JFHOD
JFHOD.COM
16-19 MARS 2023
PALAIS DES CONGRÈS DE PARIS
L'ACTIVITÉ PHYSIQUE
PAYS INVITÉ : LA SUISSE
Société Nationale Française de Gastro-Entérologie
SNFGE
FMC HGE

Prise en charge des lésions ano-périnéales de la maladie de Crohn

Dr Alexandre MERLINI – L'HERITIER
Gastro-entérologue, Proctologue
CHP Saint Grégoire

LIENS D’INTERET

- Aucun

OBJECTIFS PEDAGOGIQUES

- Connaître les différents types de LAP et leurs critères de gravité
- Connaître les examens morphologiques permettant de les caractériser
- Connaître les principales stratégies thérapeutiques médico-chirurgicales et leurs indications
- Connaître la place des traitements obturateurs et des cellules souches
- Savoir quand et comment évaluer la réponse au traitement

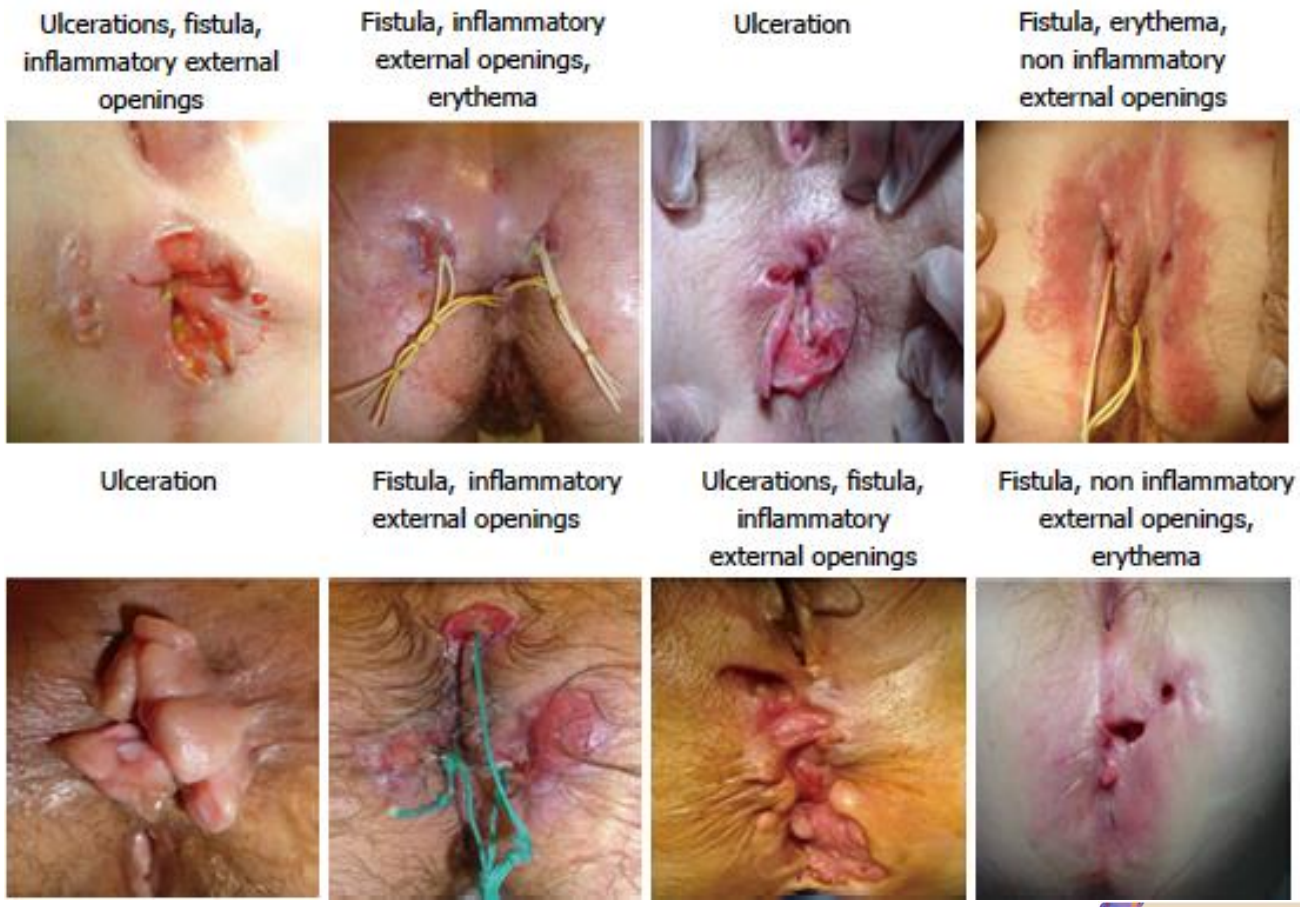
L'examen clinique:
Sémiologie des LAP

Ulcérations

Fistules

Sténoses

	Ulcération	Fistule	Sténose
0	Absente	Absente	Absente
1	Superficielle	Fistule simple	Réversible (spasme, diaphragme ou induration lié aux phénomènes suppuratifs)
2	Creusante	Fistule complexe	Irréversible (sténose longue et fibreuse)



L’examen clinique: n’est pas suffisant

		Examen clinique			
		F0	F1	F2	Total
IRM	F0	**2**	3	8	13
	F1	2	**4**	19	25
	F2	5	14	**65**	84
	Total	9	21	92	**122**

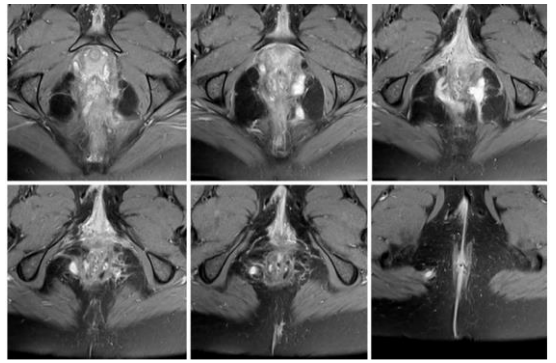
		Examen clinique			
		UO	U1	U2	TOTAL
IRM	UO	81	20	13	114
	U1	2	0	0	2
	U2	3	1	2	6
	TOTAL	86	21	15	122

Garros A, Magnetic resonance imaging and clinical assessments for perianal Crohn’s disease: gain and limits. 2014.

