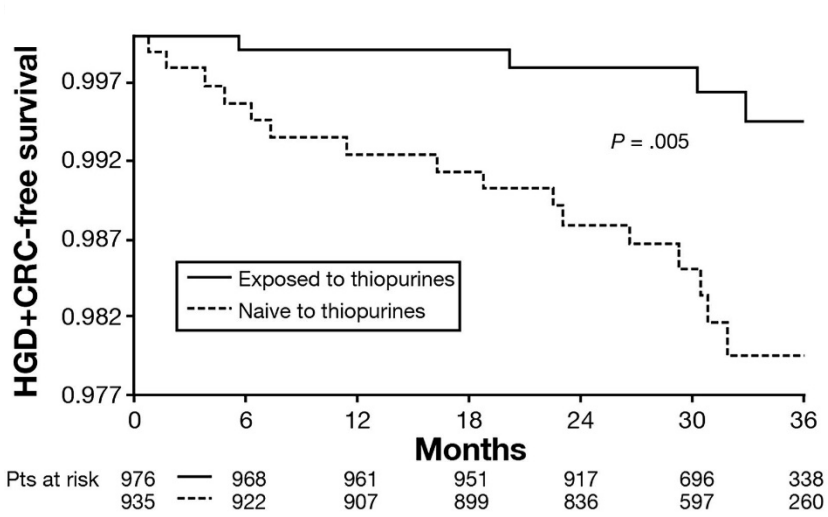
DONNEES EPIDEMIOLOGIQUES POOLEES

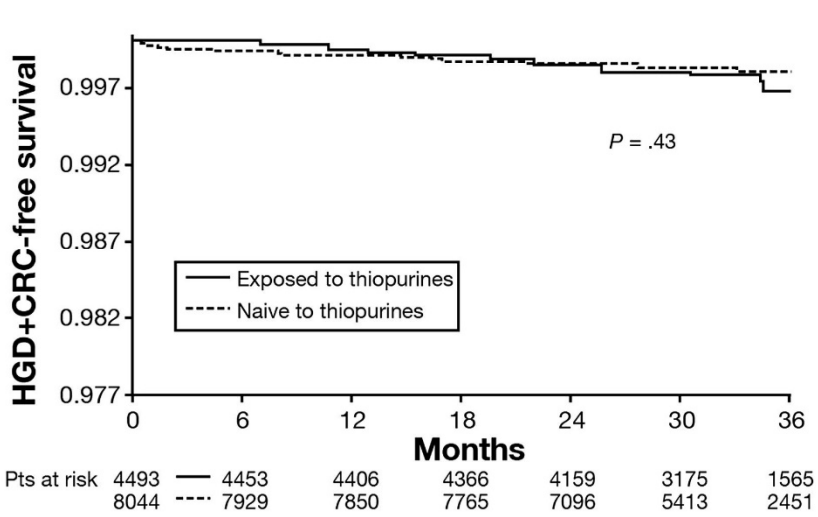
	Taux d'incidence (pour 10 000 PY)	HR (95%IC)		
		Thiopurine	Anti-TNF	Combination therapy
Tous cancers sauf cutanés	73	1.4 [1.2-1.7]	1.1 [0.9-1.4]	NA
Cancers hématologiques				
Global	5	NA	0.9 [0.4-1.9]	NA
Lymphome	3	2.6 |2.0-3.4]	2.4 [1.6-3.6]	6.1 [1.3-4.2]
Cancers cutanés				
Baso/Epidermoïde	91	1.9 [1.7-2.1]	1.1 [0.9-1.4]	NA
Mélanome	4	1.1 [0.7-1.7]	1.9 [1.1-3.3]	NA
Urinaire	3	2.8 [1.0-7.7]	1.6 [0.6-4.2]	NA

Beaugerie et al. Clin Gastroenterol Hepatol 2018; in press

Cancer colorectal et MICI

Effet des thiopurines





Beaugerie et al. Gastroenterology 2013; 145: 166-75

Risque cardiovasculaire et MICI

influence de l'activité de la MICI

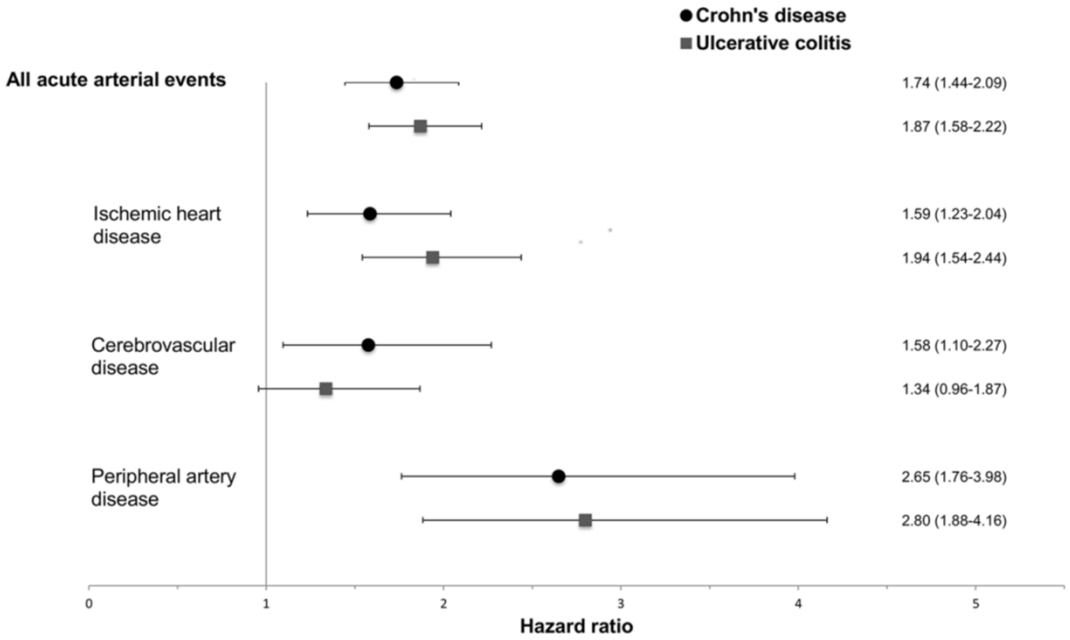


Table 3 Predictive factors of acute arterial events according to IBD subtype: Cox multivariate analysis

