# ¿Puede ser el tratamiento cíclico con biológicos una opción?

Prof. Fernando Gomollón, Facultad de Medicina, Hospital Clínico Universitario "Lozano Blesa", IIS Aragón, CIBEREHD, Zaragoza

# Razones para considerar el tratamiento ciclíco

- Riesgos reales (tumores, infeccciones)
- Costes (personales and sociales)
- Miedos (ejemplo: embarazo)
- Edad (más riesgos por la edad, generalmente se considera la edad avanzada)
- Decisión del paciente (y/o sus tutores)

GASTROENTEROLOGY 2012;142:63–70

# Maintenance of Remission Among Patients With Crohn's Disease on Antimetabolite Therapy After Infliximab Therapy Is Stopped

EDOUARD LOUIS,* JEAN–YVES MARY,‡ GWENOLA VERNIER–MASSOUILLE,§ JEAN–CHARLES GRIMAUD,‖ YORAM BOUHNIK,¶ DAVID LAHARIE,# JEAN–LOUIS DUPAS,** HÉLÈNE PILLANT,‡‡ LAURENCE PICON,§§ MICHEL VEYRAC,‖‖ MATHURIN FLAMANT,¶¶ GUILLAUME SAVOYE,## RAYMOND JIAN,*** MARTINE DEVOS,‡‡‡ RAPHAËL PORCHER,‡ GILLES PAINTAUD,§§§ ERIC PIVER,§§ JEAN–FRÉDÉRIC COLOMBEL,§ and MARC LEMANN‖‖‖‖ for the Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives

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CLINICAL AT

This article has an accompanying continuing medical education activity on page e31. Learning Objective: Upon completion of this exercise, successful learners will be able to assess the risk of relapse and the response to potential re-treatment in Crohn's disease patients in whom infliximab treatment would be stopped after prolonged stable remission under combined therapy with antimetabolite and infliximab.

**Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes; see Siegel CA et al on page 46 in *CGH*; see Covering the Cover synopsis on page 1.**

**year after discontinuation of infliximab. However, patients with a low risk of relapse can be identified using a combination of clinical and biologic markers.**

*Keywords:* Inflammatory Bowel Disease; IBD; Clinical TrialStopping Therapy Factors That Contribute to