L’IRM est plus performant que l’examen clinique pour l’évaluation de fistules

L’examen clinique est plus performant que l’IRM pour le diagnostic des ulcérations et des sténoses

L’IRM est indispensable dans le diagnostic et la prise en charge des LAP de Crohn

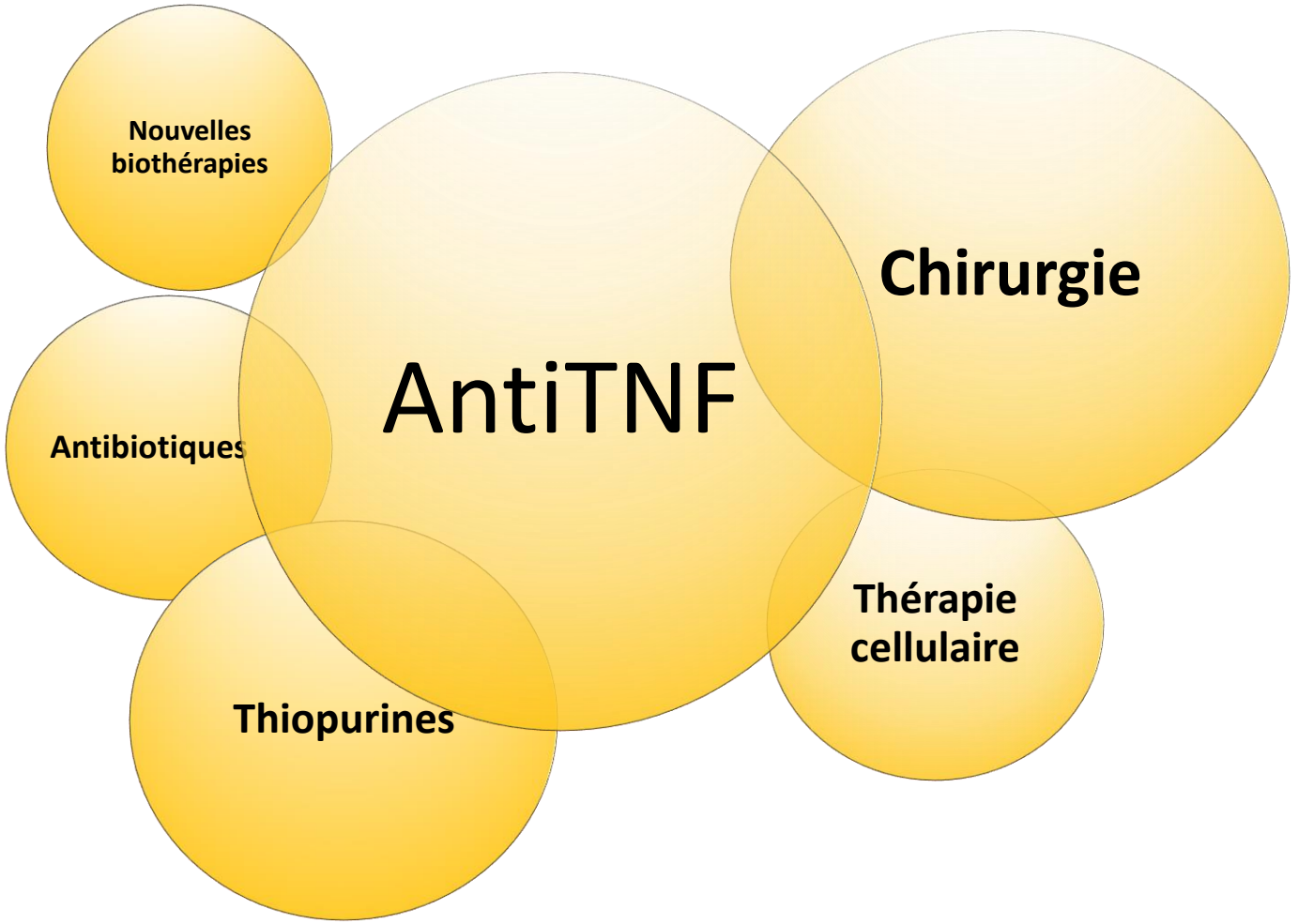


3.2.2 Detection of fistulae and abscesses

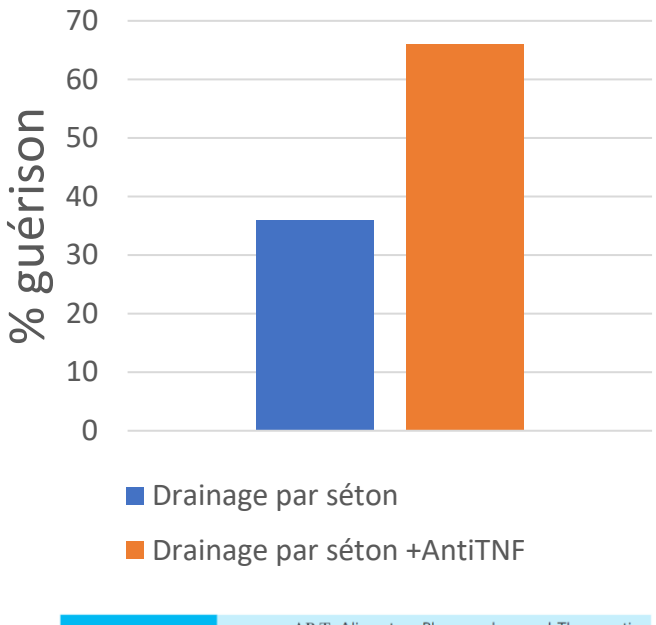
Statement 3.2.2. ECCO-ESGAR Diagnostics GL [2018]

MRI is the most accurate imaging modality for diagnosis and classification of perianal CD and is the recommended first-line test [EL1]. Transrectal ultrasonography [TRUS] is superior to clinical examination and is an alternative to MRI [EL2]. Combining any modality of MRI, examination under anaesthesia [EUA], or TRUS improves accuracy [EL2]

