
Immunomodulateurs dans les MICI : le plus tôt c'est le mieux ?

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Stratégies utilisant les IM dans la maladie de Crohn

Step up (Guidelines)



Top down (GETAID, SUTD, STORI, IMID)

Dg



Monotherapie (SONIC, RAPID)



Anti-TNF

IS

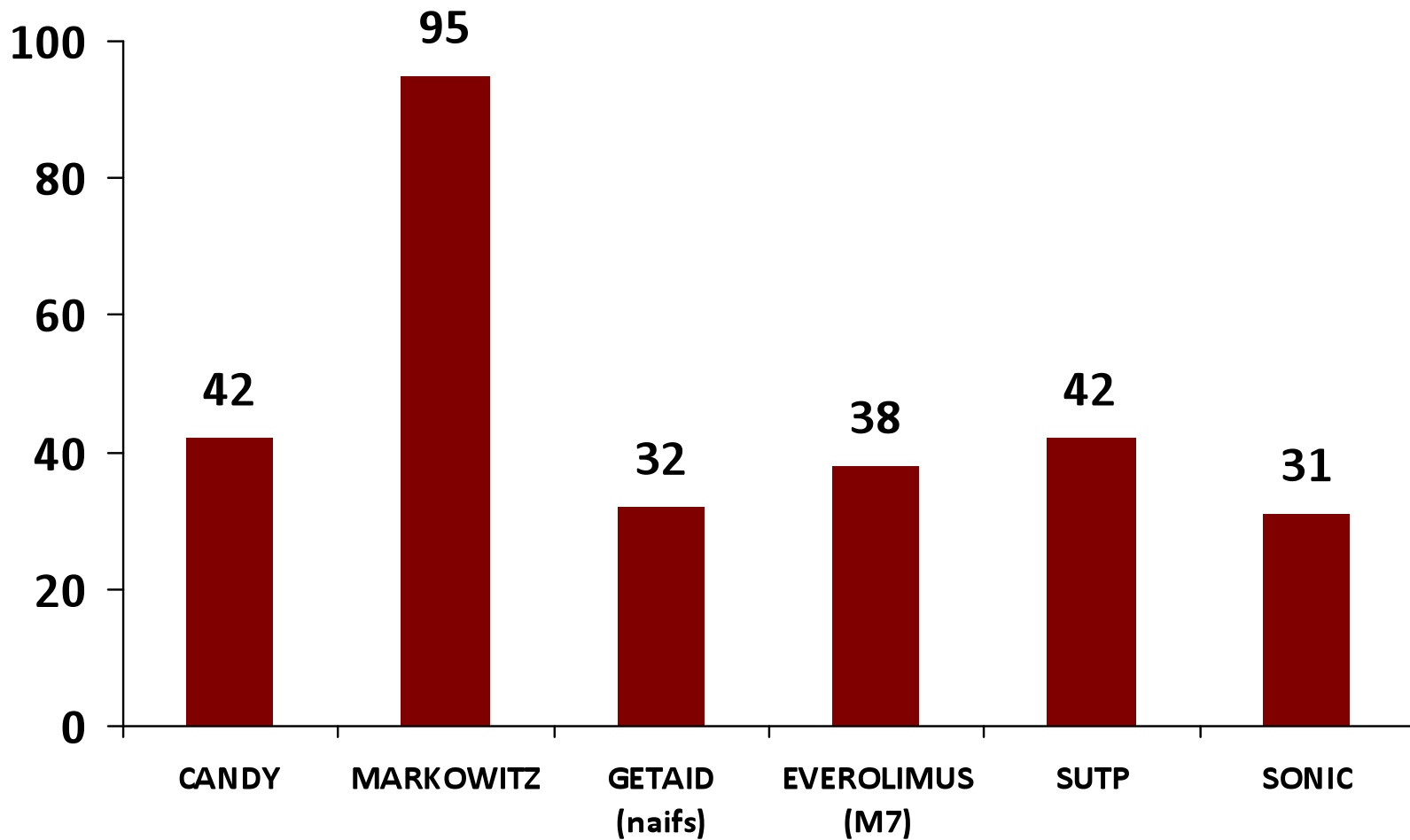
Immunomodulateurs dans les MICI : le plus tôt c'est le mieux ?

**Y-a-t-il suffisamment d'arguments pour
proposer un traitement IM précoce?**

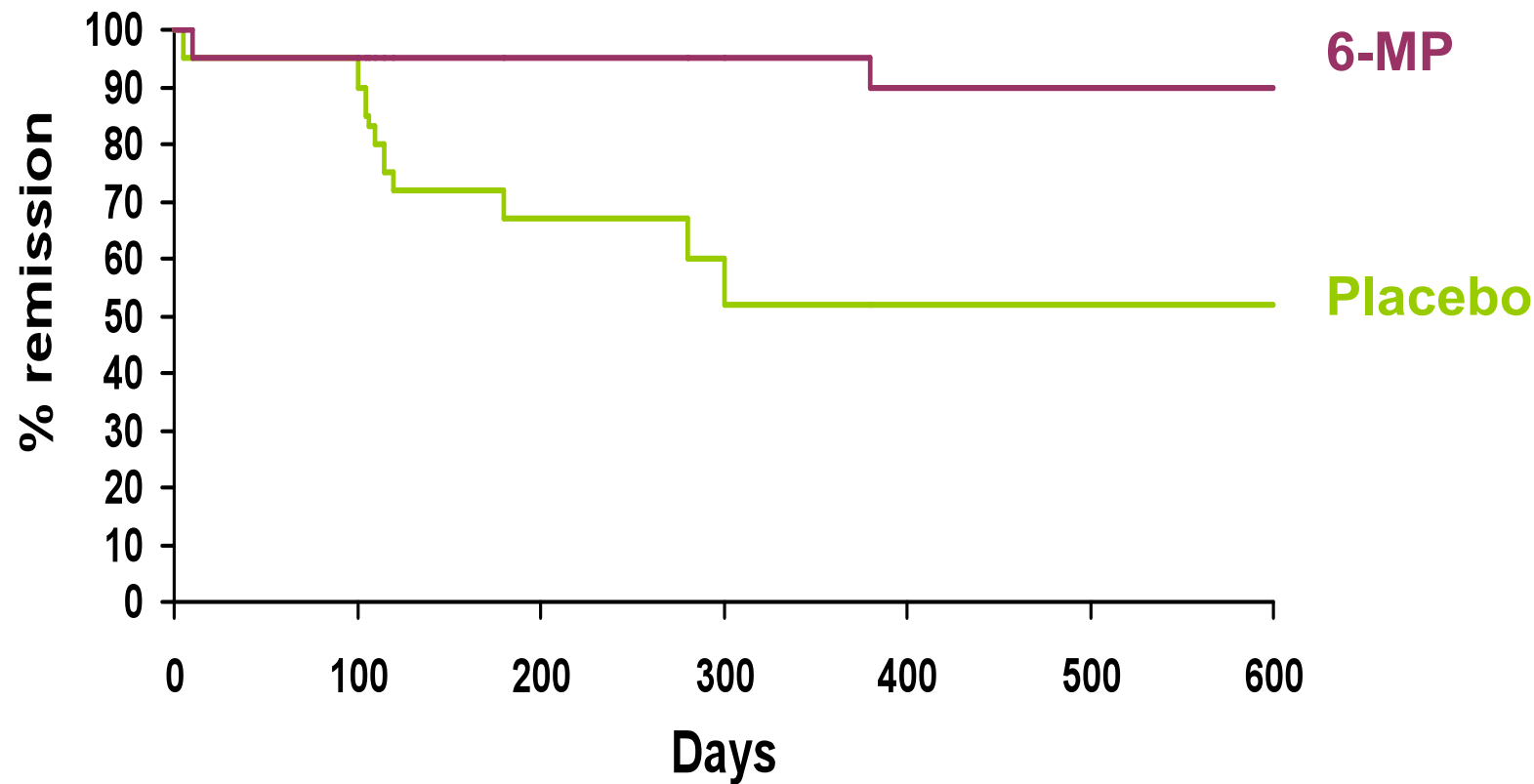
Thiopurines

Résultats dans les essais récents

% rémission sans corticoïdes (1 an)