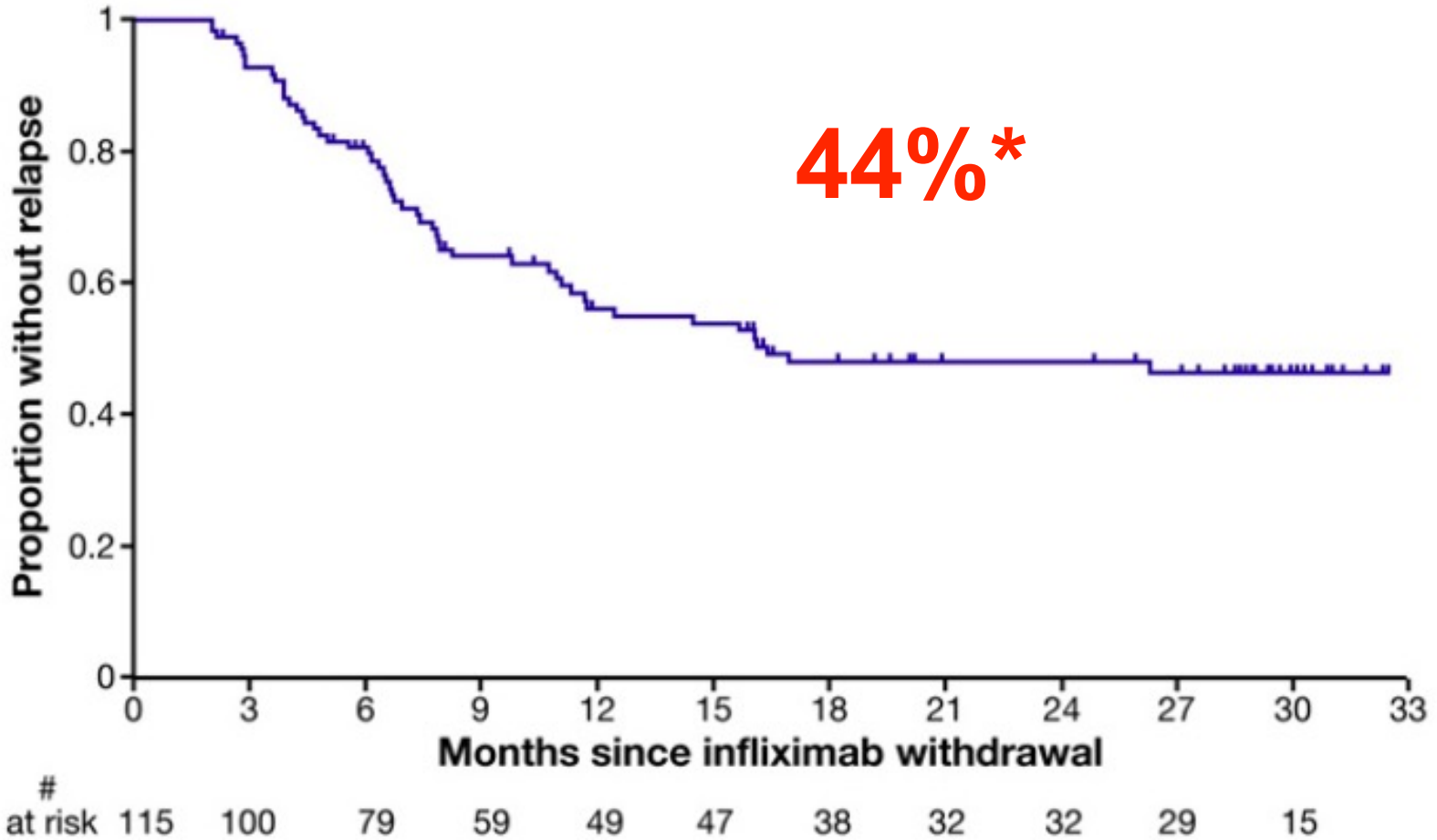



**Figure 2.** Kaplan–Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.

*One year relapse rate. Stori Trial

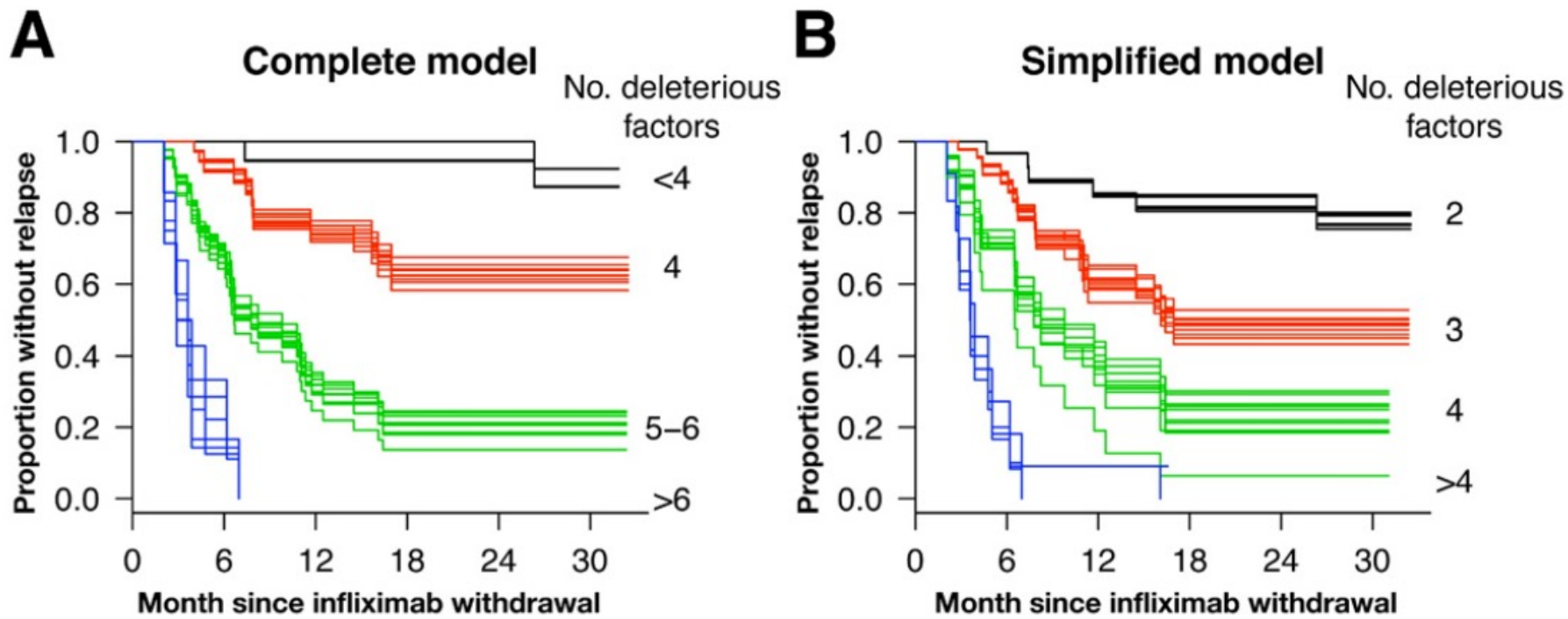


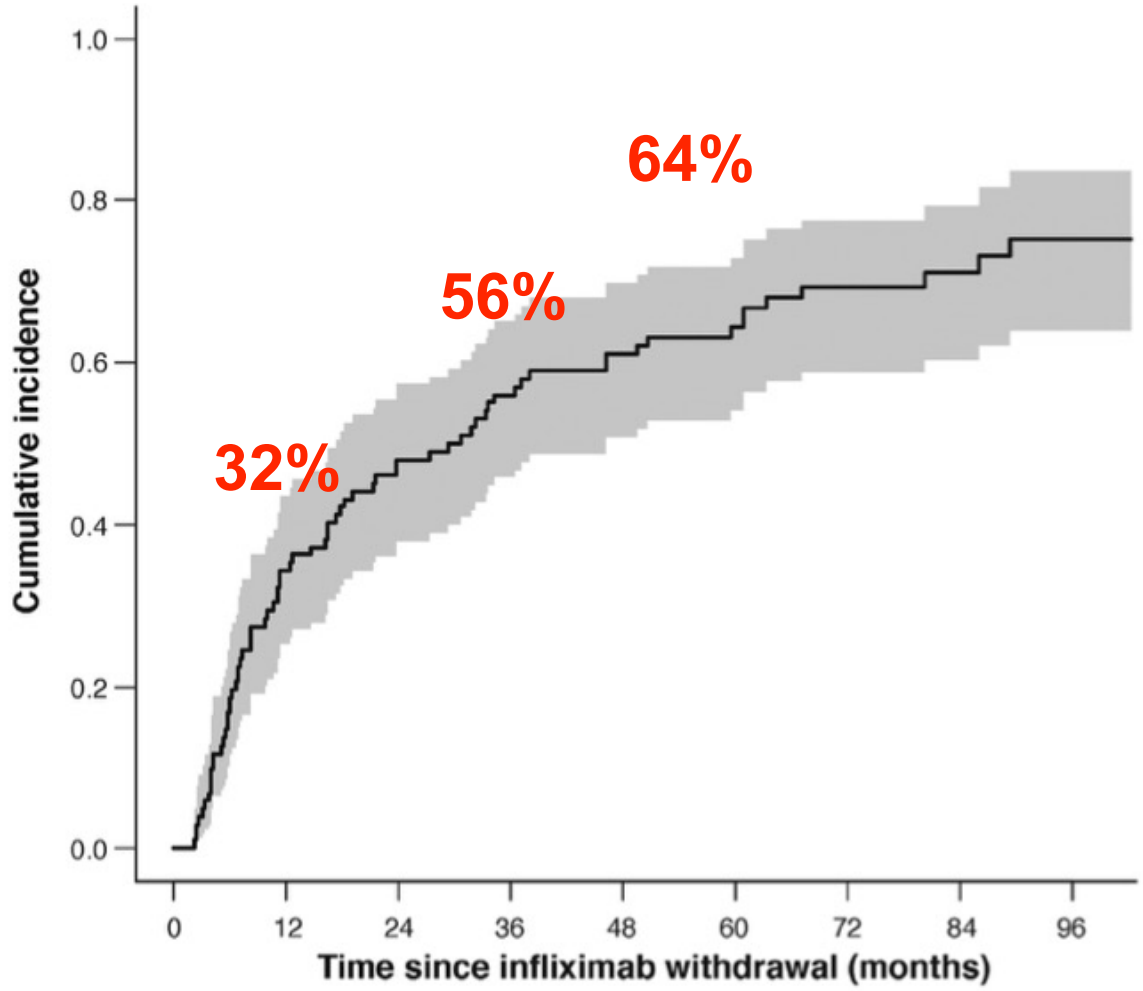

**Figure 3.** Kaplan–Meier time-to-relapse curves according to multivariable models and scores generated through the Cox model using the multiple imputation method. (*A*) According to a complete model: with this model (Table 2), the subgroup of patients presenting 3 deleterious prognostic factors or less corresponded to zero to one relapse over 1 year among 22 to 25 patients, depending on imputations. (*B*) According to a simplified model without infliximab trough levels and endoscopic data: with this model (Table 2), the subgroup presenting 2 deleterious prognostic factors or less corresponded to 4 relapses over 1 year among 32 to 35 patients, depending on imputations.