Arsenal thérapeutique:
Nouvelles cibles – Nouvelles thérapies



La référence:
Combinaison chirurgie / anti-TNF

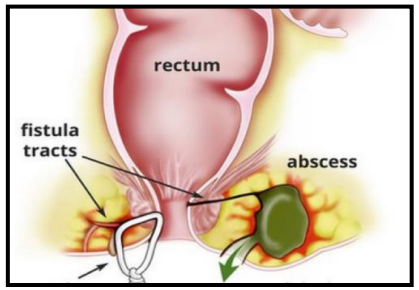


AP&T Alimentary Pharmacology and Therapeutics

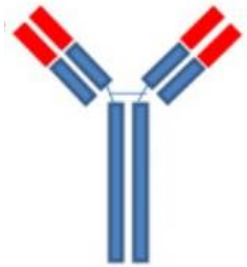
Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease

N. A. Yassin*,†,‡, A. Askari*,‡, J. Warusavitarne*,‡, O. D. Faiz*,‡, T. Athanasiou‡,§, R. K. S. Phillips*,‡ & A. L. Hart*,†,‡

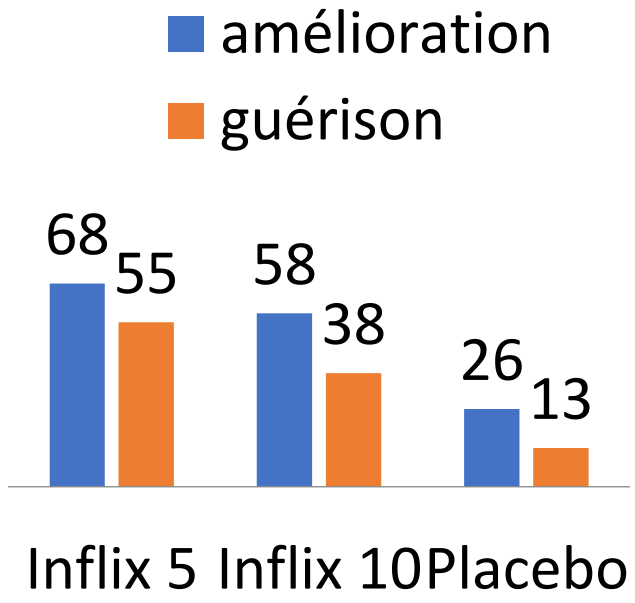
Chirurgie



Anti-TNF



Infliximab



The New England Journal of Medicine

INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN'S DISEASE

DANIEL H. PRESENT, M.D., PAUL RUTGEERTS, M.D., STEPHAN TARGAN, M.D., STEPHEN B. HANAUER, M.D., LLOYD MAYER, M.D., R.A. VAN HOGEZAND, M.D., DANIEL K. PODOLSKY, M.D., BRUCE E. SANDS, M.D., TANJA BRAAKMAN, M.D., KIMBERLY L. DEWOODY, PH.D., THOMAS F. SCHAIBLE, PH.D., AND SANDER J.H. VAN DEVENTER, M.D., PH.D.

Traitements médicaux « classiques »

Clinical Gastroenterology and Hepatology 2018;16:1879–1892

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis

Matthew J. Lee,[*,‡,§] Claire E. Parker,[‖] Sarah R. Taylor,[¶,#] Leonardo Guizzetti,[‖] Brian G. Feagan,[‖,**,‡‡] Alan J. Lobo,[¶,#] and Vipul Jairath[‖,#,**]

Study or subgroup	Drug therapy Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, fixed, 95% CI
1.2.1 Antibiotics						
Thia 2009 (ciprofloxacin)	3	10	1	4	100.0%	1.20 [0.17, 8.38]
Thia 2009 (metronidazole)	0	7	0	4		Not estimable
Subtotal (95% CI)		**17**		**8**	**100.0%**	**1.20 [0.17, 8.38]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (*P* = .85)						
1.2.2 Immunosuppressives						
Hart 2007	1	6	0	6	10.9%	3.00 [0.15, 61.74]
Klein 1974	1	5	1	5	21.8%	1.00 [0.08, 11.93]
Present 1980	9	29	1	17	27.5%	5.28 [0.73, 38.11]
Sandborn 2003	2	21	2	25	39.8%	1.19 [0.18, 7.74]
Subtotal (95% CI)		**61**		**53**	**100.0%**	**2.47 [0.85, 7.21]**
Total events	13		4			
Heterogeneity: Chi² = 1.68, df = 3 (*P* = .64); I² = 0%						
Test for overall effect: Z = 1.65 (*P* = .10)						
1.2.3 TNF-alpha antagonists						
Colombel 2009	23	70	6	47	22.5%	2.57 [1.13, 5.84]
Hanauer 2006(CLASSIC-1)	3	26	1	6	5.1%	0.69 [0.09, 5.55]
Present 1999	29	63	4	31	16.8%	3.57 [1.38, 9.25]
Sandborn 2004	26	60	8	26	35.0%	1.41 [0.74, 2.68]
Sandborn 2007	1	20	2	25	5.6%	0.63 [0.06, 6.41]
Schreiber 2011(PRECISE-2)	10	28	5	30	15.1%	2.14 [0.84, 5.50]
Subtotal (95% CI)		**267**		**165**	**100.0%**	**2.06 [1.40, 3.04]**
Total events	92		26			
Heterogeneity: Chi² = 4.97, df = 5 (*P* = .42); I² = 0%						
Test for overall effect: Z = 3.65 (*P* = .0003)						

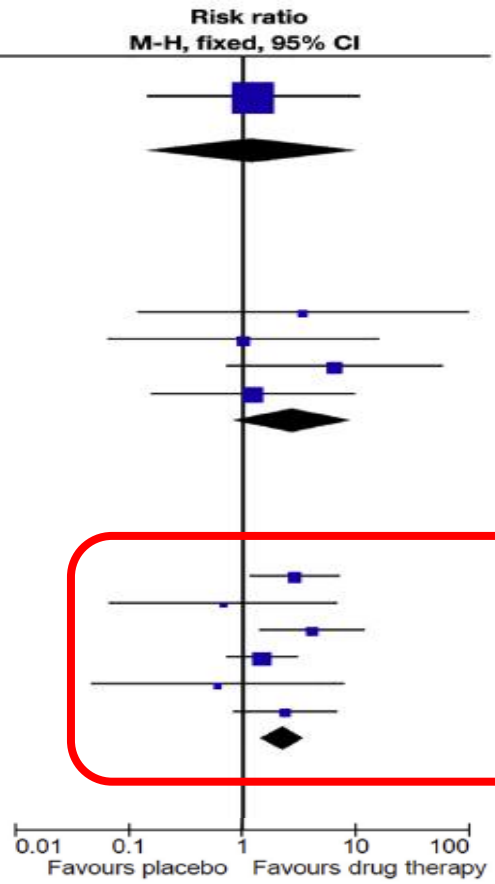


Figure 2. Drug therapy vs placebo for induction of fistula remission.