	HR (95% CI)	
	CD	UC
Male sex	1.71 (1.56 to 1.87)	2.08 (1.93 to 2.24)
Disease activity (3-month periods before and after IBD-related hospitalisation or surgery)	1.74 (1.44 to 2.09)	1.87 (1.58 to 2.22)
Cardiovascular risk factors		
Hypertension	1.18 (1.05 to 1.32)	1.24 (1.14 to 1.35)
Hyperlipidaemia	1.34 (1.16 to 1.56)	1.16 (1.05 to 1.30)
Diabetes mellitus	1.32 (1.14 to 1.52)	1.48 (1.33 to 1.64)
Obesity	1.02 (0.86 to 1.20)	1.01 (0.89 to 1.15)
Tobacco smoking	1.82 (1.58 to 2.09)	1.49 (1.28 to 1.74)
Alcohol use disorders	1.52 (1.26 to 1.84)	1.51 (1.27 to 1.79)

Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.

Kirchgesner et al. Gut 2018; 67: 1261-8

Risque cardiovasculaire et MICI

Effet des anti-TNF

Risque infarctus du myocarde	sDMARD n = 3 058	Anti-TNF n = 11 200
Nombre IDM	58	194
Taux d'incidence (/10 000 PY)	56 [43-73]	35 [30-40]
Unadjusted HR	1	0,78 [0,58-1,05]
	sDMARD n = 3 058	**Anti-TNF n = 11 200**
HR ajusté sur l'age et le sexe	1	1,19 [0,41-0,89]
HR ajusté sur le score de propension	1	0,61 [0,41-0,89]

Score de propension: age, sexe, DAS28, durée maladie, HAQ score, ATCD traitements, HTA, DNID, BPCO, tabac, statins, corticoids, anti-agregant plaquettaire, AINS, anti-COX2, date de diagnostic

Low et al Ann Rheum Dis 2017; 76: 654-60

Arrêt des anti-TNF

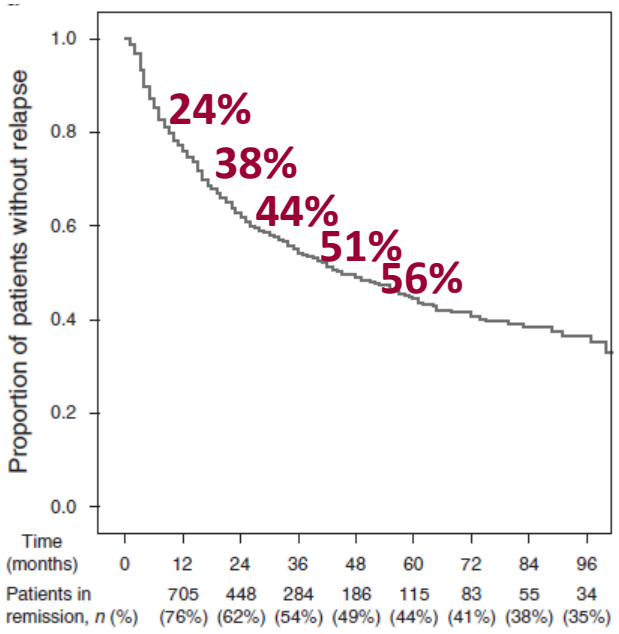


Table 4. **Factors associated with the risk of relapse after discontinuation of anti-TNF therapy in the multivariate analysis in CD**

Factors	HR	95% CI	*P* value
Maintenance of IMMs after discontinuation[a]	0.67	0.51–0.87	0.003
Older age at discontinuation[a]	0.98	0.97–0.99	0.001
Treatment with ADA (vs. IFX)[a]	1.29	1.01–1.66	0.04
Elective discontinuation (vs. discontinuation for top-down strategy)[a]	1.90	1.07–3.37	0.03
Discontinuation because of adverse events (vs. discontinuation as part of a top-down strategy)[a]	2.33	1.27–4.29	0.006
Colonic localization (vs. ileal)[a]	1.51	1.13–2.02	0.005
Stricturing behavior (vs. inflammatory)[a]	1.50	1.09–2.05	0.01

+ tabac + maladie anopérinéale

Casanova et al. Am J gastroenterol 2017; 112: 120-31

Conclusion

→ **Les biothérapies ont révolutionnée la prise en charge des MICI … et continue de le faire**

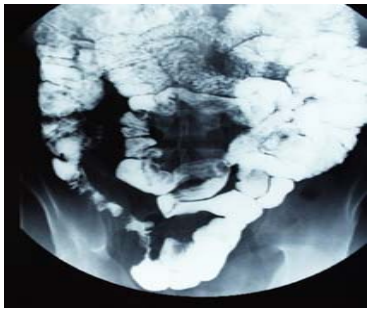
→ **Leur utilisation va se poursuivre en tenant compte**