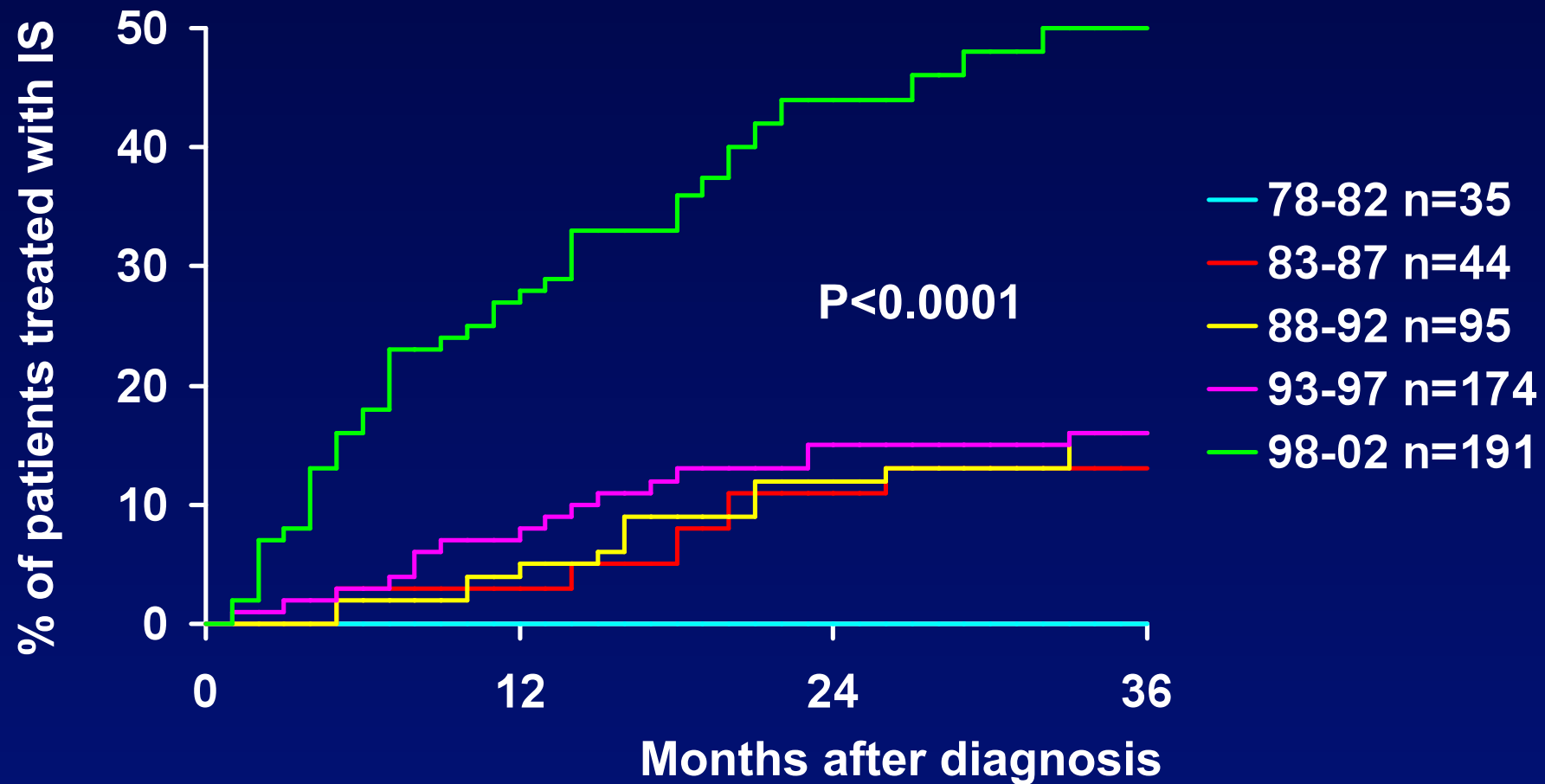


6-MP in children with newly diagnosed CD treated with prednisone

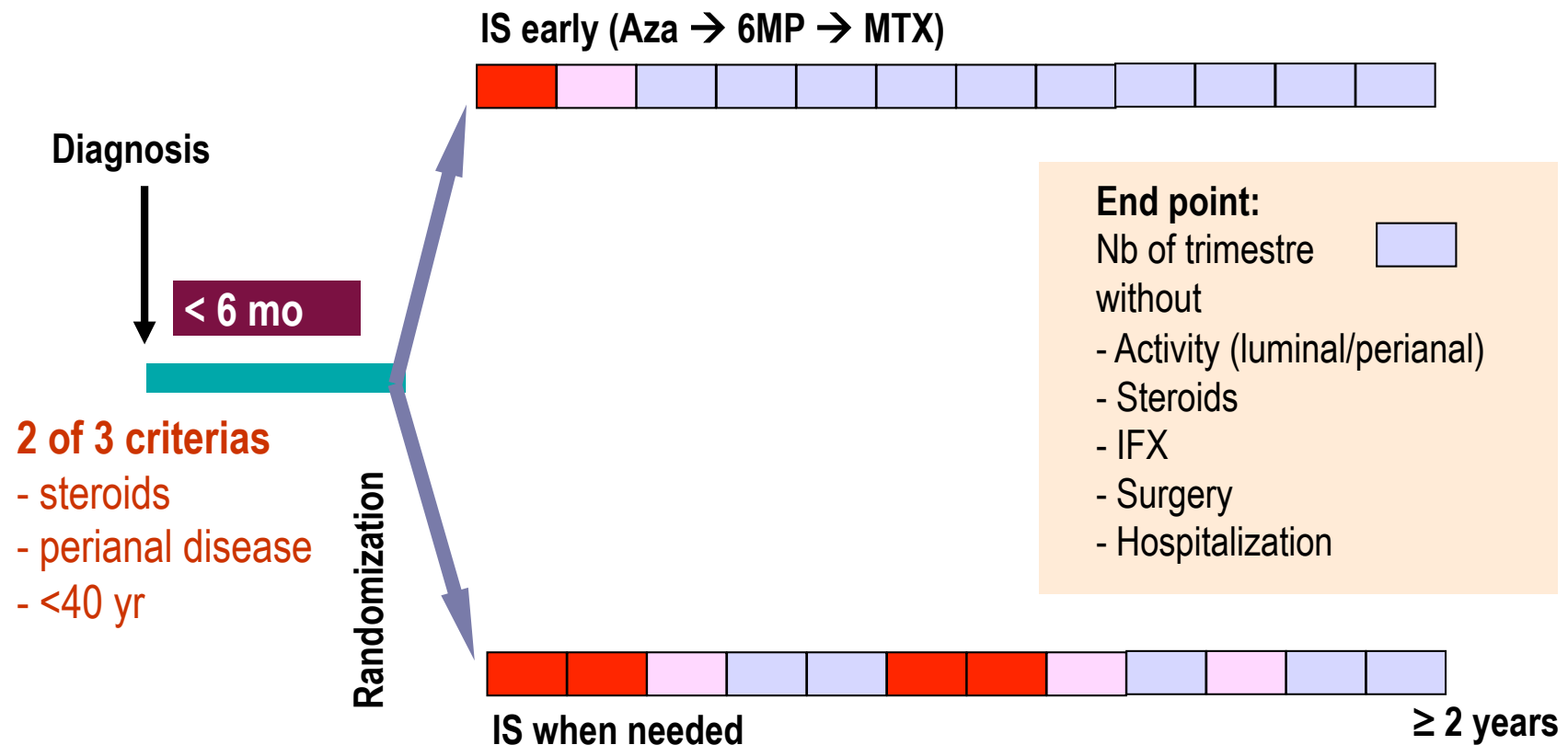


Markowitz et al. Gastroenterology 2000; 119: 895-902

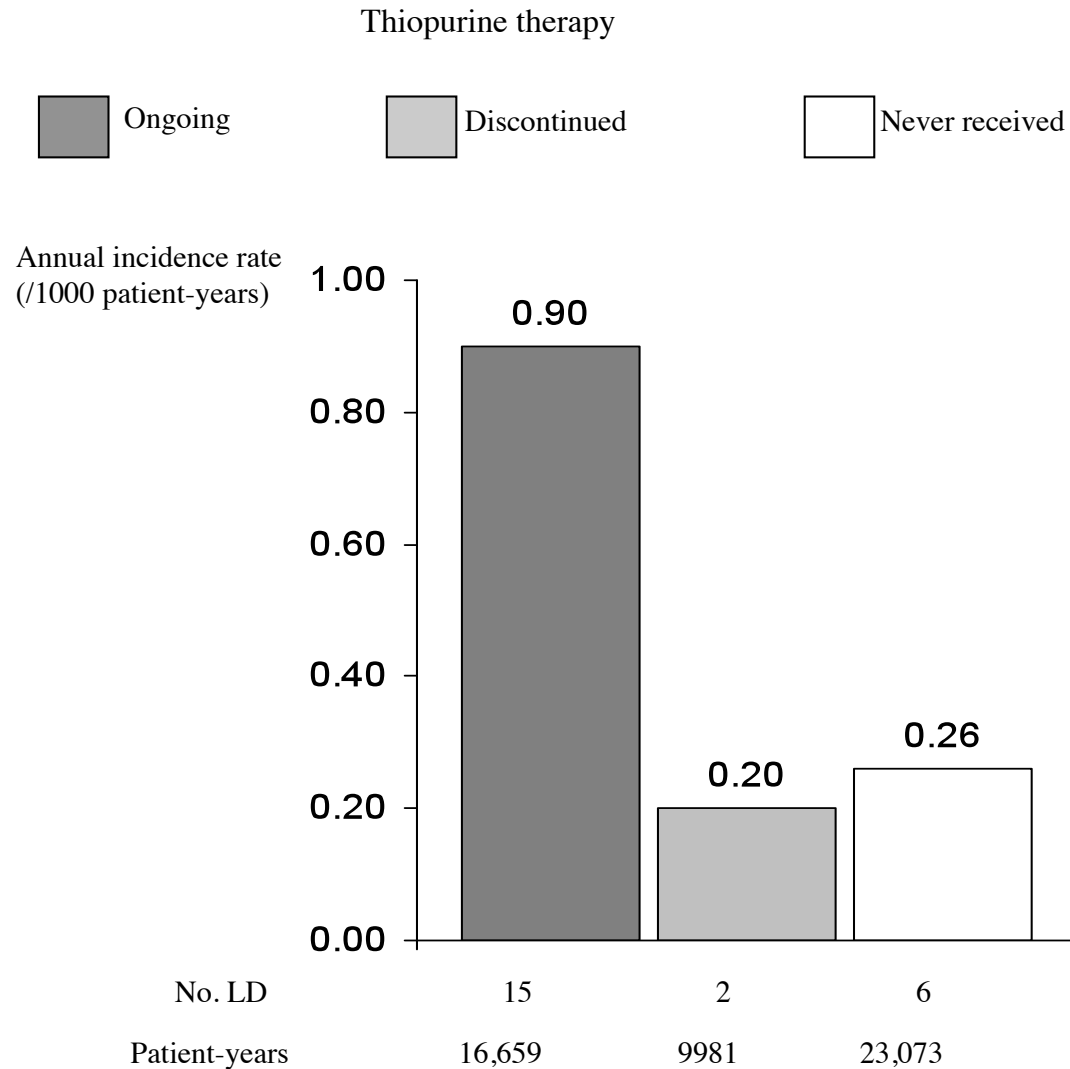
Cumulative use of immunosuppressants in clinical practice



Rapid study (RAPid ImmunoDepression)



Excess risk of Lymphoproliferative Disorders (LPD) in Inflammatory Bowel Diseases (IBD): results of the CESAME cohort (Beaugerie et al, DDW 2008)



Responder: Baseline Demographics

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total Infliximab
Patients	110	113	112	225
Males/Females	46/64	43/70	41/71	84/141
Mean age (years)	38	37	36	36
Mean Weight (kg)	74.4	67.3	71.6	69.4
Nonsmoker	51 (46.4%)	45 (40.2%)	43 (38.4%)	88 (39.3%)