Recommendation 3.6. ECCO CD Treatment GL [2019]

We suggest against using antibiotics alone for fistula closure in patients with Crohn's disease and complex perianal fistulae [weak recommendation, low-quality evidence].

Recommendation 3.7. ECCO CD Treatment GL [2019]

We suggest against using thiopurine monotherapy [azathioprine, mercaptopurine] for fistula closure in patients with Crohn's disease and complex perianal fistulae [weak recommendation, very low-quality evidence].

Anti-TNF alpha

Recommendation 3.1. ECCO CD Treatment GL [2019]

We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in Crohn's disease [strong recommendation; low quality of evidence].

Peut-on optimiser la réponse?
Antibiotiques

Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI)

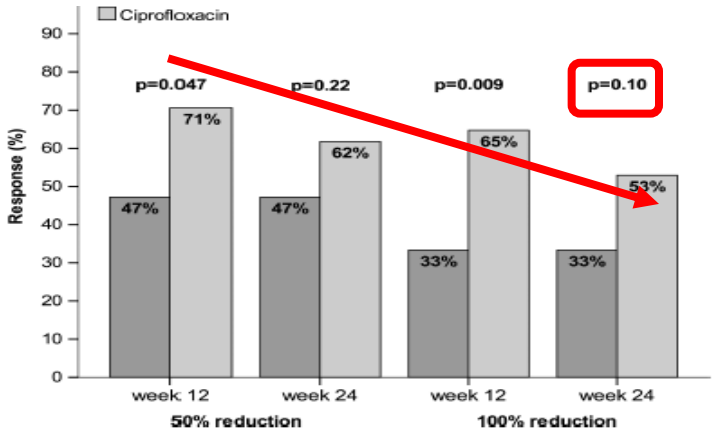


Figure 2 Percentage of patients with response (≥50% closure of draining fistulas from baseline) and remission (100% closure of draining fistulas) at week 12 (primary endpoint) and at week 24 in the two treatment arms.

GUT 2014

Les antibiotiques (quinolones) sont efficaces en induction

Effets secondaires / résistances

Effet suspensif

En pratique:

- Parfois utiles en induction (suppuration active et symptomatique)
- Ne remplacent pas le drainage

Peut-on optimiser la réponse? Combothérapie

Supplementary Table 3. Summary Estimates for Odds of Partial and Complete Fistula Closure

Adverse event	Pooled summary estimate (OR with 95% CI)	Summary estimate by anti-TNF agent (OR with 95% CI)
Partial fistula closure	1.25 (0.84–1.88)	
Infliximab		0.77 (0.38–1.54)
Adalimumab		1.68 (0.65–4.31)
Certolizumab		1.59 (0.66–3.82)
Complete fistula closure	1.10 (0.68–1.79)	
Infliximab		0.76 (0.38–1.52)
Adalimumab		0.93 (0.18–4.70)
Certolizumab		1.85 (0.86–3.97)

Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti-TNF Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials

J.L. Jones, G.G. Kaplan, L. Peyrin-Biroulet, L. Baidoo, S. Devlin, G.Y. Melmed, D. Tanyingoh, L. Raffals, P. Irving, P. Kozuch, M. Sparrow, F. Velayos, B. Bressler, A. Cheifetz, J.-F. Colombel, C.A. Siegel

D

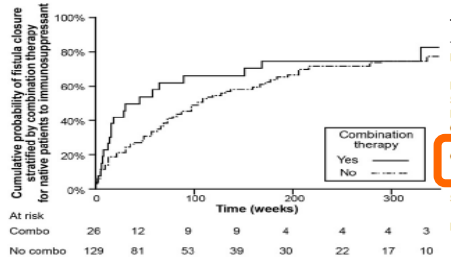


Table 2. Factors Associated With First Perianal Fistula Closure, as Determined by Multivariate Analysis

Covariates	HR	95% CI of HR	*P* value
L1 (isolated ileal disease) behavior	0.77	0.25–1.98	.631
L3 (ileocolonic disease) behavior	1.88	1.08–3.32	.0255
Seton drain duration <34 wk	2.31	1.32–4.1	.003
IFX duration >118 wk	1.76	1.003–2.95	.0485
Combination therapy of immunosuppressant/IFX	1.44	0.79–2.66	.23
Combination therapy of immunosuppressant/IFX for naive patients	2.58	1.16–5.6	.02
Simple vs complex perianal fistula[a]	2.26	0.86–5.18	.09
Interval between seton drainage and IFX initiation less than 6 wk	1.07	0.57–2.07	.82

Long-term Outcome of Perianal Fistulizing Crohn's Disease Treated With Infliximab

GUILLAUME BOUGUEN,* LAURENT SIPROUDHIS,* EMMANUEL GIZARD,‡ TIMOTHÉE WALLENHORST,* VINCENT BILLIOUD,‡ JEAN-FRANÇOIS BRETAGNE,* MARC-ANDRÉ BIGARD,‡ and LAURENT PEYRIN-BIROULET‡