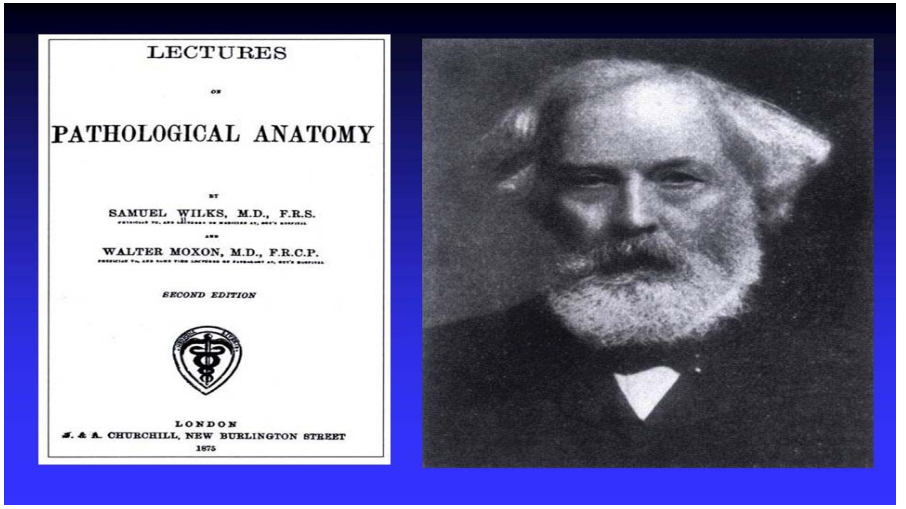
- → D'une meilleure connaissance de leur utilisation optimale pharmacologique
- → D'une meilleure connaissance de leur optimisation au-delà des symptômes
- → De nouvelle molécules: anti-IL12, anti-JAK, anti-S1P …;

→ **Il reste encore beaucoup de choses à accomplir, notamment pour**

- → Identifier des marqueurs pré-emptifs guidant les choix thérapeutiques
- → Améliorer le rapport bénéfice / risque
- → Pérenniser l'aspect médico-économique vers une utilisation plus large

Il était une fois les MICI …

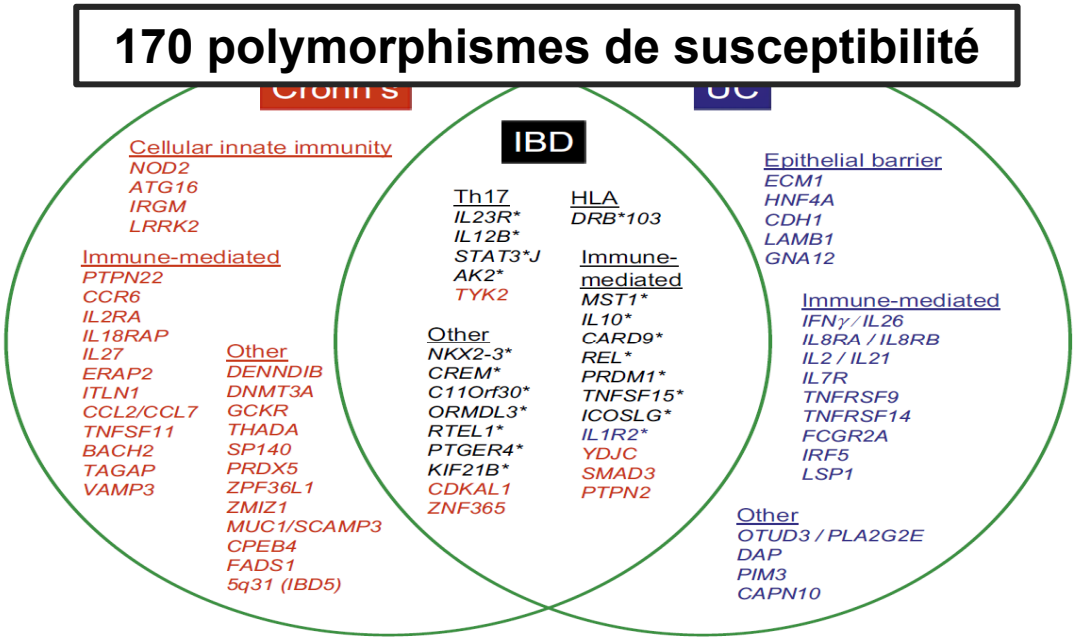


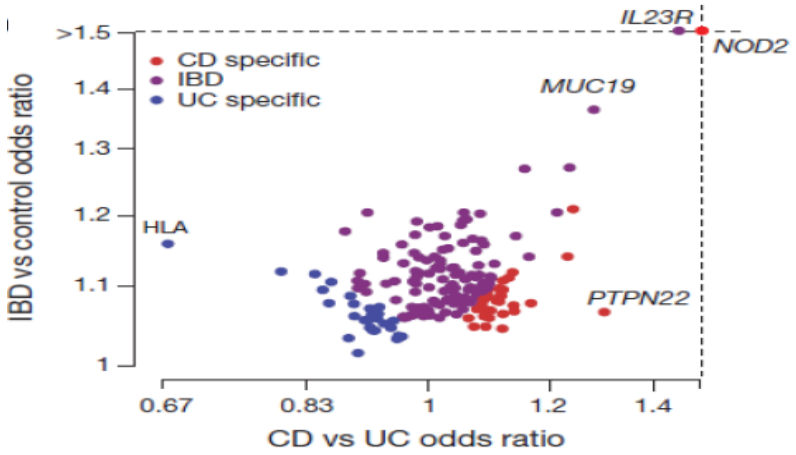


Crohn BB et al. JAMA 1932:99:1323-29

Wilks S, Moxon W. Lectures on pathological anatomy, 2nd Ed 1875.

Génétique et MICI





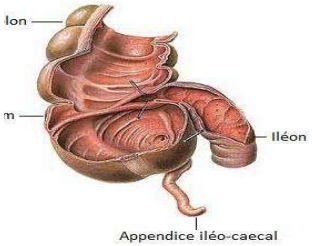
Jostins et al. Nature 2012; 491: 119-24

Environnement et MICI

General external
Social capital, education, financial status, psychological and mental stress, urban–rural environment, climate, etc

Internal
Metabolism, endogenous hormones, body morphology, physical activity, gut microflora, inflammation, lipid peroxidation, oxidative stress, ageing etc

Specific external
Radiation, infectious agents, chemical contaminants and environmental pollutants, diet, lifestyle factors (e.g. tobacco, alcohol), occupation, medical interventions, etc