**Mean Crohn's
Disease (yrs)**

9.8

9.1

9.9

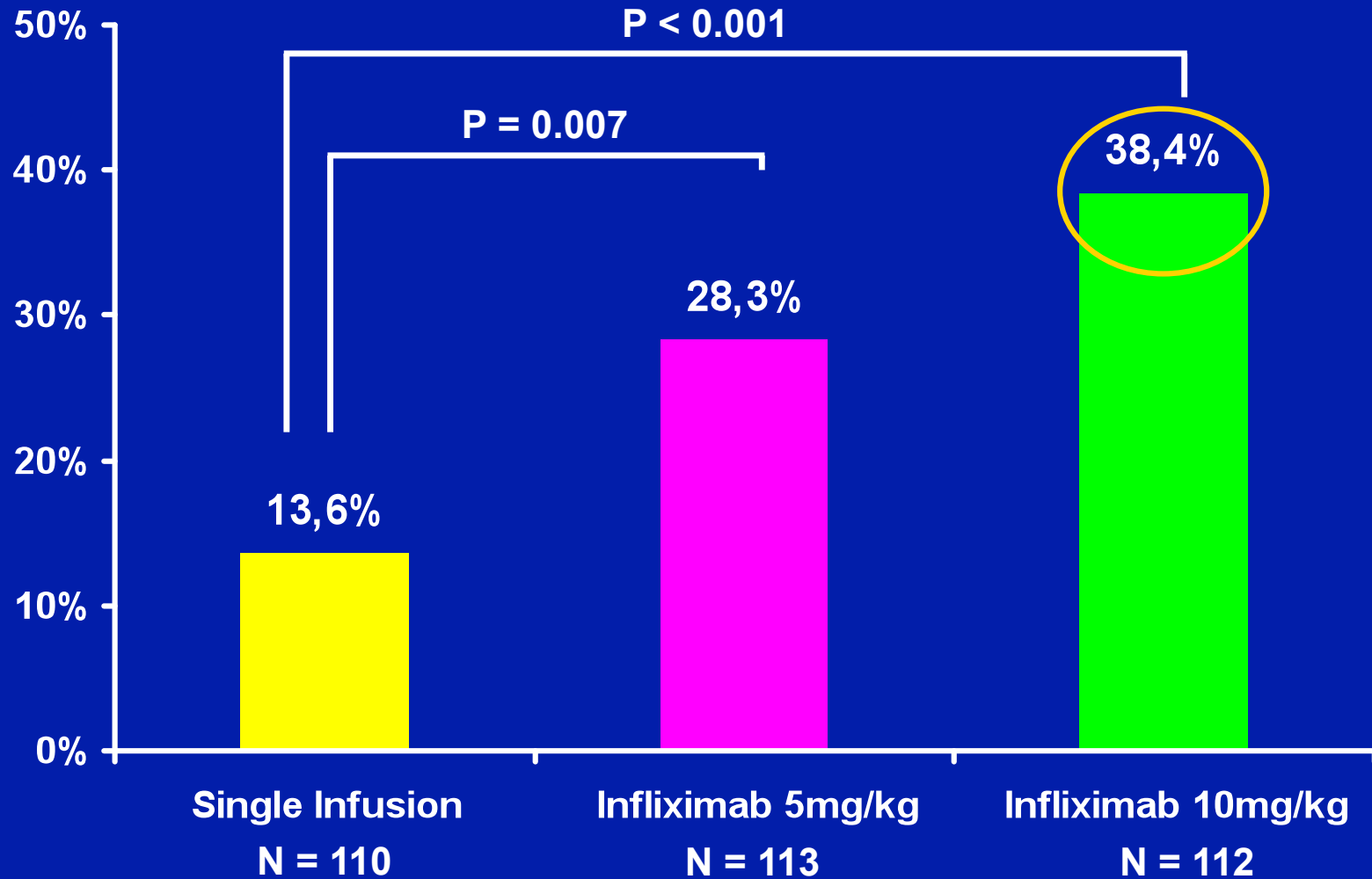
9.5

ACCENT I

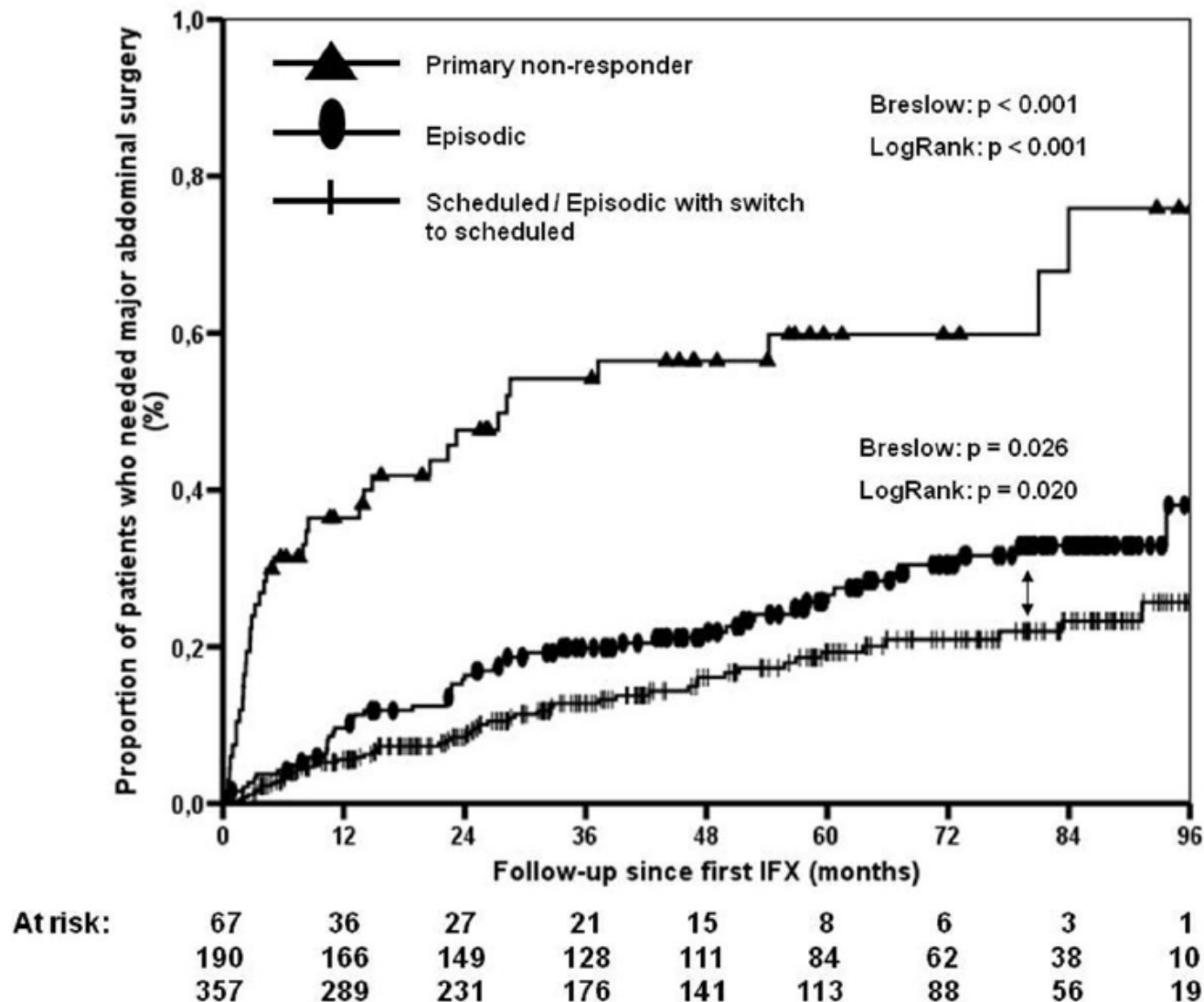
Accent 1

Clinical Remission At Week 54 In responders at week 2

Percentage of Patients in
clinical remission (CDAI < 150)

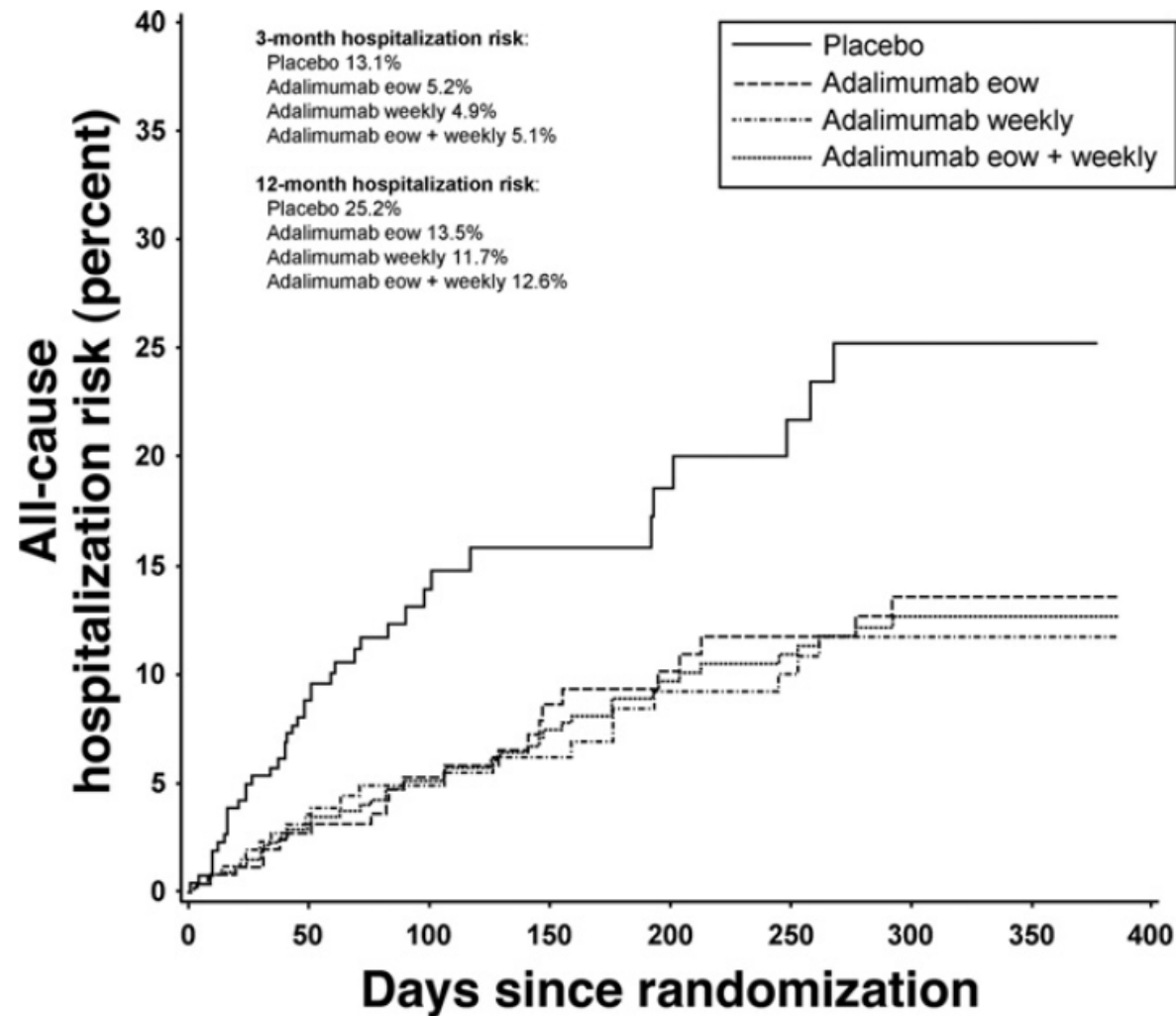


Long-term outcome of treatment with infliximab in 614 Crohn's disease patients: results from a single centre cohort