Ni prouvée, ni recommandée

Signal en faveur de la combothérapie

Peut-on optimiser la réponse?
Taux résiduels

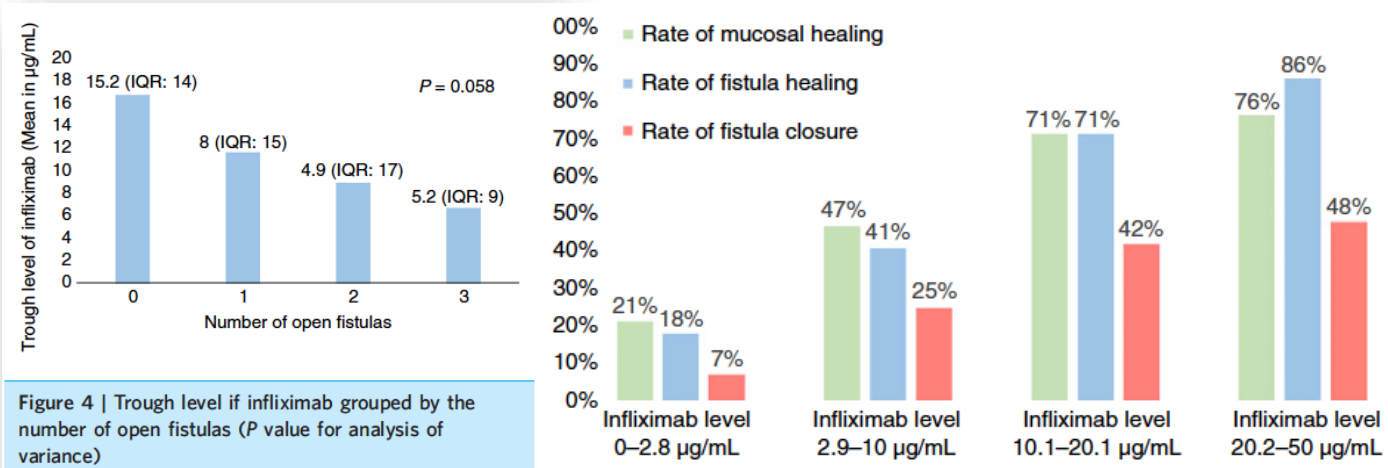
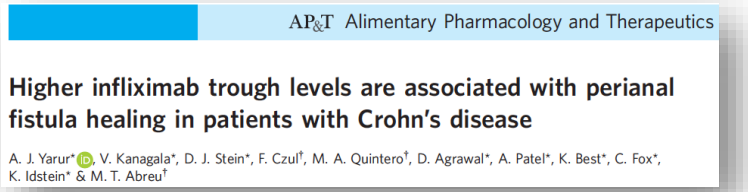


Figure 4 | Trough level if infliximab grouped by the number of open fistulas (*P* value for analysis of variance)

Surveiller les taux résiduels

Viser des taux supra-thérapeutiques

Optimiser les patients en cas de fistule active malgré un drainage chirurgical optimal


APT Alimentary Pharmacology and Therapeutics

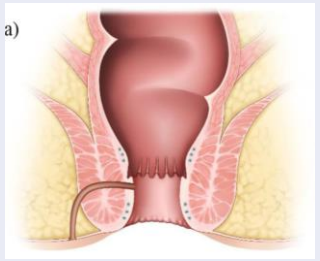
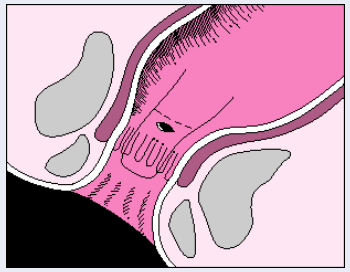
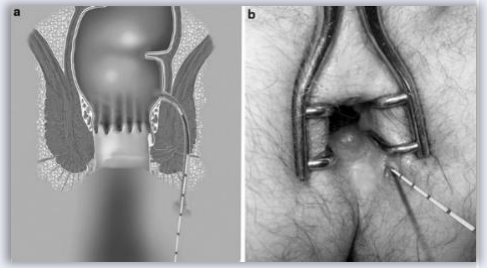
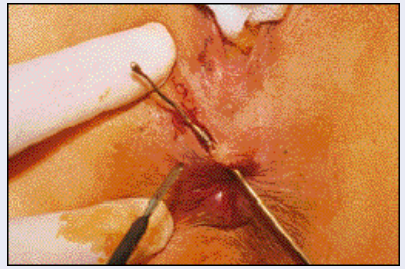
Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease

A. J. Yarur*, V. Kanagala*, D. J. Stein*, F. Czul†, M. A. Quintero†, D. Agrawal*, A. Patel*, K. Best*, C. Fox*, K. Idstein* & M. T. Abreu†

En cas d'échec aux anti-TNF: Quelles alternatives?

Ustekinumab				Vedolizumab			
Etude	Type étude	n	résultat	Etude	Type d'étude	n	Résultat
UNITI	Contrôlée Post hoc	26	24%vs14% S8 80% vs46% S44	GEMINI2	Contrôlée Post hoc	57	28%vs11% à S14 31%vs11% à S52
BIOLAP	Prospective Observationnelle	207	38% (6 mois)	BIOLAP	Prospective Observationnelle	151	23% à 6 mois
Méta-Analyse (Etudes rétrospectives)		396	17% réponse complète 56% réponse partielle à S52	ENTER PRISE	« contrôlé » Comparaison 2 schémas posologiques	32	54% réponse partielle 43% réponse complète À S30
USTAP	Contrôlée	En cours					

Fistule drainée…
Que faire ensuite ?

Abstention	Chirurgie d'épargne sphinctérienne			Mise à plat
Retrait du séton	Obturation du trajet: Colle, Plug	Fermeture de l'orifice interne: Lambeaux et LIFT	Cautérisation du trajet: FilaC, RF et VAAFT	Fistulotomie
				
Le plus simple	A oublier	Les plus repondus > Retrait du séton (PISA II)	Peu évaluées	A éviter sauf en cas de fistule superficielle