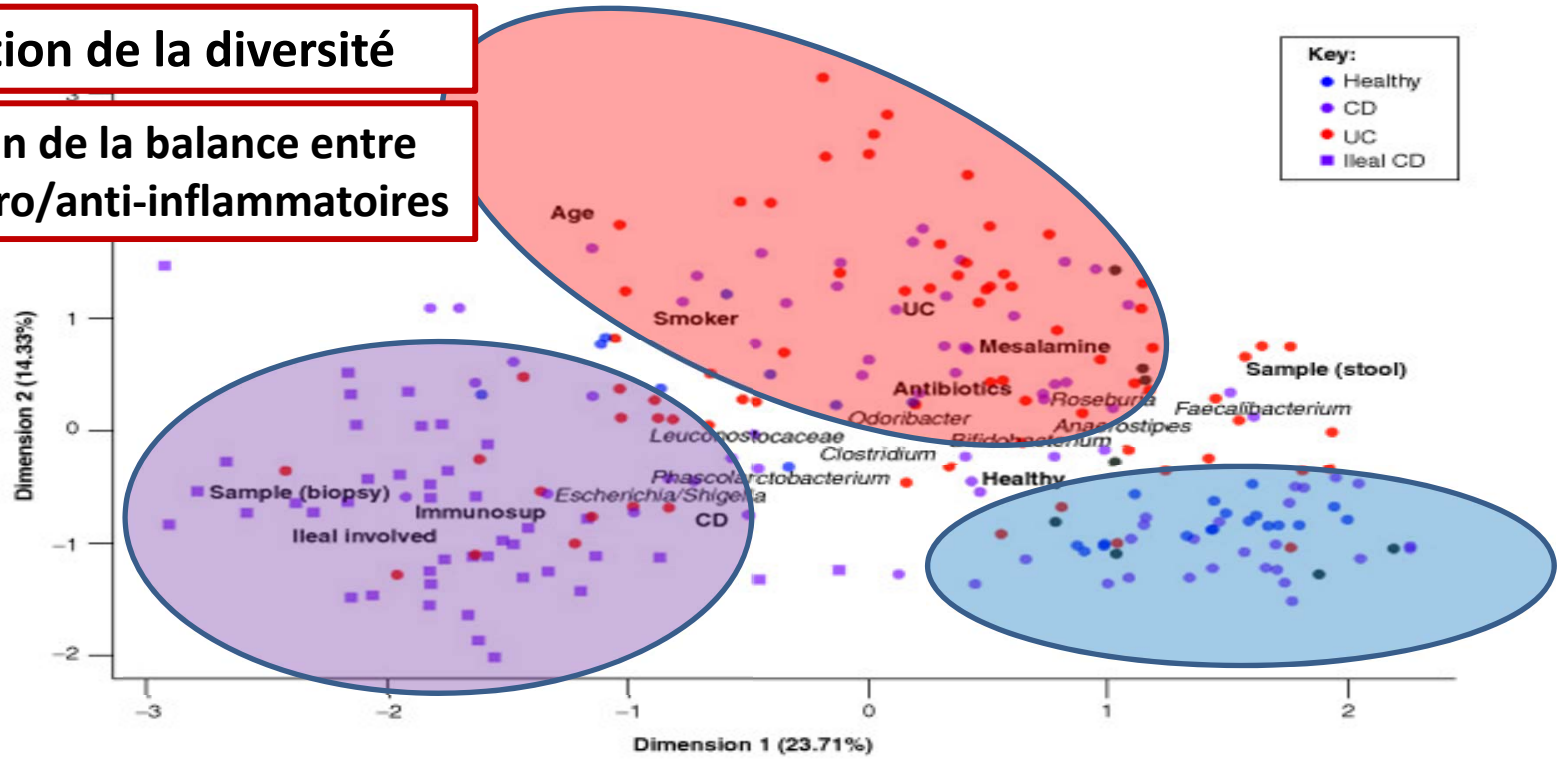


MICI

Dysbiose microbienne et MICI

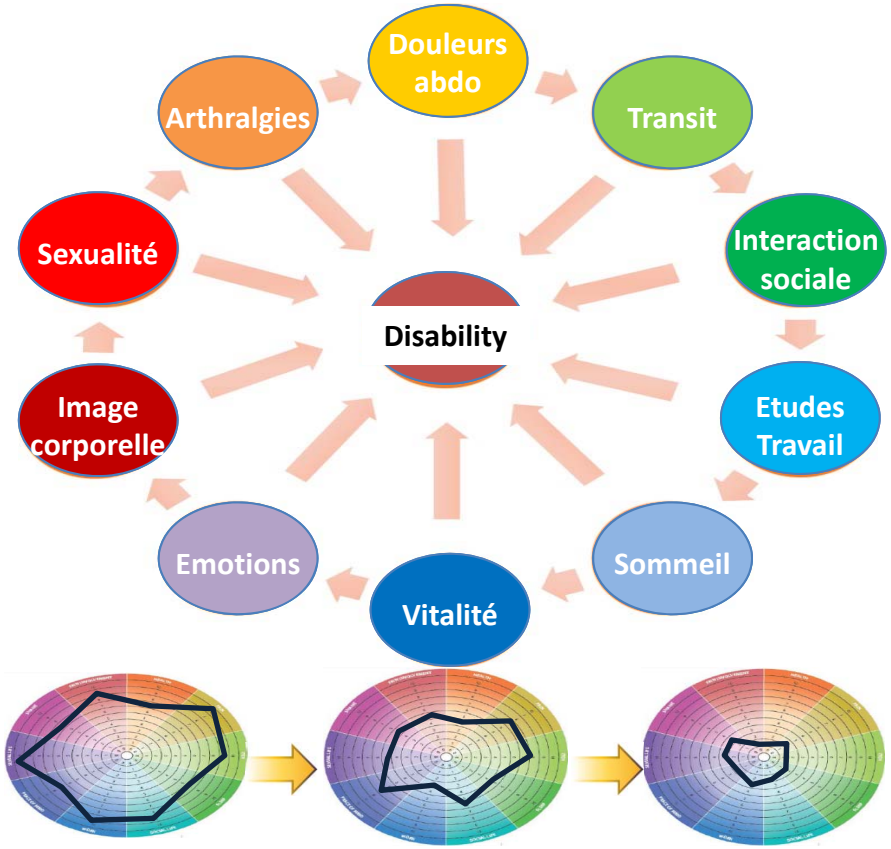
Réduction de la diversité

Altération de la balance entre bactérie pro/anti-inflammatoires



Morgan et al Genome Biol 2012; 13: R79

Handicap fonctionnel



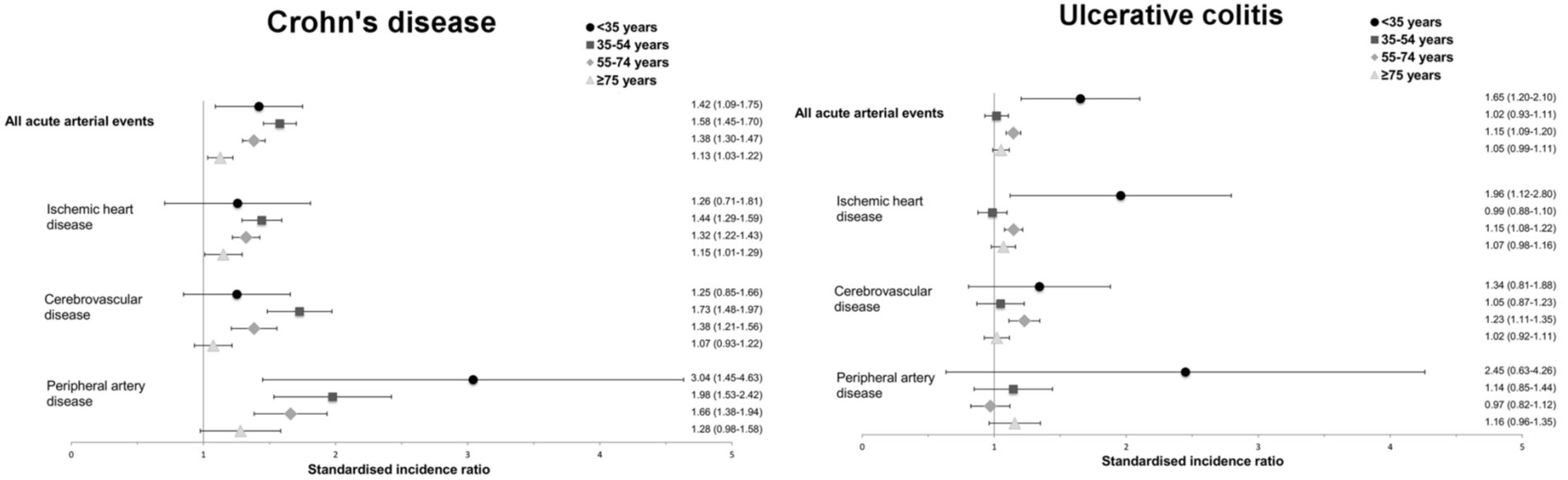
STRIDE

Selecting targets of remission in inflammatory bowel disease

… any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.

Allen et al. Therap Adv Gastroenterol 2017; 10: 865-76
Ghosh et al. Inflamm Bowel Dis. 2017 Mar;23(3):333-340

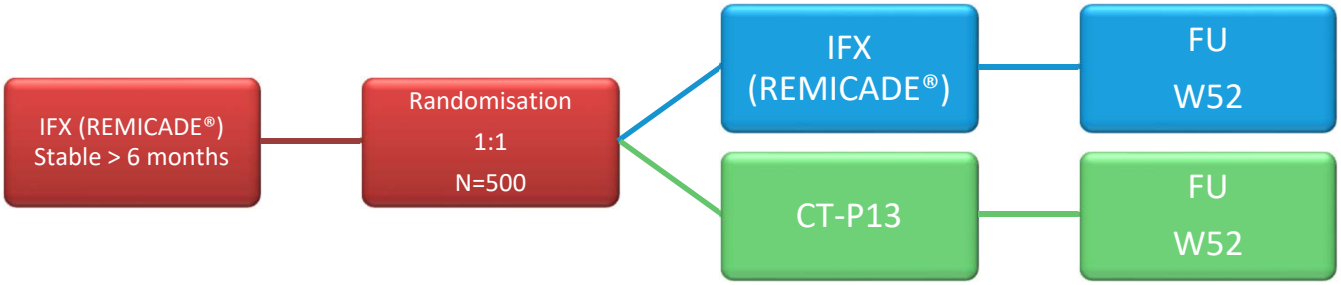
Risque cardiovasculaire et MICI