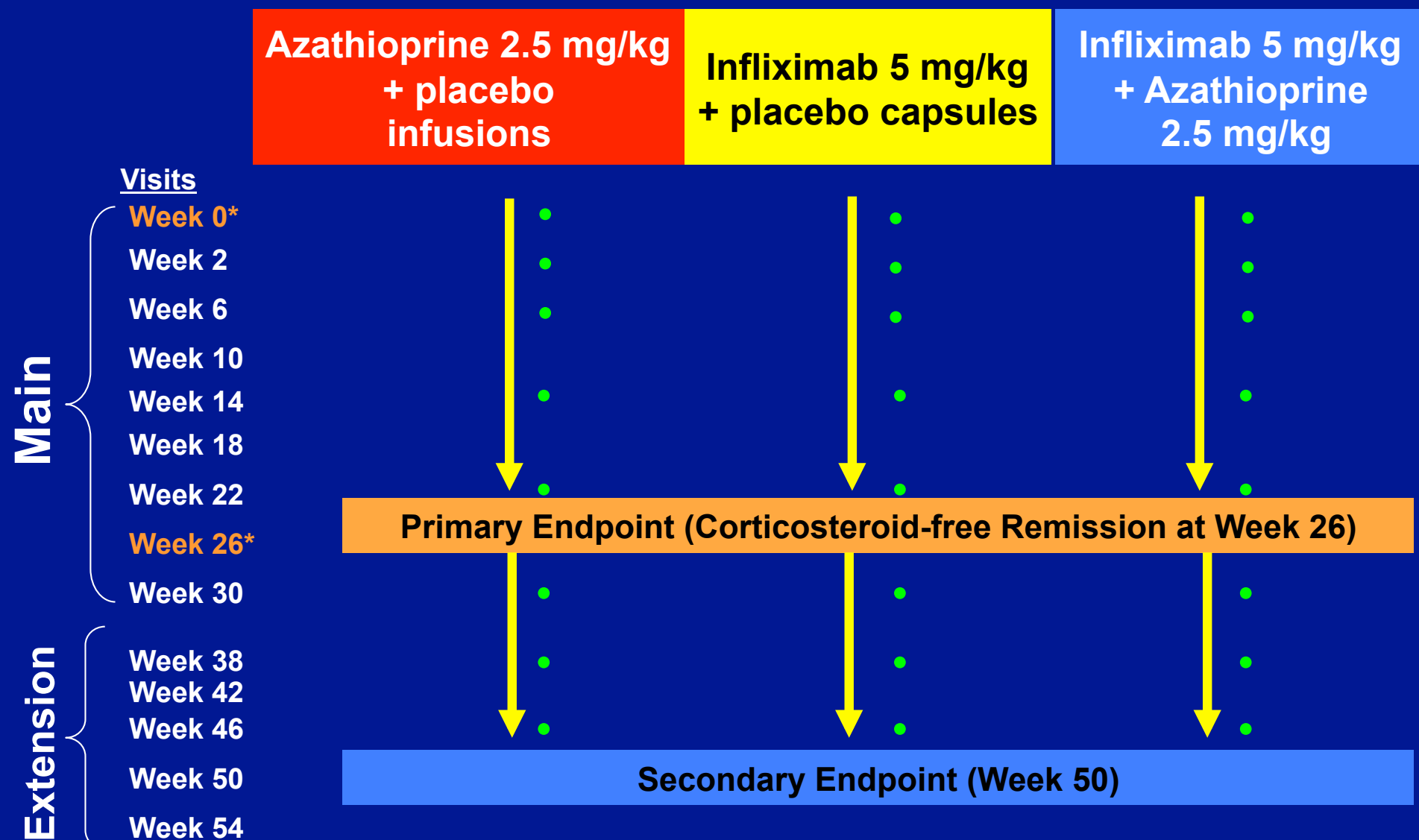
Effects of Adalimumab Therapy on Incidence of Hospitalization and Surgery in Crohn's Disease: Results From the CHARM Study

FEAGAN ET AL



SONIC

Study Design



* Endoscopy performed at Weeks 0 & 26

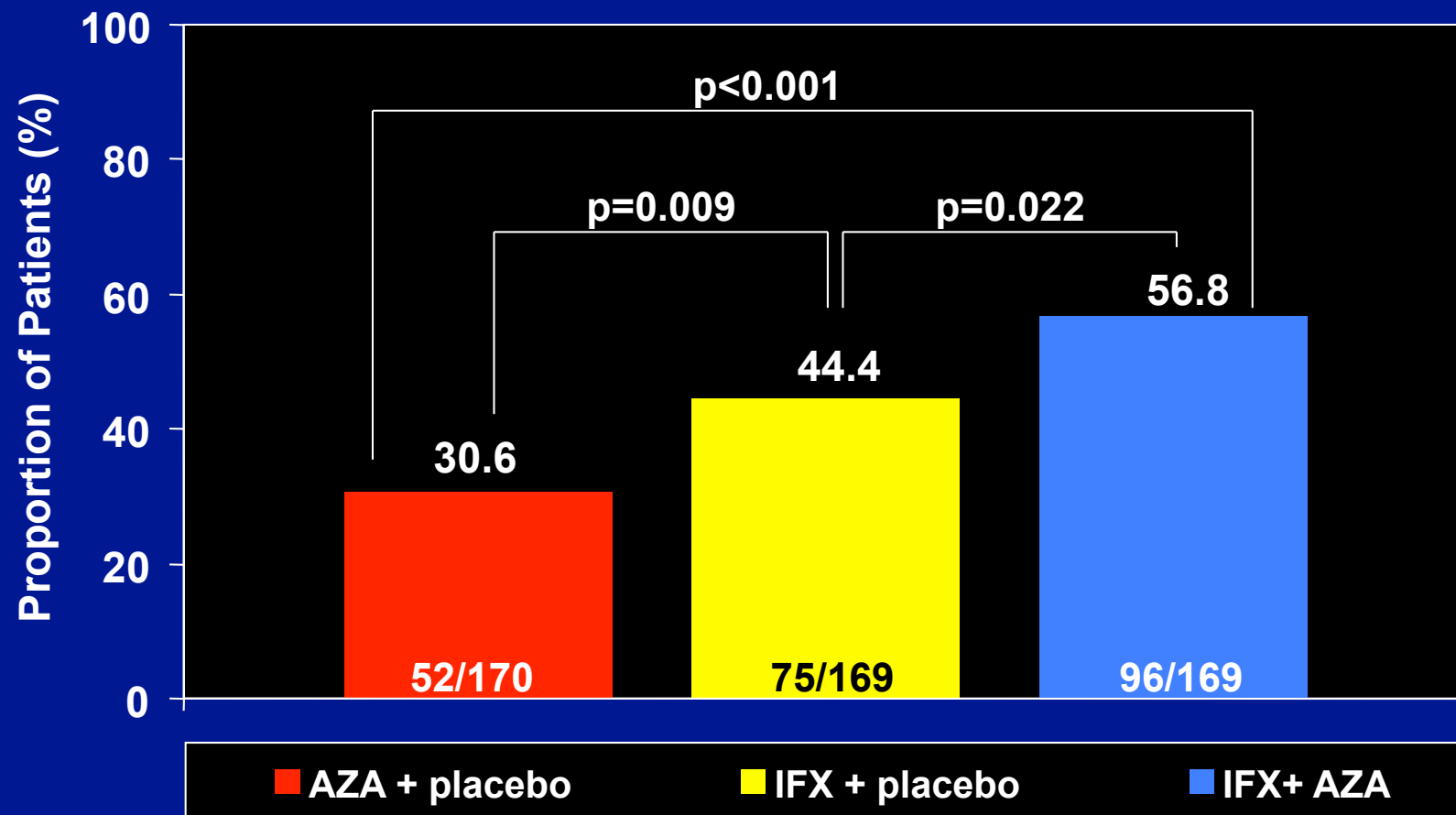
• Infusions

- Subjects 21 years of age or older with:
 - Moderate-to-Severe Crohn's disease (CD)
 - CDAI ≥ 220 and ≤ 450
 - No prior exposure to biologic agents or immunomodulators
- Subjects must meet at least 1 of the following criteria:
 - Corticosteroid-dependent
 - Being considered for second (or more) course of steroids (prednisone or equivalent) in past year
 - 5-ASA failures
 - Inadequate response to mesalamine 2.4 g/dy or more (or equivalent) for at least 4 weeks
 - Budesonide failures
 - Inadequate response to budesonide 6 mg/dy or more for at least 4 weeks

Baseline Characteristics

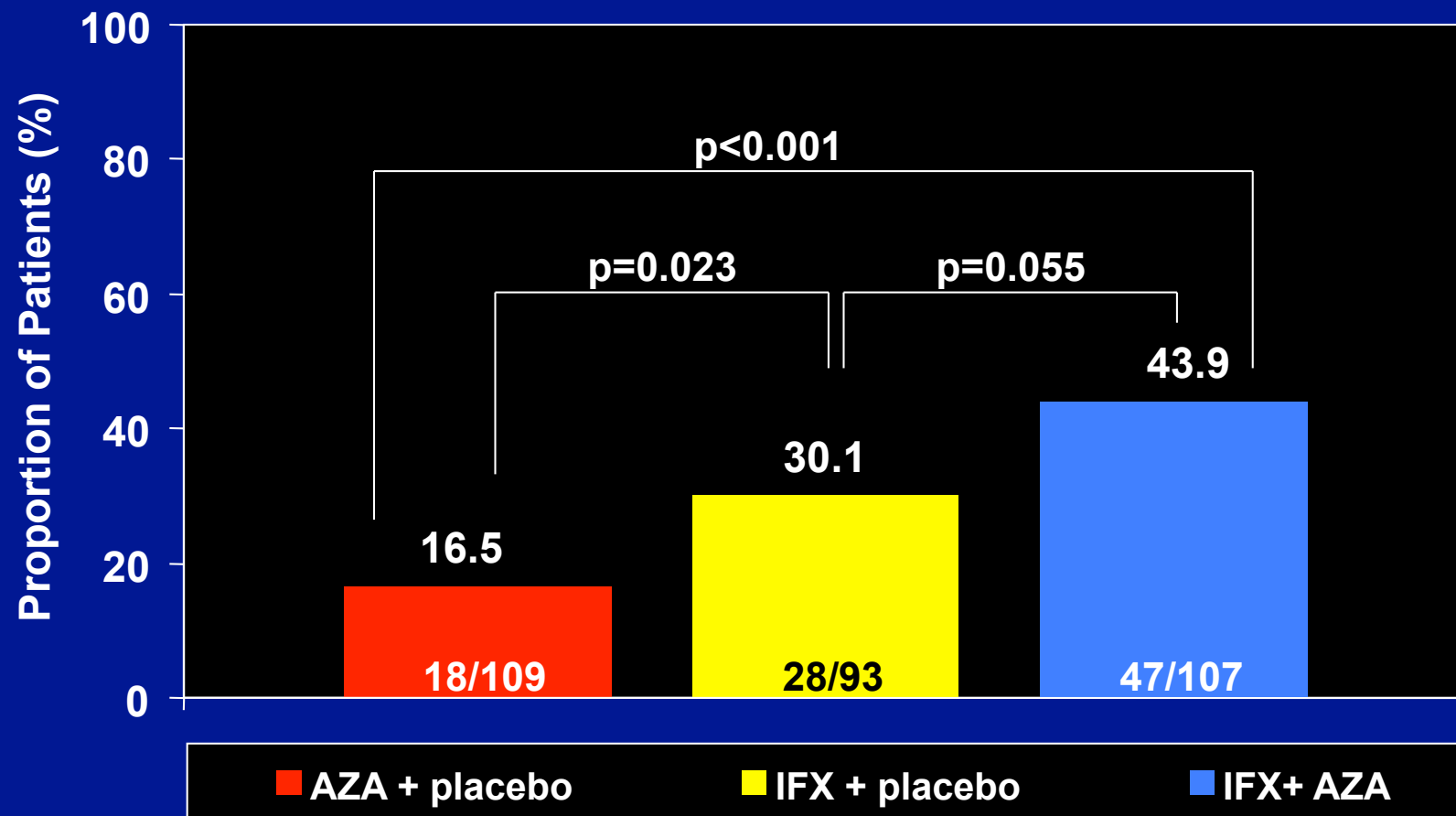
Characteristic	AZA + placebo (n=170)	Infliximab + placebo (n=169)	Infliximab + AZA (n=169)
Male sex – n (%)	90 (52.9%)	84 (49.7%)	88 (52.1%)
White race – n (%)	147 (91.3%)	146 (93.0%)	142 (94.0%)
Age (yr) - median (IQ range)	35 (26,43)	35 (26,46)	34 (26,45)
Weight (kg) - median (IQ range)	69.6 (58.5,81.6)	68.9 (60.0,80.5)	72.0 (61.0,85.0)
Duration of CD (yr) - median (IQ range)	2.4 (1,8)	2.2 (1,9)	2.2 (1,9)
CDAI – median (IQ range)	275 (247,322)	272 (239,320)	278 (248,327)
CRP (mg/dL) – median (IQ range)	1.0 (0.4,3.1)	1.1 (0.4,3.1)	1.0 (0.3,2.3)
IBDQ - median (IQ range)	123.0 (98,146)	125.5 (106,146)	127.0 (103,144)