Clinical Gastroenterology and Hepatology 2018;16:234–243

# Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission

Catherine Reenaers,[*] Jean-Yves Mary,[‡] Maria Nachury,[§] Yoram Bouhnik,[‖] David Laharie,[¶] Matthieu Allez,[#] Mathurin Fumery,[**] Aurélien Amiot,[‡‡] Guillaume Savoye,[§§] Romain Altwegg,[‖‖] Martine Devos,[¶¶] Georgia Malamut,[##] Arnaud Bourreille,[***] Bernard Flourie,[‡‡‡] Philippe Marteau,[§§§] Lucine Vuitton,[‖‖‖] Benoît Coffin,[¶¶¶] Stéphanie Viennot,[###] Jérôme Lambert,[‡] Jean-Frédéric Colombel,[****] and Edouard Louis,[*] and the Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif

*[*]Gastroenterology Department, Centre Hospitalier Universitaire de Liège, Liège, Belgium; [‡]INSERM U717, Biostatistics and Clinical Epidemiology, [‖]Hôpital Beaujon, [#]Hôpital Saint-Louis, [¶¶¶]Hopital Louis Mourier, Université Paris Diderot-Paris 7, Paris, France; [§]Centre Hospitalier Régional Universitaire de Lille, Université Lille Nord de France, Lille, France; [¶]Hôpital Haut-Lévêque, INSERM U853, Université Bordeaux 2, Bordeaux, France; [**]Centre Hospitalier Universitaire d'Amiens, Hôpital Nord, Amiens, France; [‡‡]Hôpital Henri Mondor, Paris Est-Créteil Val de Marne University, Creteil, France; [§§]Hôpital Charles Nicolle, Université de Rouen, Rouen, France; [‖‖]Hôpital Saint-Eloi, University Hospital of Montpellier, Montpellier, France; [¶¶]Faculty of Medicine and Health Science, University of Ghent, Ghent, Belgium; [##]Hôpital Européen Georges Pompidou Assistance Publique-Hôpitaux Paris, Université Paris Descartes-Sorbonne Paris Centre, Paris, France; [***]Centre Hospitalier Universitaire de Nantes, Hôtel-Dieu, Nantes, France; [‡‡‡]Centre Hospitalo-Universitaire Lyon-Sud, Hospices Civils de Lyon, Pierre Bénite, France; [§§§]Hôpital Lariboisière, Assistance Publique-Hôpitaux Paris, University Denis Diderot, Paris, France; [‖‖‖]Hôpital Universitaire de Besançon, Besançon, France; [###]Hôpital Universitaire de Caen, Caen, France; [****]Icahn School of Medicine at Mount Sinai, Feinstein Inflammatory Bowel Disease Clinical Center, New York, New York*




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 102 | 66 | 51 | 42 | 32 | 24 | 18 | 11 | 3 |
| Number events | | | | | | | | | |
| Anti-TNF resumption | 0 | 35 | 49 | 57 | 62 | 65 | 69 | 70 | 72 |
| Major complication | 0 | 1 | 2 | 2 | 6 | 6 | 7 | 7 | 8 |

**Figure 2.** Cumulative incidence of biologic resumption. The cumulative incidence of biologic resumption was 34.3% (95% CI, 25.2–43.6), 56.0% (95% CI, 45.8–65.1), and 64.4% (95% CI, 54.0–73.0), respectively, at 1, 3, and 5 after IFX withdrawal.

…on antimetabolite therapy

GASTROENTEROLOGY 2012;142:63–70

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CLINICAL AT

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NEJM Evidence

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ORIGINAL ARTICLE

# Discontinuation of Infliximab Therapy in Patients with Crohn's Disease

Sine Buhl, M.D.,[1] Casper Steenholdt, M.D.,[1] Jørn Brynskov, M.D.,[1] Katrine Risager Christensen, M.D.,[1] Maria Dorn-Rasmussen, M.D.,[1] Ole Østergaard Thomsen, M.D.,[1] Klaus Bendtzen, M.D.,[2] Tobias Wirenfeldt Klausen, M.Sc.,[1] Jens Frederik Dahlerup, M.D.,[3] Niels Thorsgaard, M.D.,[4] Jørgen Jahnsen, M.D.,[5] Akbar Molazahi, M.D.,[6] Natalia Pedersen, M.D.,[7] Jens Kjeldsen, M.D.,[8] Sven Almer, M.D.,[9,10] Eva Efsen Dahl, M.D.,[11] Ida Vind, M.D.,[12] Annett Gerhardt Cannon, M.D.,[13] Jan Marsal, M.D.,[14] Taina Sipponen, M.D.,[15] Jørgen Steen Agnholt, M.D.,[3] Hendrika Adriana Linda Kievit, M.D.,[4] Synnøve Louise Aure, M.D.,[5] Lars Martinsen, M.D.,[6] Svetlana Meisner, M.D.,[7] Jane Møller Hansen, M.D.,[8] and Mark Andrew Ainsworth, M.D.[1,8] on behalf of the Stop Infliximab Treatment (STOP-IT) Study Group*