Kirchgesner et al. Gut 2018; 67: 1261-8

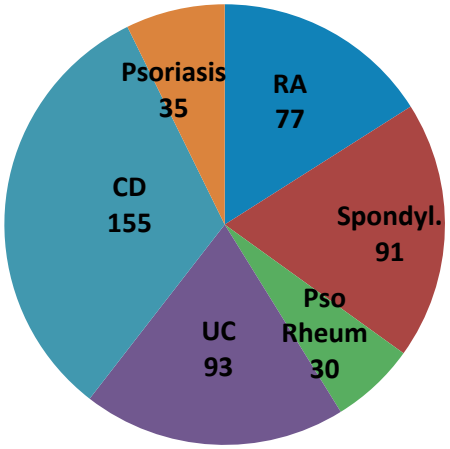
Histoire naturelle des MICI

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



NOR SWITCH

	INX (N=241)	CT-P13 (N=240)
Age (years)	47·5 (14·8)	48·2 (14·9)
Female	99 (41·1%)	87 (36·2%)
Disease duration (years)	16·7 (10·9)	17·5 (10·5)
Duration of ongoing INX treatment (years)	6·7 (3·6)	6·9 (3·8)
Concomitant immunosuppressive therapy*	113 (46·9%)	129 (53·8%)
Harvey-Bradshaw Index	2.0 (1–4)	2.0 (0–4)
Partial-Mayo score	0 (0–1)	0 (0–1)
Fecal calprotectin (mg/kg)	56 (25–173)	53 (22–210)
C-reactive protein (mg/L)	2.2 (1.0–5.0)	2.0 (1.0–5.0)