Corticosteroid-Free Clinical Remission at Week 26



Mucosal Healing at Week 26

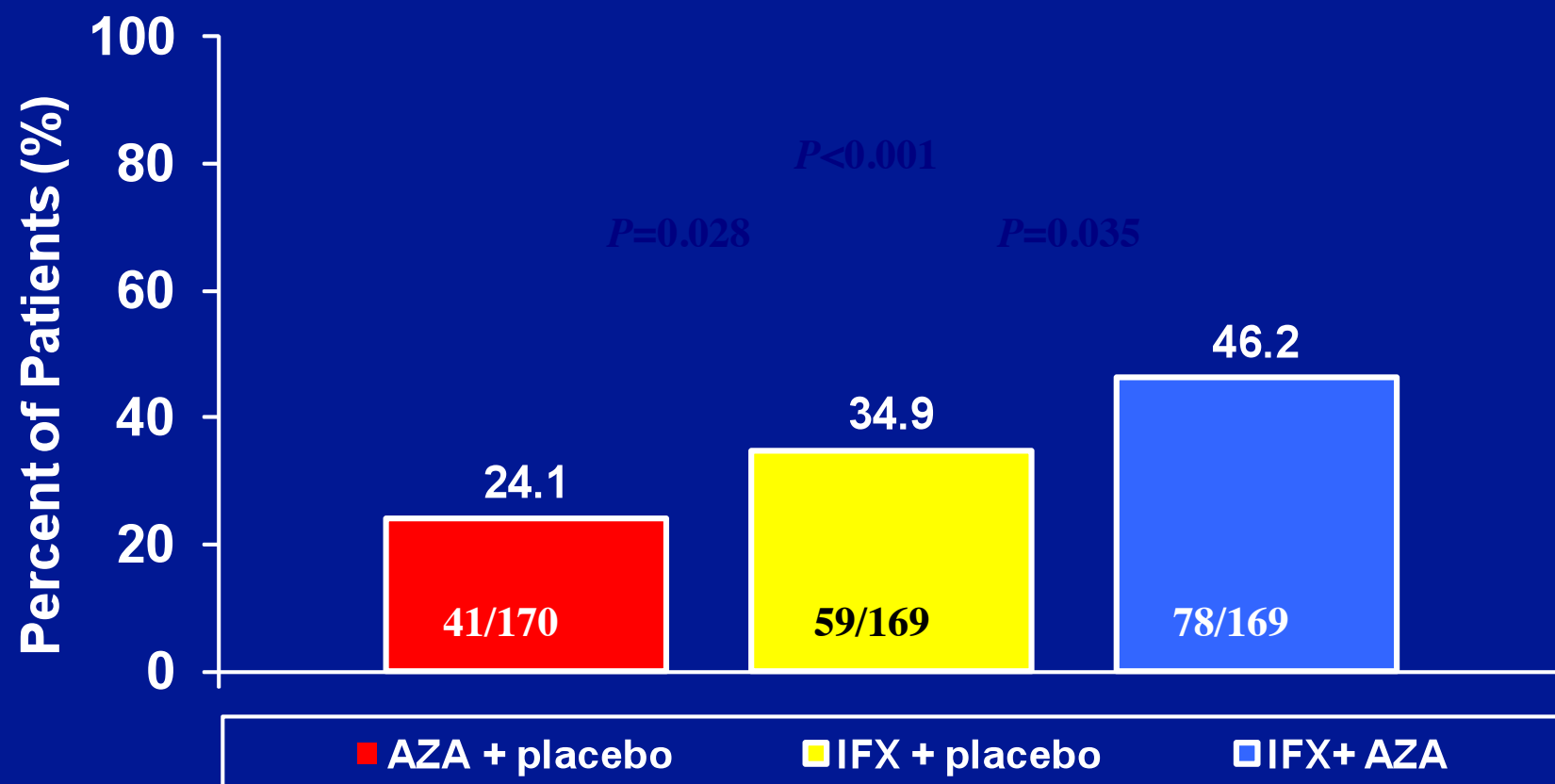
SONIC



Corticosteroid-Free Clinical Remission at Week 50 (pre-specified endpoint)

SONIC

All Randomized Patients (N=508)*



*Patients who did not enter the Study Extension were treated as non-responders

Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease

SUTD

An open randomised trial

131 CD patients

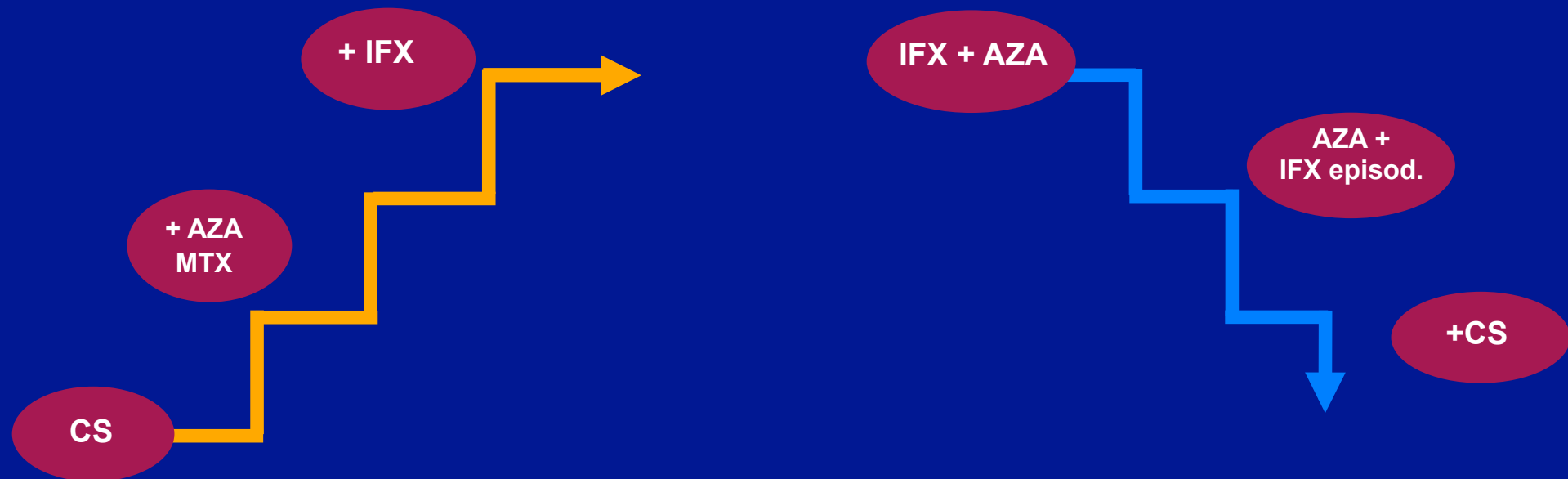
CDAI 220-450

Diagnosis < 4 yrs

Naïve for CS and IS

Step-up (N=67)

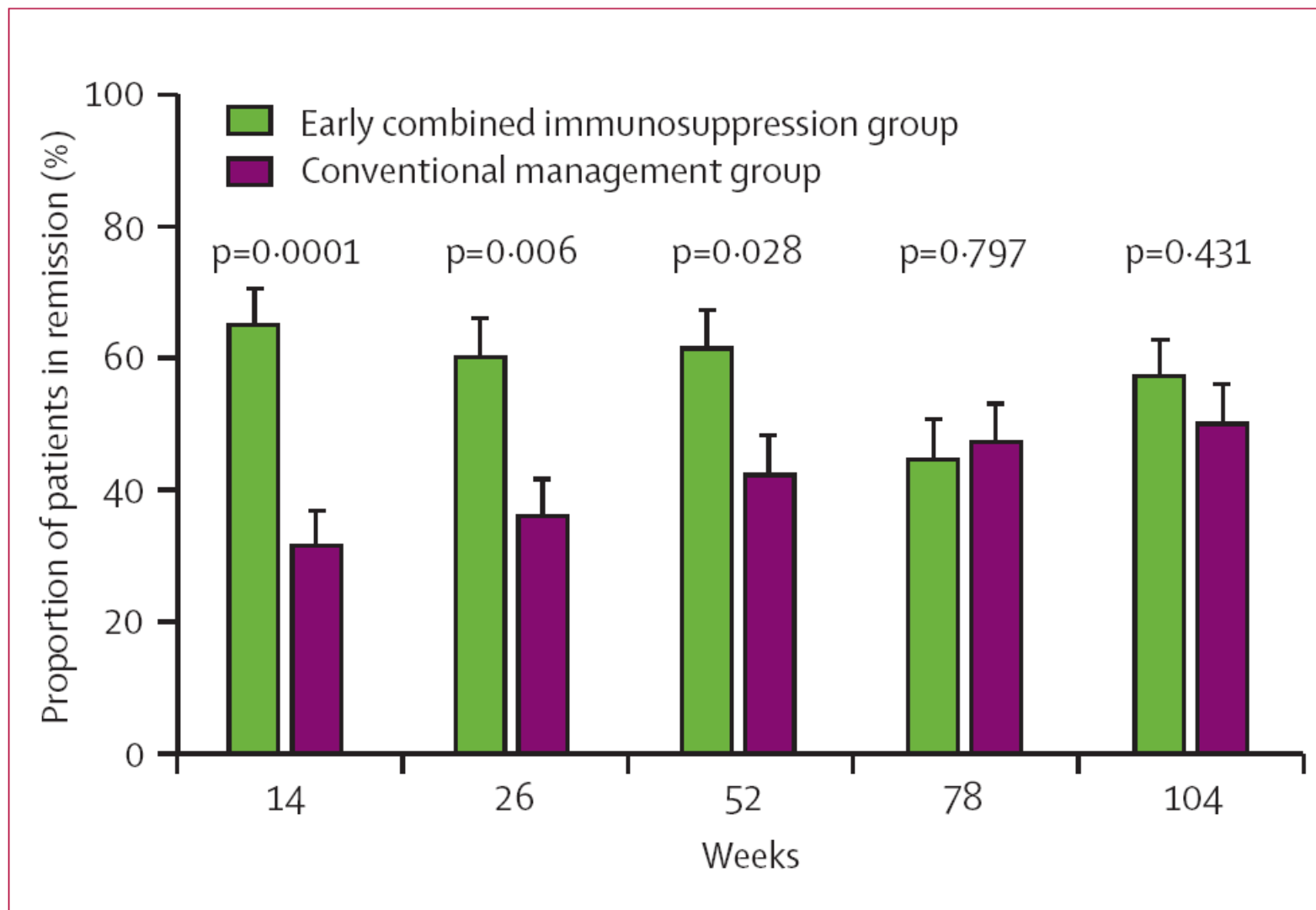
Top-down (N=66)



Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease

SUTD

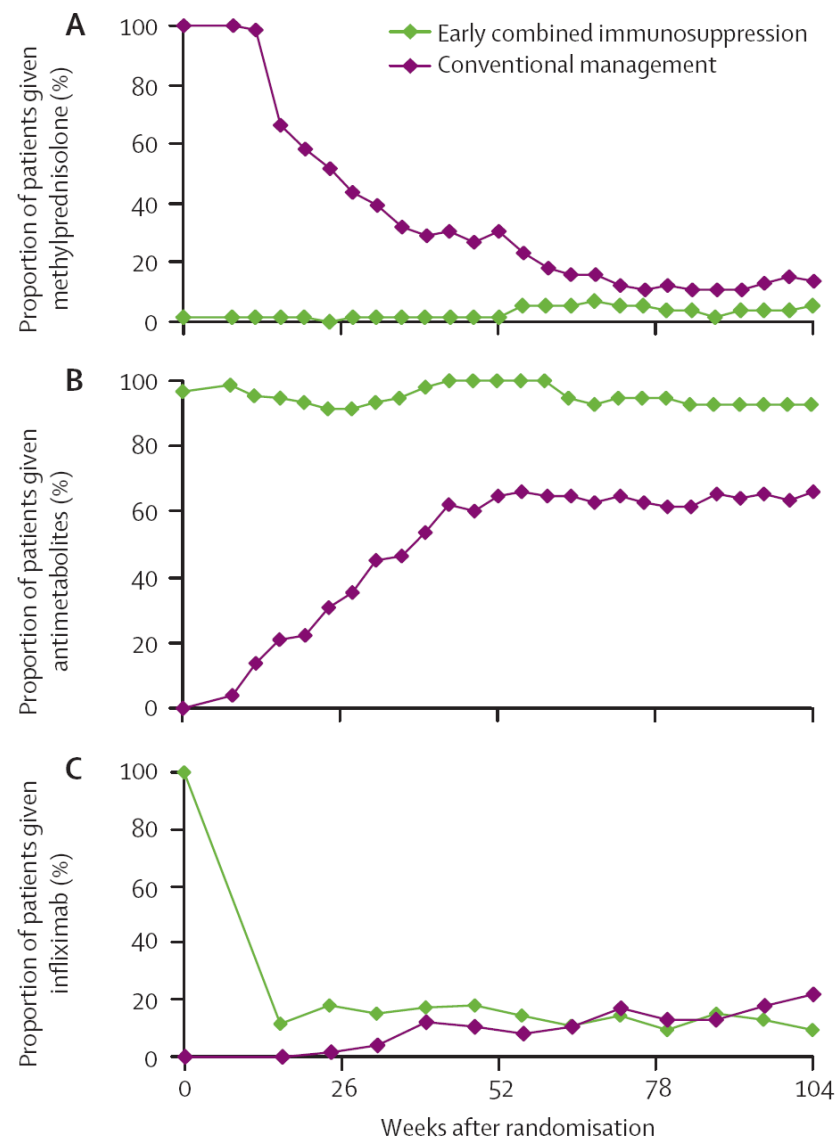
An open randomised trial



Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease

An open randomised trial

SUTD



Corticosteroids

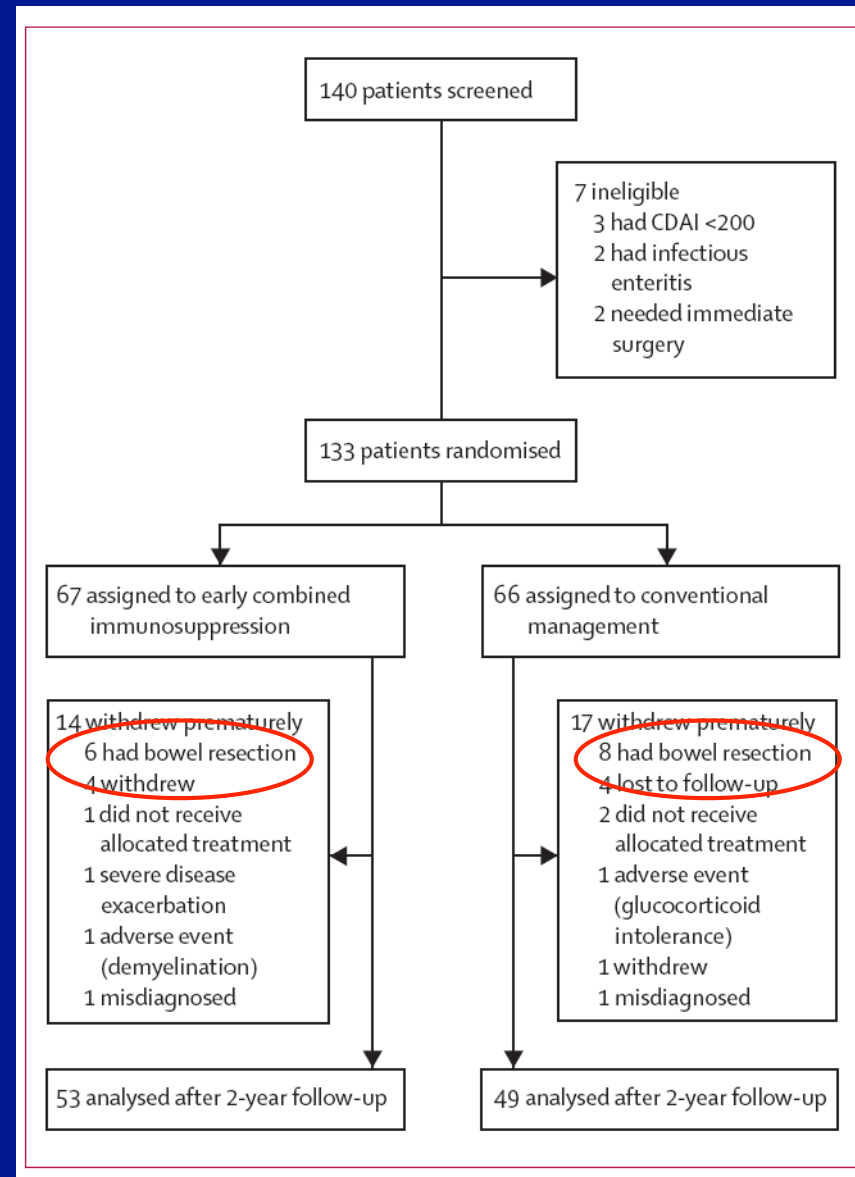
Immunosuppressives

Infliximab

Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease

An open randomised trial

SUTD

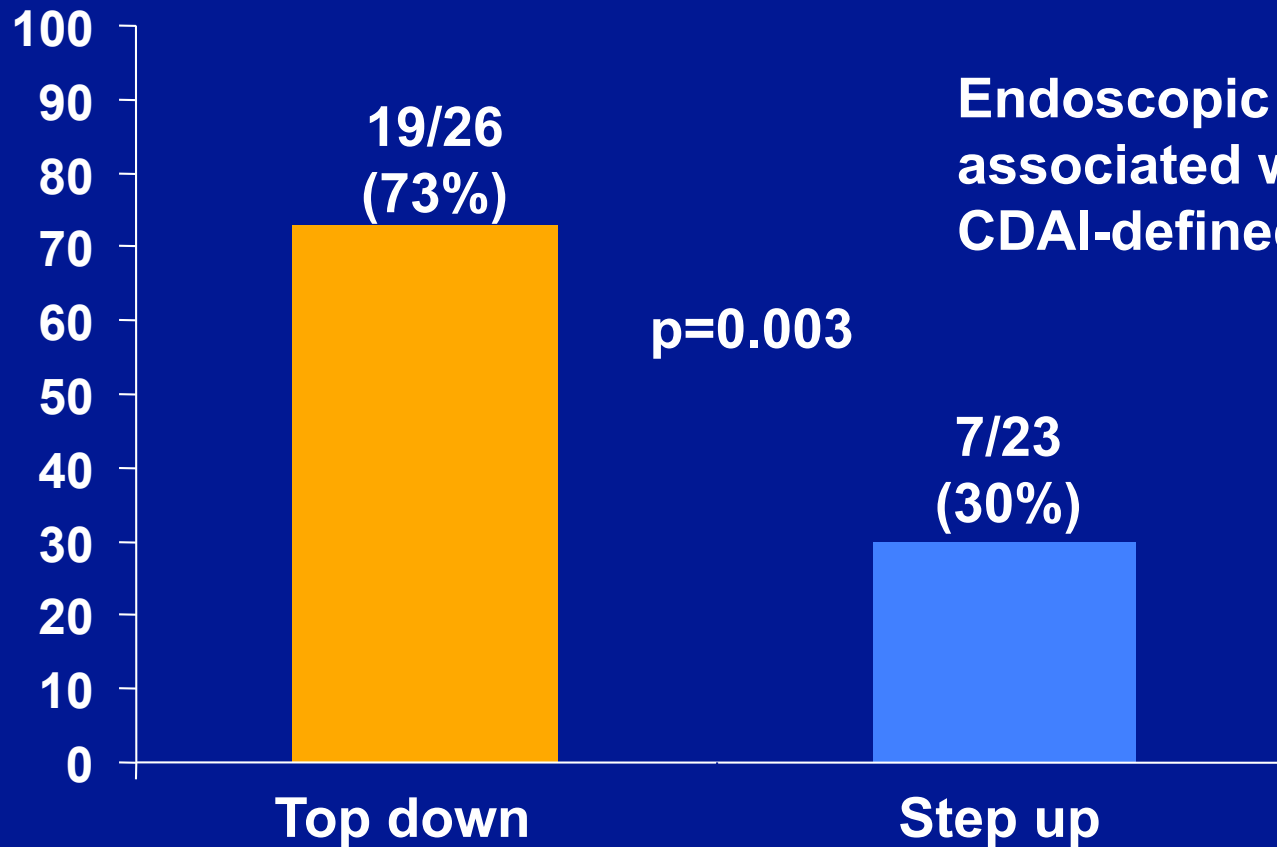


Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease

SUTD

An open randomised trial

No ulcer at M24
(Evaluable patients)