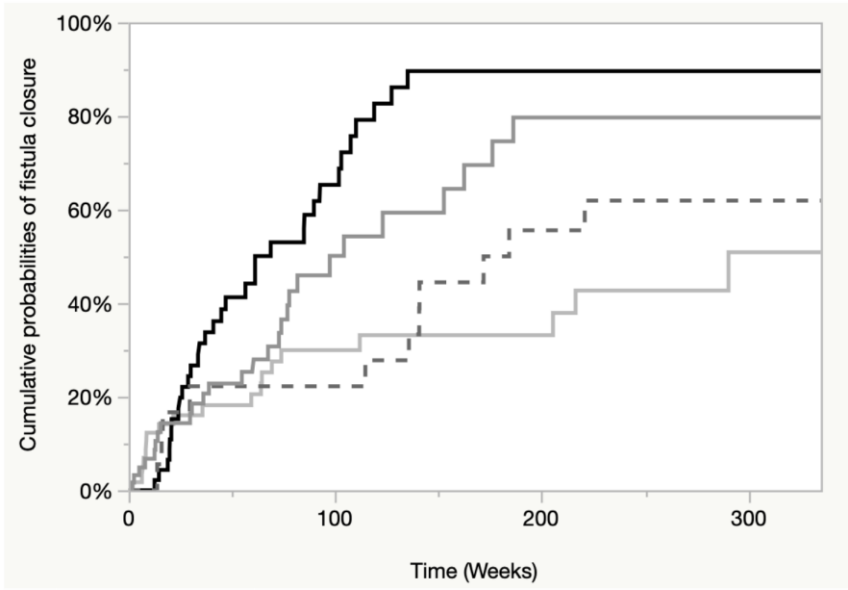
Chirurgie:
Points importants

Abcès = drainage urgent

Drainer les collections / fistules
Séton sans tension

Limiter les sections sphinctériennes

Démarche chirurgicale pro-active



Seton and additional surgery within 1 y	47	11	11	2
Seton alone	62	13	5	4
Seton and additional surgery > 1y	18	15	9	5
No seton	58	24	15	6

M.Laland, Colorectal Disease, 2022

Nouvelles cibles de traitement

Avivement du trajet

Chirurgie

Fermeture de l'orifice interne

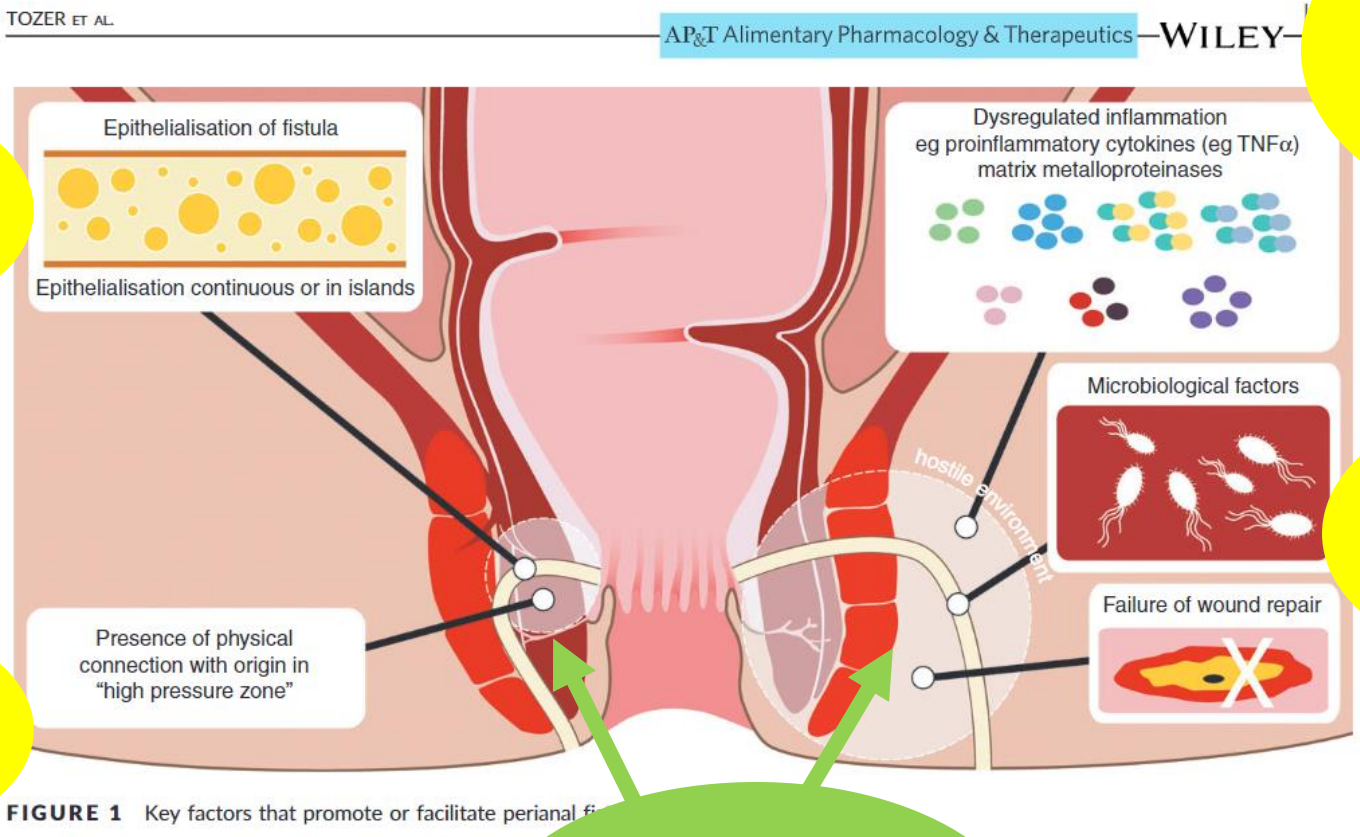


FIGURE 1 Key factors that promote or facilitate perianal fi

Anti-TNF, IS, Biothérapies

Traitement médical

Antibiotiques

Cellules souches

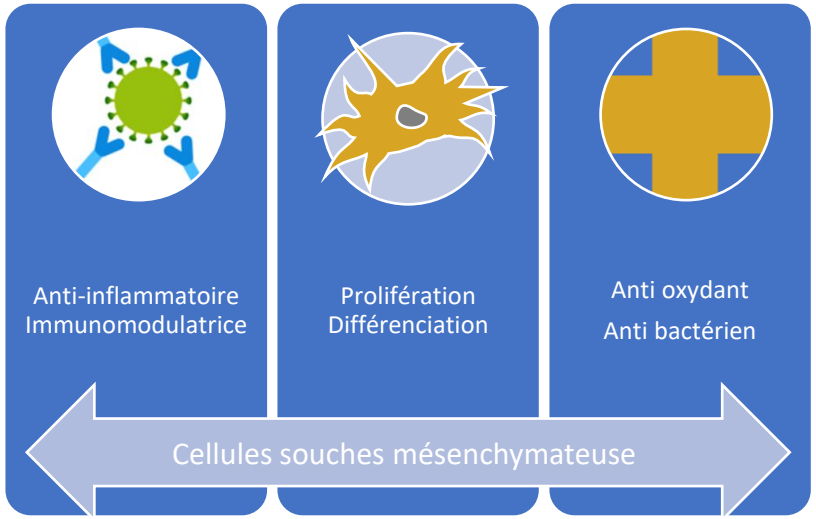
Thérapie Cellulaire:

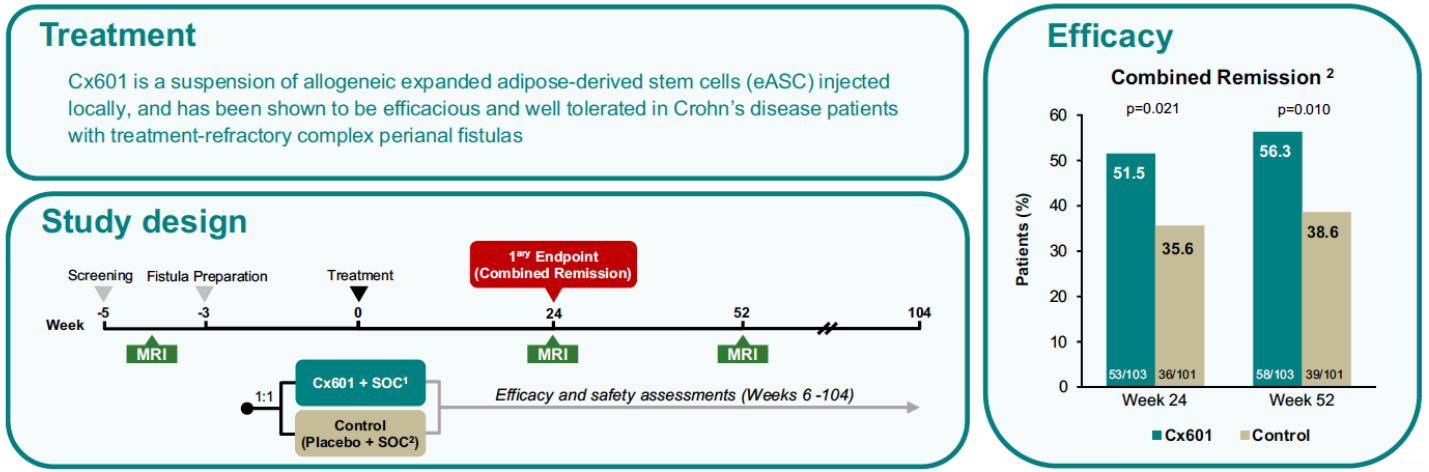
Etude ADMIRE CD

Gastroenterology 2018;154:1334–1342

Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease

Julián Panés,[1] Damián García-Olmo,[2] Gert Van Assche,[3] Jean Frederic Colombel,[4]



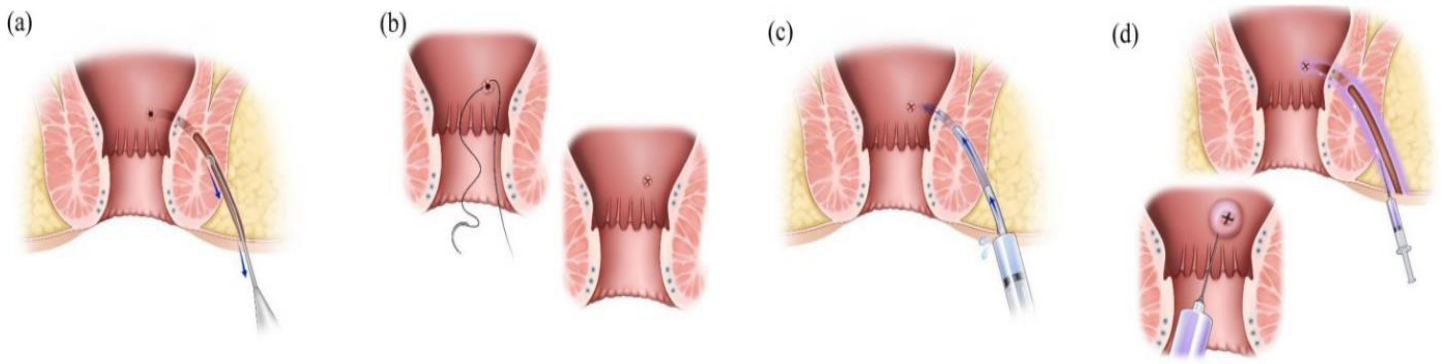


En vraie vie:
Succès clinique 60 à 75%

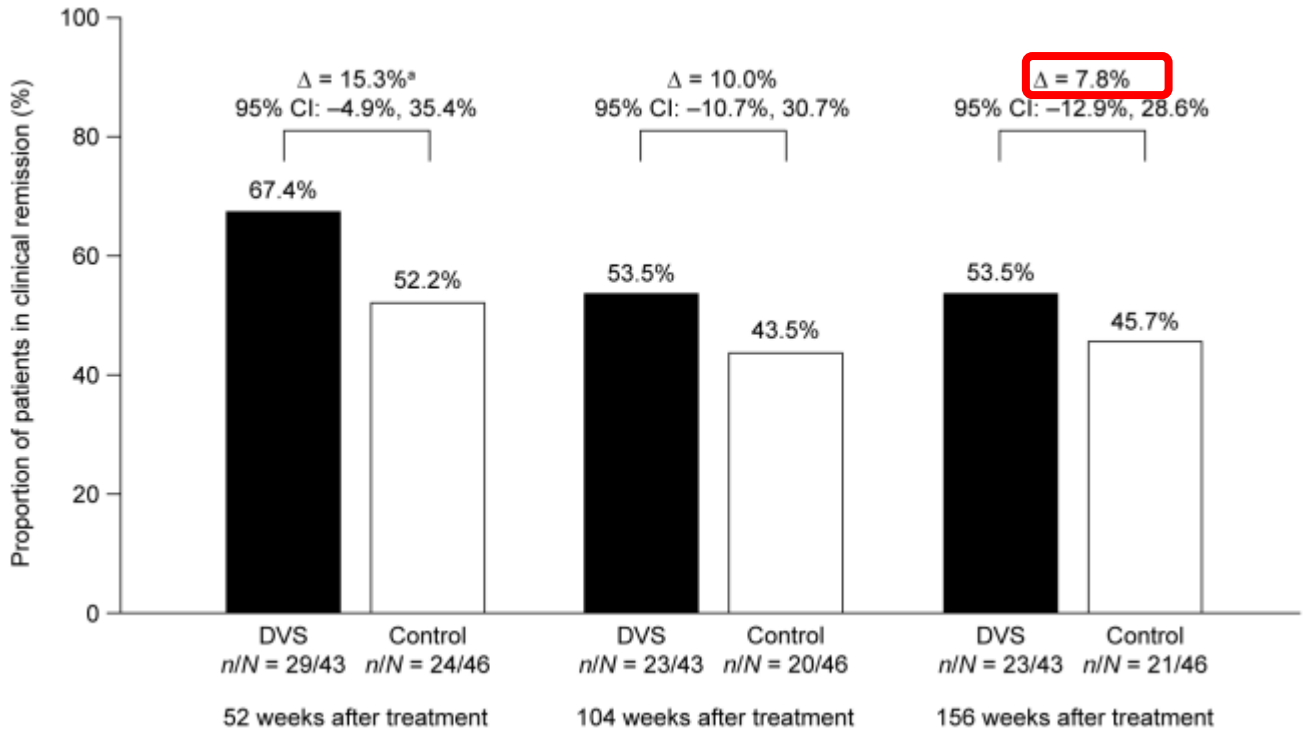
DARVADSTROCEL
EI : Proctalgies, Abcès/fistules