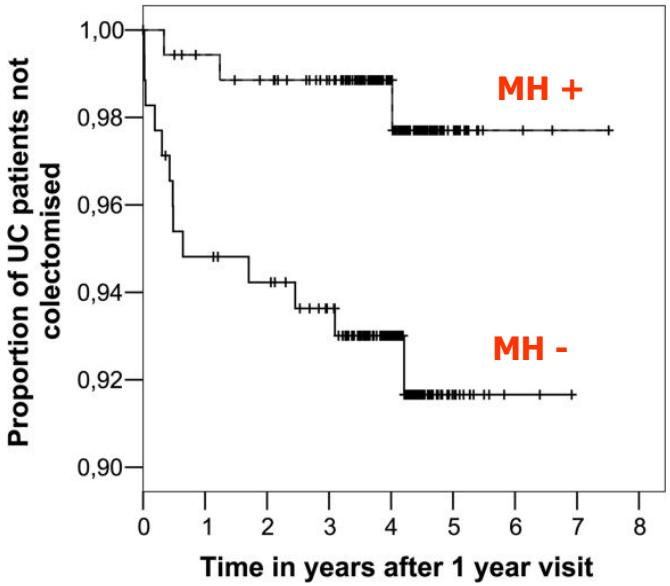


Jørgensen K, et al. UEGW 2016. Abstract #LB15.

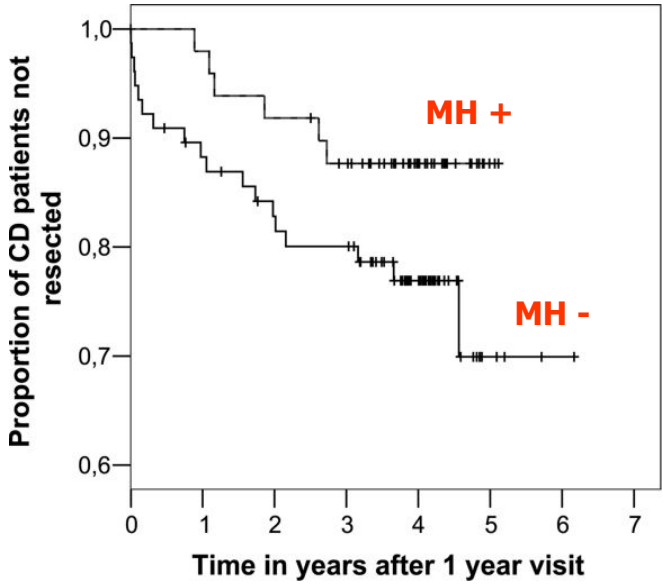
EudraCT Number: 2014-002056-40[1]