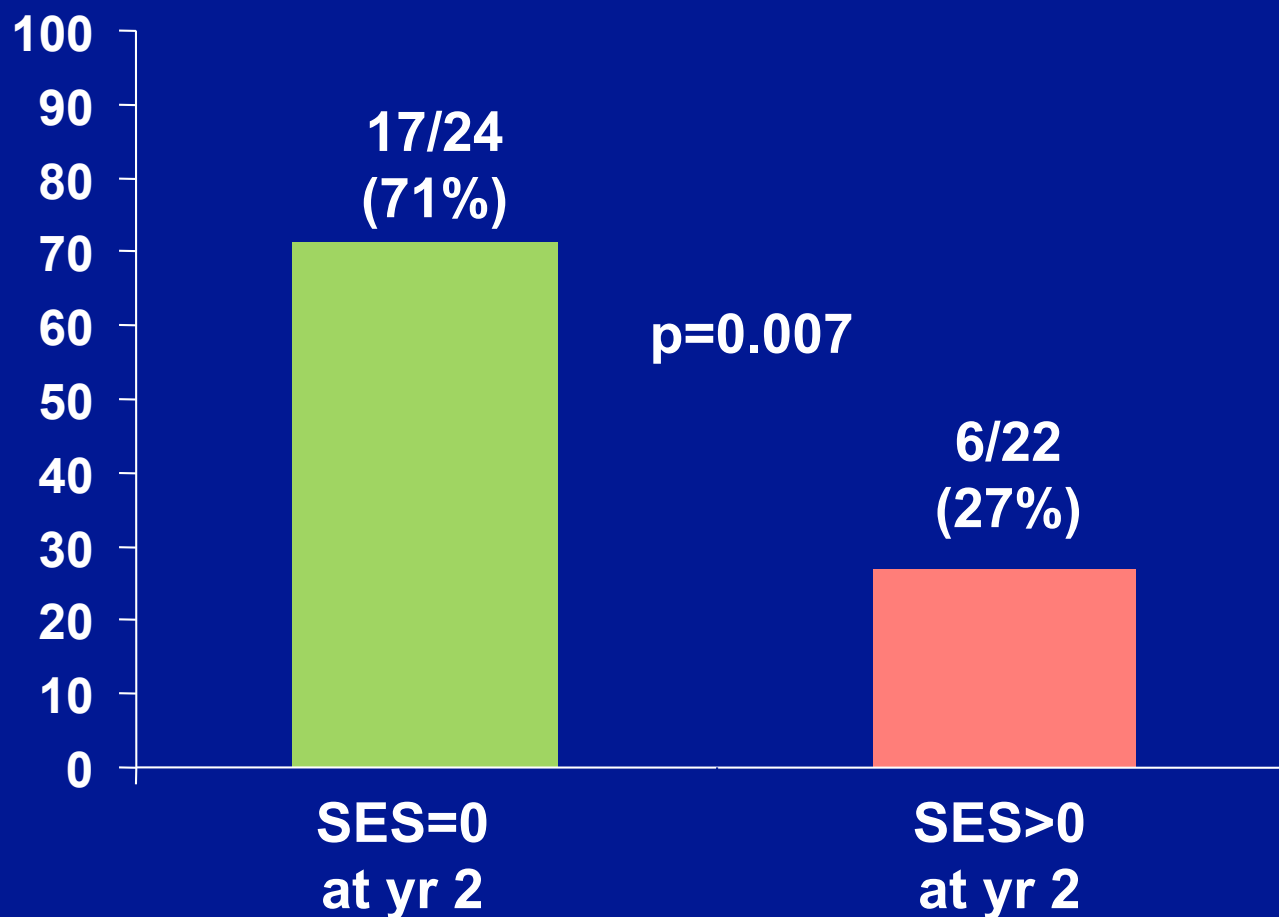
The corresponding endoscopy scores were 0.7 (SD 1.5) and 3.1 (2.9) ($p < 0.001$).

Endoscopic healing was not associated with CDAI-defined remission.

Mucosal Healing predicts sustained clinical remission in early Crohn's disease

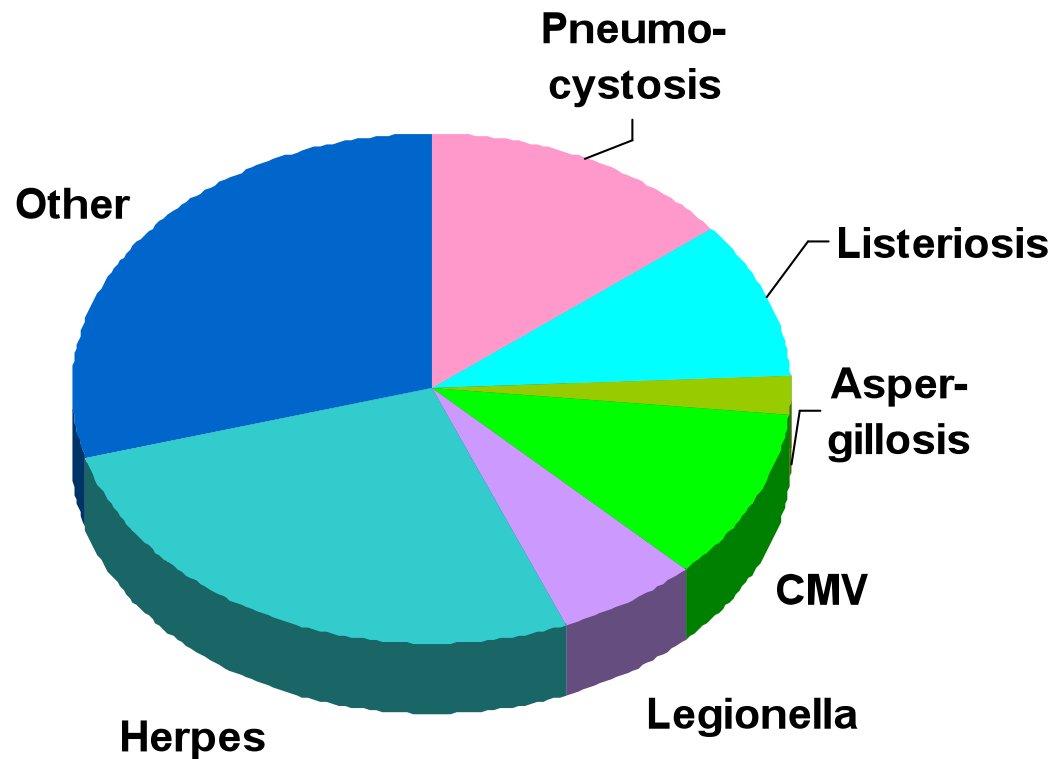
SUTD

Steroid free remission
during year 3-4



Opportunistic Infections: Worldwide experience with Infliximab

PSUR 14 Interval (6 mos): 24 Feb 2006 – 23 Aug 2006



**Most common
opportunistic infections**

**N total: 112
in 361,020 pts exposed**

Lymphome T hépatospléniques

- Forme rare de LNH
150 cases décrit depuis 1990, certains sous AZA
Souvent fatal
- **16 HSTL reportés sous anti-TNF**
Sujets jeunes, hommes
IFX et ADA + azathioprine

Immunomodulateurs dans les MICI : le plus tôt c'est le mieux ?

**Comment sélectionner les patients susceptibles
de bénéficier de ce traitement précoce?**

Selection of patients

Predictors of surgery or complications

- Young age^{1,2,4}
- Smoking⁶
- Upper tract involvement²
- Perianal disease^{1,4}
- Severe colonic lesions⁷
- Phenotype B2⁸
- ASCA^{3,5}
- Serotype (OmpC, CBir1, I2)⁵
- NOD2
- Need for corticosteroids^{1,4}