Thérapie Cellulaire
En pratique

- Chirurgie en deux temps
  - Curetage / Nettoyage
  - Injection en deux sites
  - +/- Fermeture de l’orifice interne
- Logistique complexe (Patient doublon)



Thérapie Cellulaire:
Une révolution à long therme?



Inflammatory Bowel Diseases, 2022, **28**, 1737–1745
https://doi.org/10.1093/ibd/izab361
Advance access publication 31 January 2022
Original Research Articles - Clinical

CROHN'S & COLITIS FOUNDATION

INSPECT: A Retrospective Study to Evaluate Long-term Effectiveness and Safety of Darvadstrocel in Patients With Perianal Fistulizing Crohn's Disease Treated in the ADMIRE-CD Trial

Julian Panés, MD, PhD,[·] Gerd Bouma, MD,[†] Marc Ferrante, MD,[‡] Torsten Kucharzik, MD,[§] Maria Nachury, MD,[¶] Fernando de la Portilla de Juan, MD,[‖] Walter Reinisch, MD,[··††] Francesco Selvaggi, MD,[‡‡] Jörg Tschmelitsch, MD,[§§] Neil R. Brett, PhD,[¶¶] Martin Ladouceur, PhD,[¶¶] Matthias Binek, MD,[‖‖] Gary Hantsbarger, PhD,[···] Sarah Campbell-Hill, DPhil,[††††] Chitra Karki, MPH,[···] and Christianne Buskens, MD[††††]

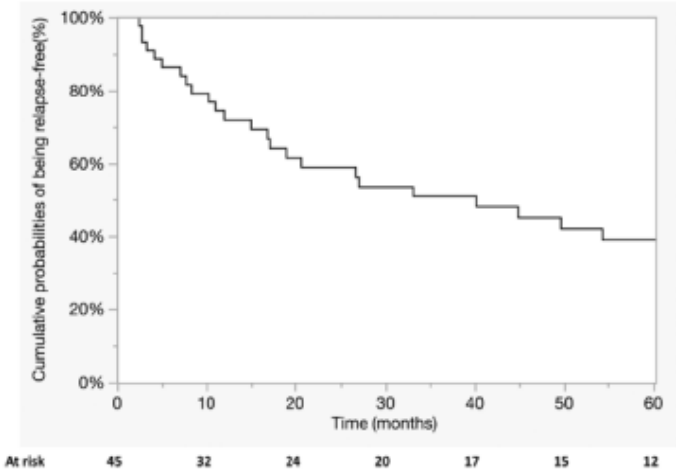


Figure 1: Cumulative probability of perianal relapse

Histoire naturelle à l'arrêt de la biothérapies

Outcomes of Perianal Fistulising Crohn's Disease Following Anti-TNF alpha Treatment Discontinuation

Clémence Legué, Charlène Brochard, Gregoire Bessi, Timothée Wallenhorst, Marie Dewitte, Laurent Siproudhis, Guillaume Bouguen

Thérapie Cellulaire:
A quel prix?

DARVADSTROCEL
50K

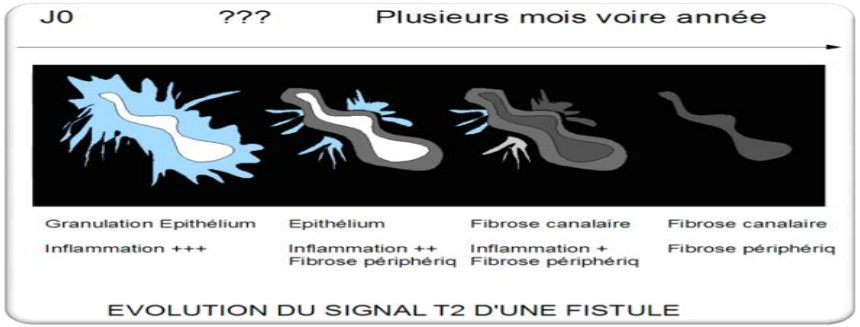
Anti-TNF
10-20K/an

La cicatrisation en IRM
Nouvel objectif?

Maladie luminale

Cicatrisation muqueuse endoscopique

Lésions ano-périnéales



Perte signal T2 en IRM

POINTS FORTS

- La combinaison d'un traitement anti-TNF alpha et d'un drainage chirurgical reste le traitement de réference pour les fistules de Crohn.
- Les techniques chirurgicales d'obturation sont nombreuses et pour la plupart décevantes. La fermeture de l'orifice interne est à privilégier.
- L'injection de cellules souches est une technique innovante et prometteuse. Son résultat à long terme doit être évalué car son coût est important.
- La cicatrisation en IRM doit devenir l'objectif.