Cicatrisation muqueuse

Ulcerative colitis



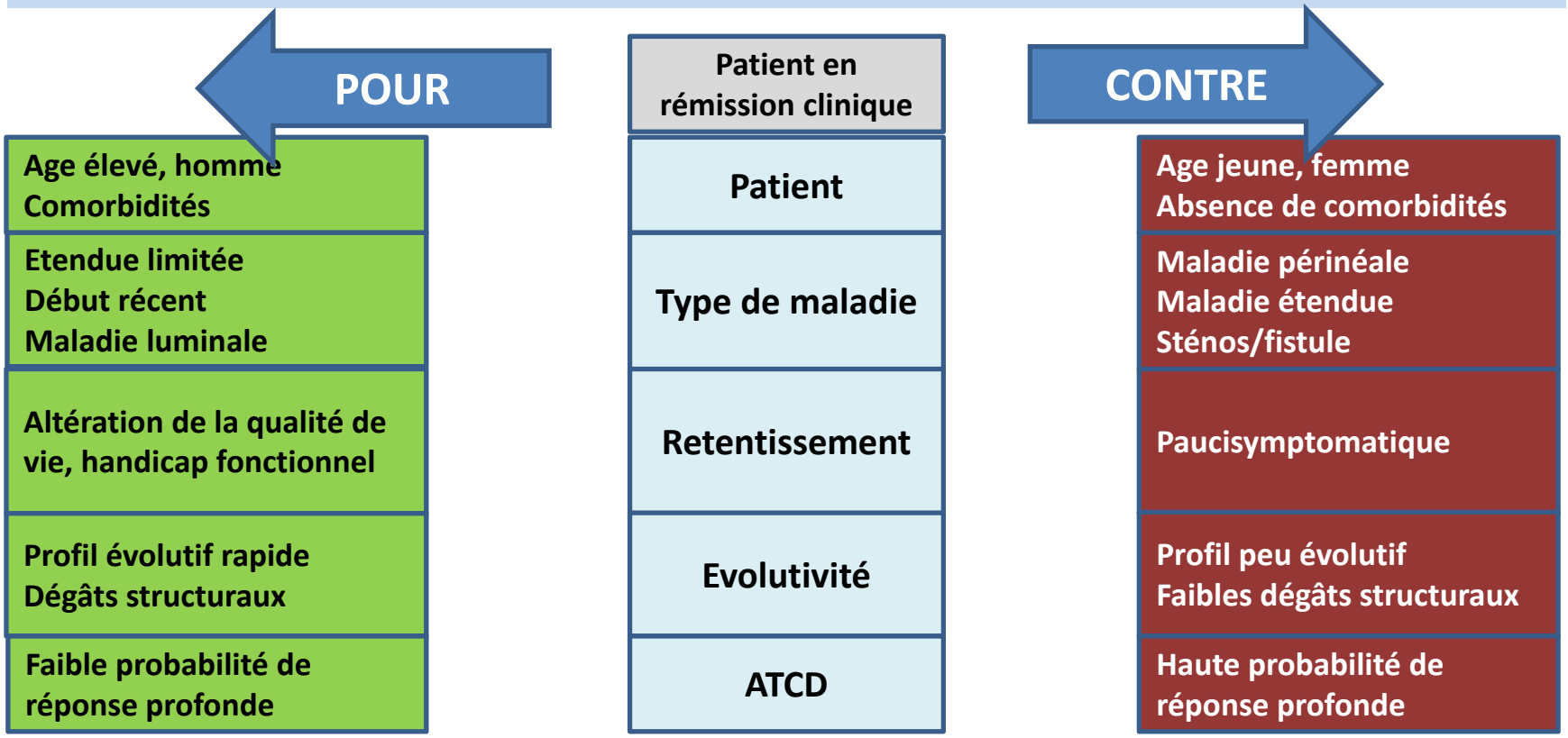
Crohn's disease



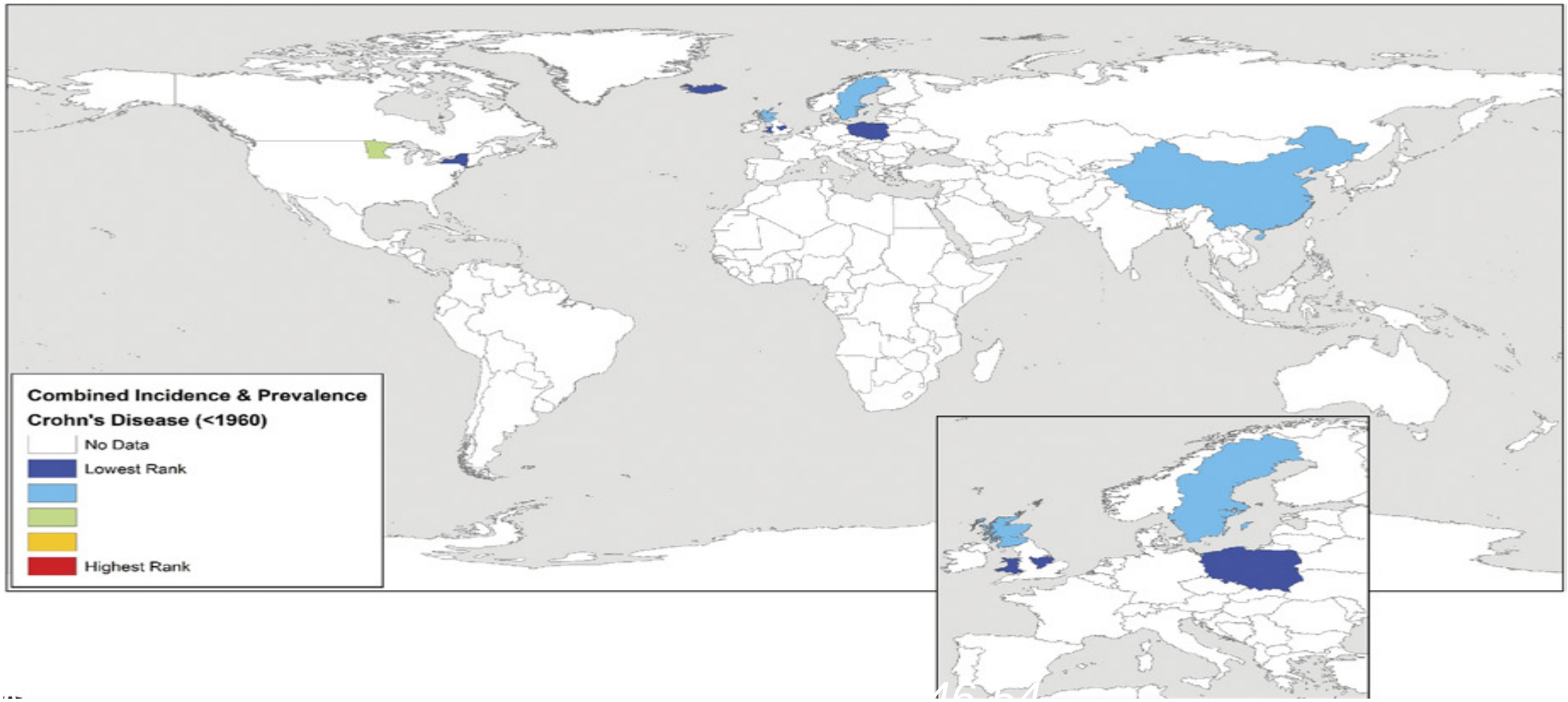
MH: mucosal healing

Froslie et al. Gastroenterology 2007; 133(2): 412-22