¹Beaugerie L et al. Gastroenterology 2006;130:650-656

²Wolters FL et al, Gut 2006; 55: 1124-30

³Vermeire, DDW 2007

⁴Seksik DDW 2007

⁵Dubinsky DDW 2007

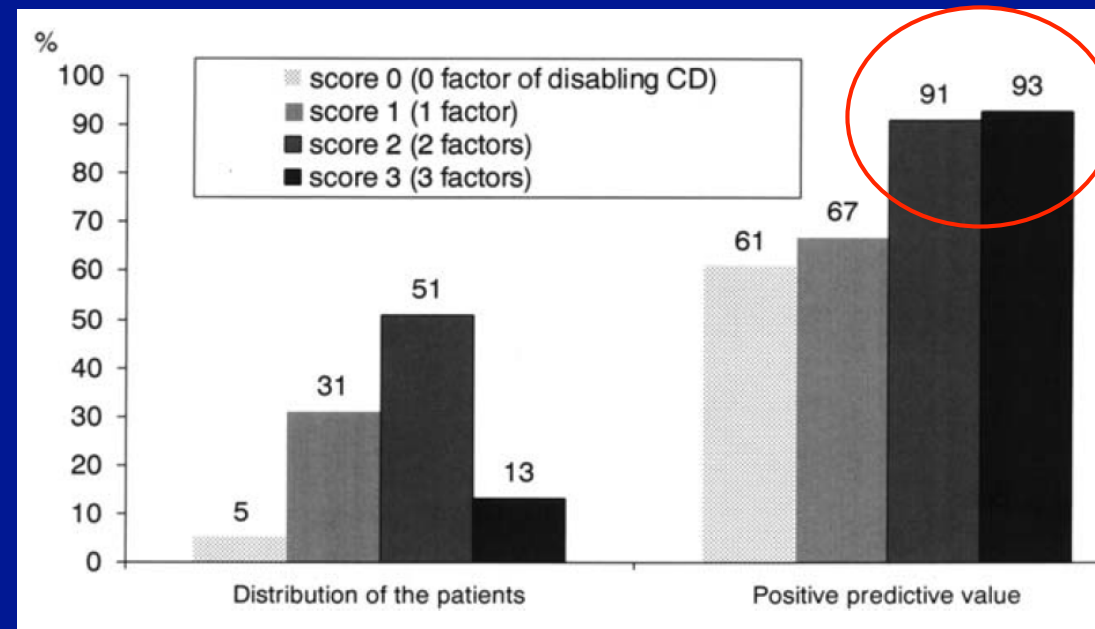
⁶Sands et al, Am J GE 2003; 98:2713-8

⁷Allez et al, Am J GE, 1999

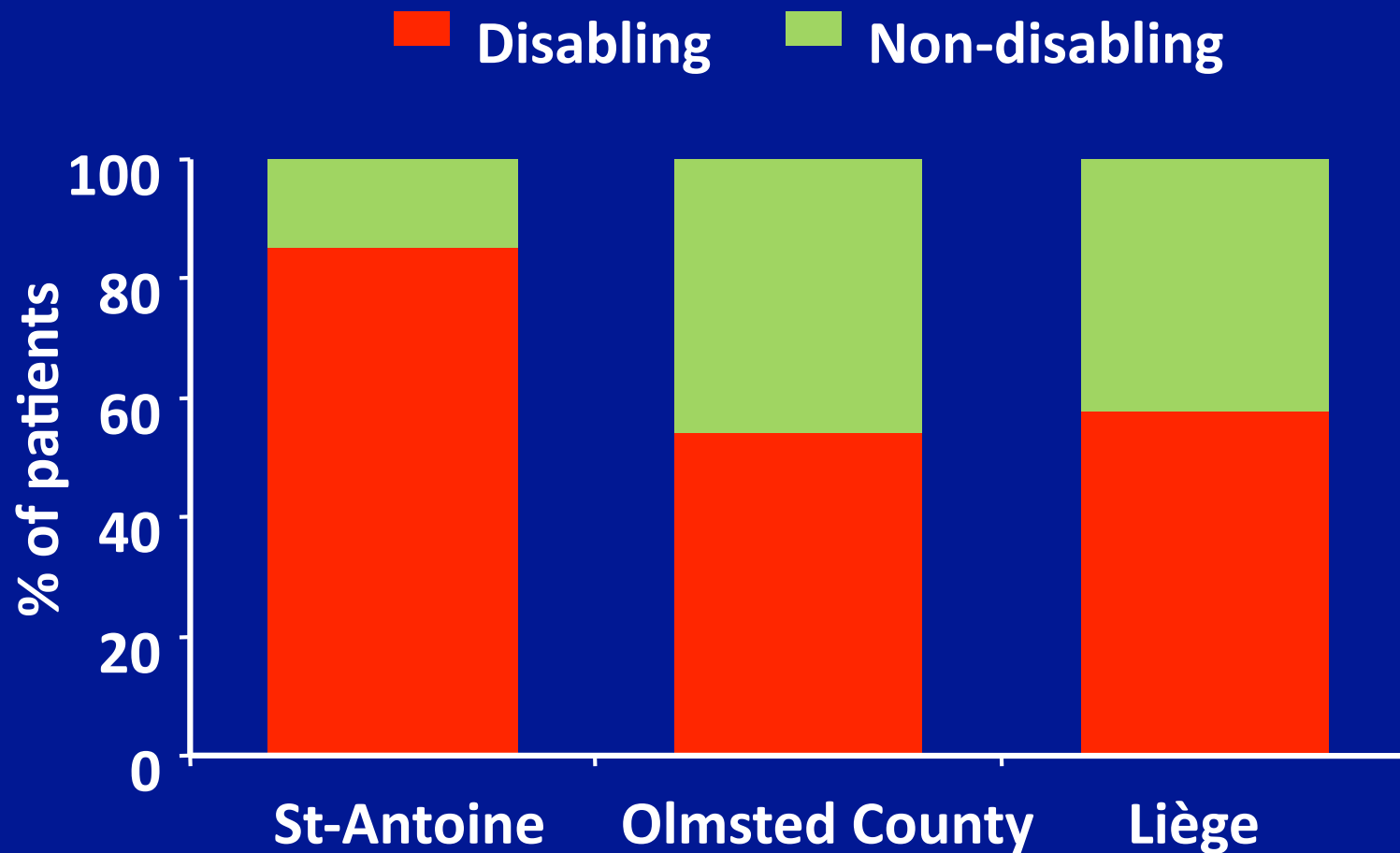
⁸Loly et al, Scand J GE, 2008

Selection of patients Disabling Crohn's Disease

- N=1188 pts
- >5yr follow-up
- Disabling CD
 - 85% of pts
 - definition
 - > 2x corticosteroids
 - > 1 hospitalisation
 - Any complication
 - IS use
 - or surgery
- 3 independent risk factors
 - <40 yr
 - perianal disease
 - CS for first attack



Selection of patients Disabling Crohn's disease



Beaugerie L, *et al. Gastroenterology* 2006;130:650–656
Seksik, *et al. Gastroenterology* 2007; 132 a17.80
Loly, *et al. Gastroenterology* 2007; 132 a17.81

Immunomodulateurs dans les MICI : le plus tôt c'est le mieux ?

Si l'on débute tôt les immunomodulateurs, que faire ensuite ?

STORI : Arrêt de l'IFX chez des patients en "Rémission profonde"

Objectif & Méthode :

Evaluer le risque de rechute et identifier des facteurs prédictifs de rechute associés chez les patients après l'arrêt de l'infliximab dans un essai prospectif de 115 patients atteints de maladie de Crohn.

- Les patients avec une Maladie de Crohn luminale ont été recrutés prospectivement dans les centres du GETAID
 - Traitement combiné par Infliximab + IS durant au moins un an
 - Rémission sans corticoïdes depuis au moins 6 mois
- Les patients ont reçu leur dernière perfusion d'infliximab à la baseline et ont été suivis à 2 semaines et ensuite tous les 2 mois.
- L'immunosuppresseur a été maintenu à dose stable

STORI : Caractéristiques de la population

Sexe (Hommes) (%)	43
Tabagisme actif (%)	39
Age (ans) (med-IQR)	32 (26-39)
Durée de la maladie (ans) (med-IQR)	8 (5-12)
Antécédent de chirurgie (%)	22
Purine/methotrexate (%)	83/17
IS-naïf (%)	44
Durée des IS (ans) (med-IQR)	2.8 (2.0-4.6)
Durée de l'IFX (ans) (med-IQR)	2.2 (1.5-3.1)
IFX en traitement d'entretien depuis le début (%)	95
Corticoïdes (mois -12 to -6) (%)	7

STORI : une population à l'inclusion en « Rémission profonde »

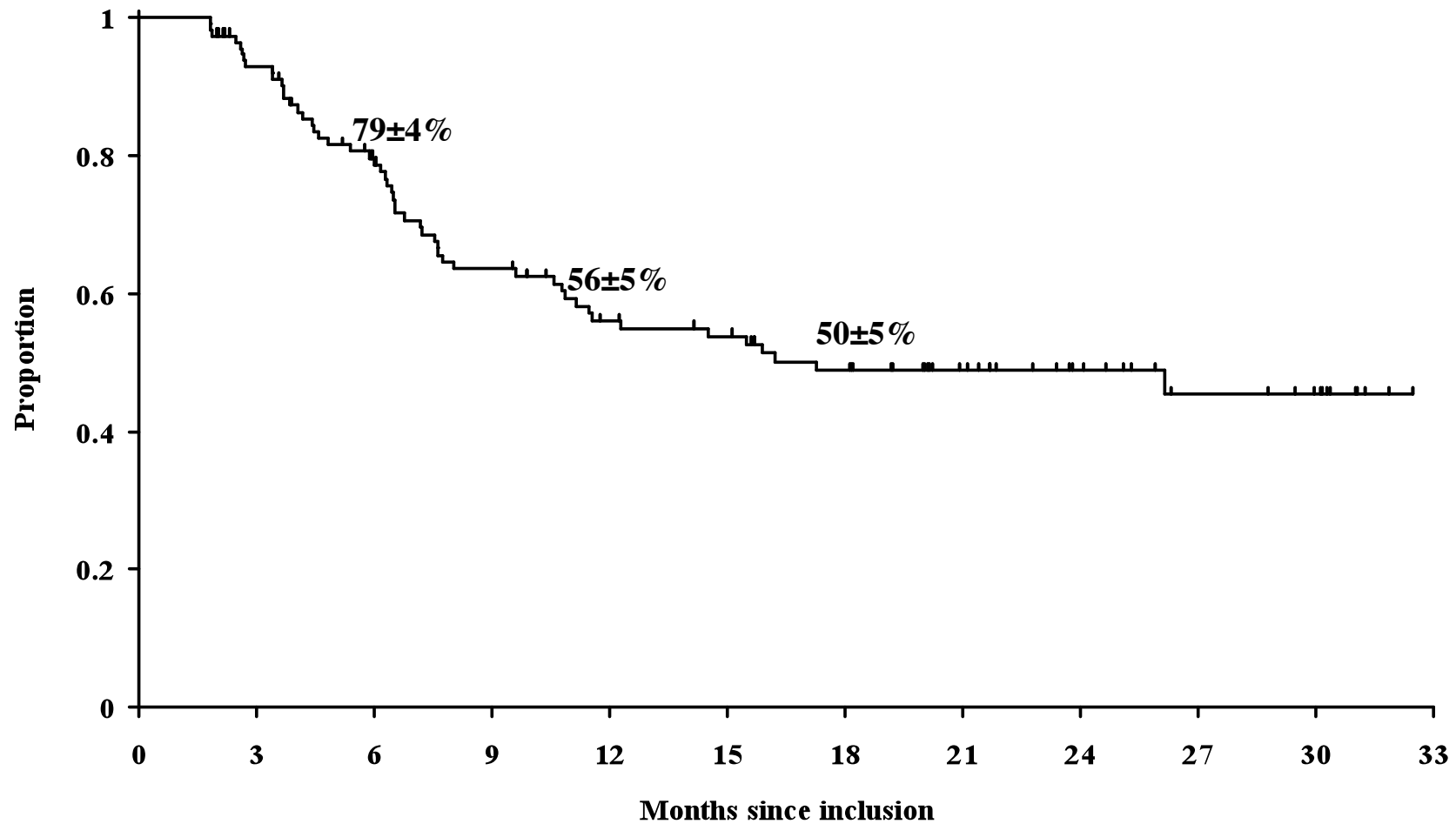
Scores cliniques et caractéristiques biologiques à la
baseline (med-IQR)

CDAI (n=115)	37 (19–61)
CDEIS (n=115)	0.7 (0.0–3.0)
US CRP mg/l (n=106)	2.0 (0.8–4.8)
Calprotectine fécale (microg/g) (n=85)	51 (30–318)
IFX niveau résiduel (microg/mL) (n=107)	3.8 (1.9–8.0)

Results (3)

Kaplan-Meier curve of relapse (52 relapses in 115 patients)

Median ($\pm$ SE) follow up 21 $\pm$ 1 months



at risk : 115 102 79 63 51 47 39 27 20 12 9

Results (5)

Multivariate analysis of factors predicting time-to-relapse:

Model on 109 patients

Factor	HR (95%CI)	P
Male	3.6 (1.9-6.9)	0.0001
No surgery	4.5 (1.8-11.6)	0.0003
Steroid treat. (month -12 to -6)	4.2 (1.5-11.8)	0.02
Hemoglobin $\leq$ 14.5 (g/dl)	5.3 (2.1-13.2)	0.0001
WBC $>$ 6 (10^3 /ml)	2.2 (1.2-4.2)	0.01
CRP hs $>$ 5 (mg/l)	3.1 (1.6-5.9)	0.0009
CDEIS $>$ 0	2.6 (1.3-5.3)	0.005

Results (8)

Remission (CDAI<150) rate in relapsers

	1 month	4 months
Assessed according to protocol at 1 month (n=39)	36/39	31/36
Assessed out of delay at 1 month (n=4)	4/4	1/1
Non assessed at 1 month (n=5)		5/5
Total (n=48)	40/43 (93%)	37/42 (88%)

No infusion reaction was observed over the first 3 infusions

Conclusions

- L'introduction précoce des immunomodulateurs diminue le risque de rechute
- Il reste à démontrer les bénéfices sur le plus long terme.
- Les critères de sélection des patients candidats à une introduction précoce des IM sont imparfaits.
- Une autre stratégie est d'appliquer un contrôle strict de l'activité inflammatoire, fondé sur des paramètres biologiques ou morphologiques (tight-control) pour moduler la thérapeutique.