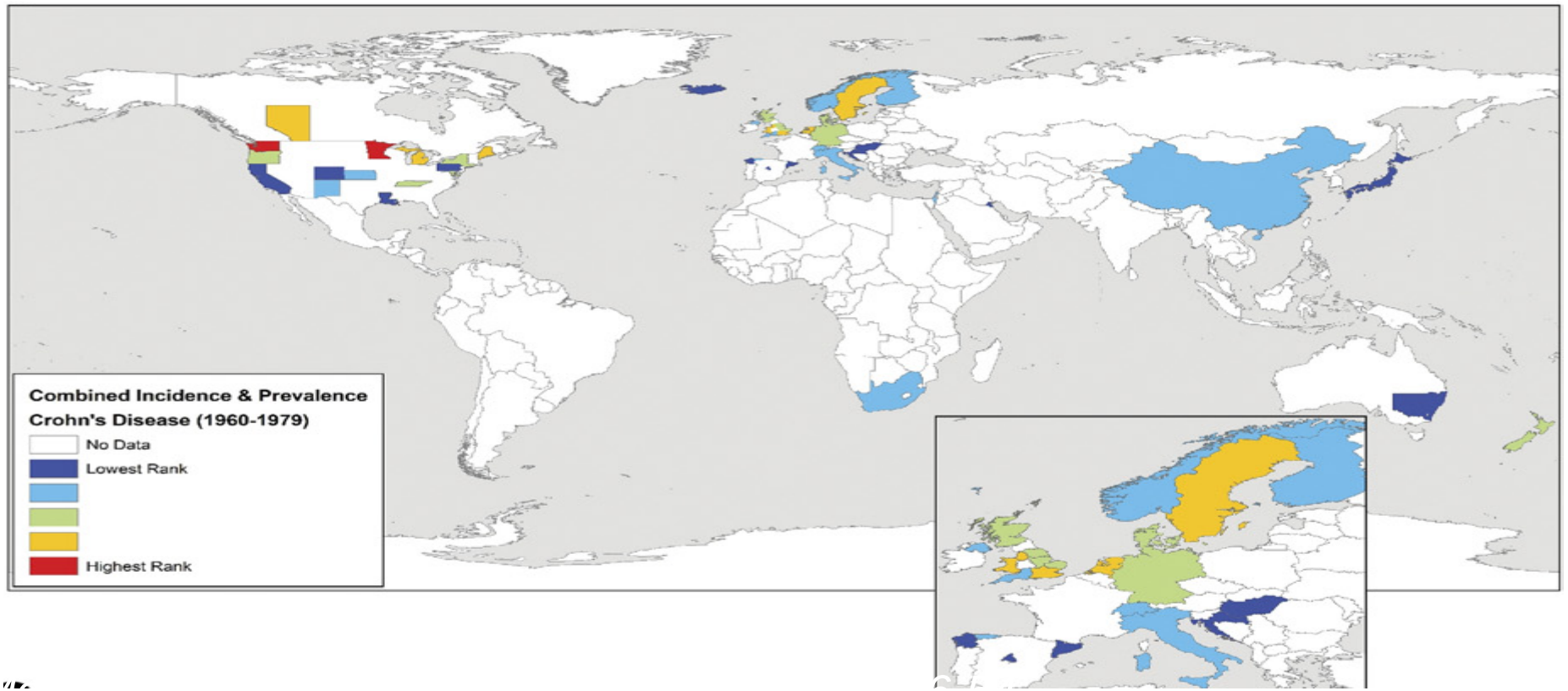
Stratification



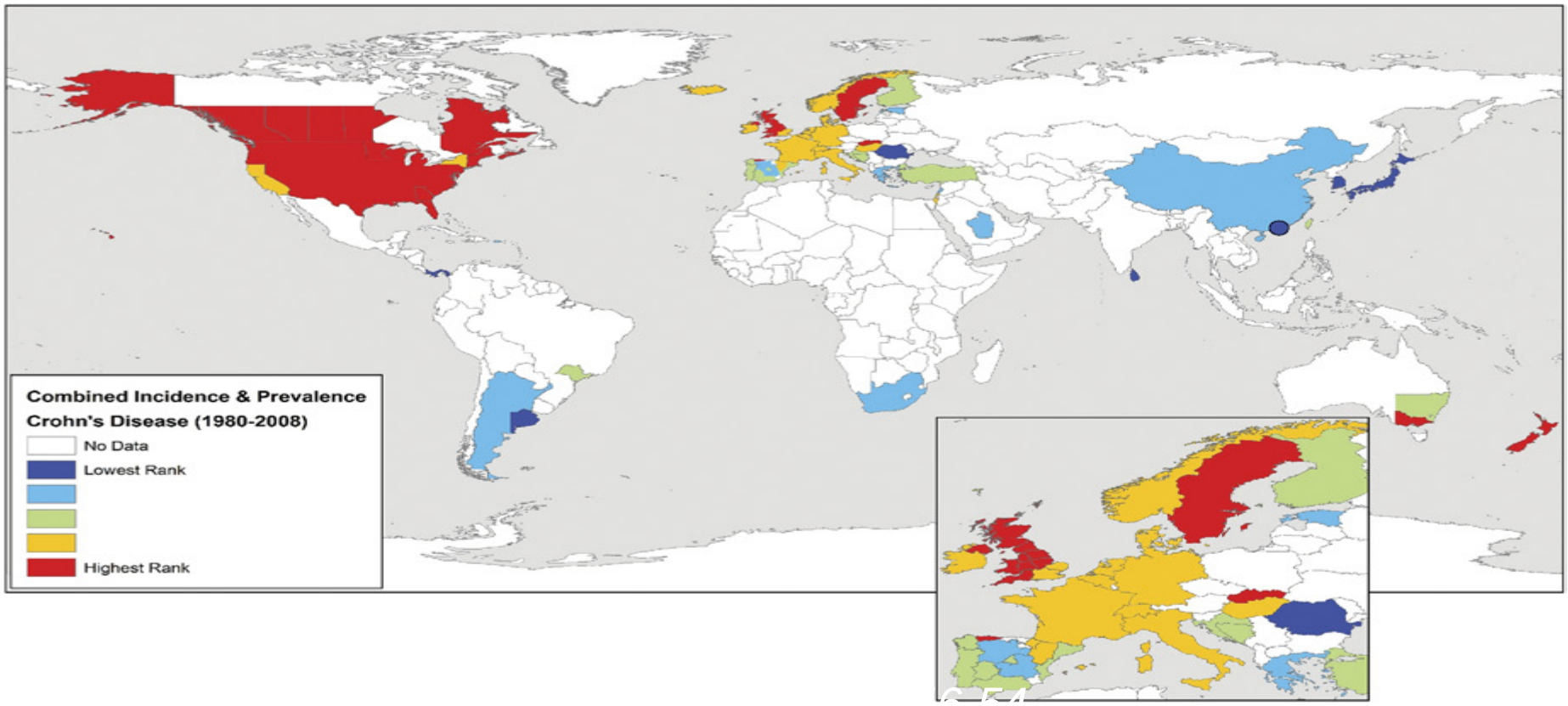
Epidémiologie des MICI



Epidémiologie des MICI



Epidémiologie des MICI



Epidémiologie migratoire des MICI