## Abstract

**BACKGROUND** Whether infliximab therapy can be successfully discontinued after patients with Crohn's disease have attained sustained, clinical, biochemical, and endoscopic remission is unknown.

**METHODS** We conducted a multicenter, randomized, double-blind, placebo-controlled withdrawal study of infliximab in patients with Crohn's disease who were in clinical, biochemical, and endoscopic remission after standard infliximab maintenance therapy for at least 1 year. Patients were randomly assigned 1:1 to continue infliximab therapy or to receive matching placebo for 48 weeks. The primary end point was time to relapse.

**RESULTS** This study randomly assigned 115 patients to either the infliximab-continuation group or to the infliximab-discontinuation group. No relapses were observed among the 59 patients continuing infliximab, whereas 23 of 56 patients discontinuing infliximab experienced relapse. Time to relapse was significantly shorter among patients who discontinued infliximab than among those who continued infliximab (hazard ratio, 0.080; 95% confidence interval [CI], 0.035 to 0.186; P<0.001). At the end of the trial at week 48, relapse-free survival was 100% in the infliximab-continuation group and 51% in the infliximab-discontinuation group. The key secondary end point, time to loss of remission, was significantly shorter among patients discontinuing infliximab therapy than those continuing infliximab (hazard ratio, 0.025; 95% CI, 0.003 to 0.187; P<0.001). No unexpected adverse events were reported.

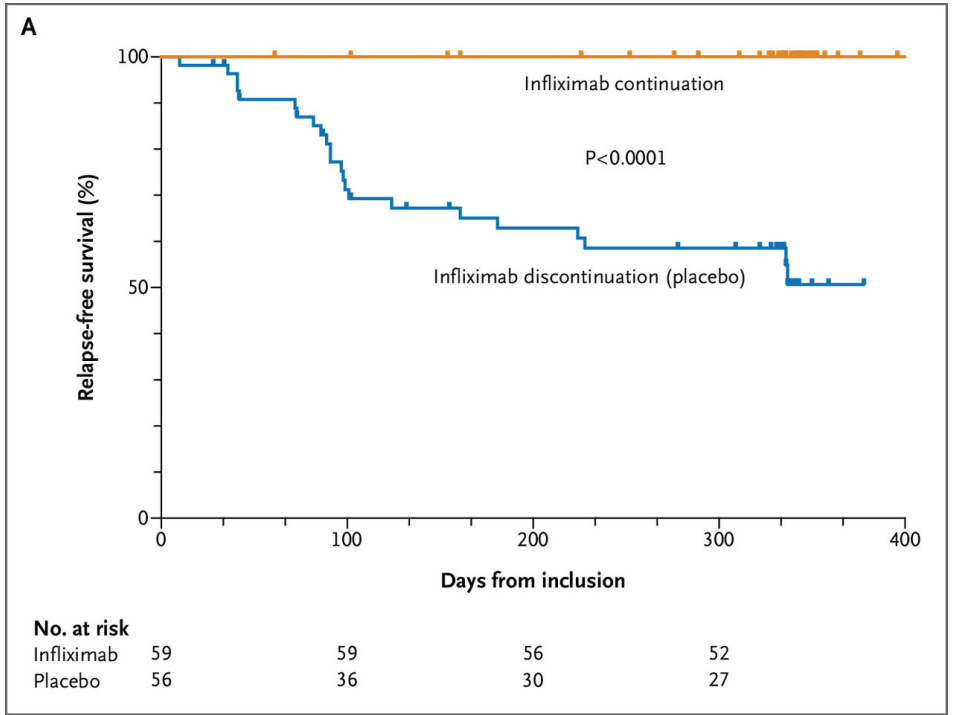
**CONCLUSIONS** Discontinuation of infliximab for patients with Crohn's disease receiving long-term infliximab therapy and in clinical, biochemical, and endoscopic remission leads to a considerable risk of relapse. (Funded by the Nordic Trial Alliance [NordForsk], the

**A complete list of collaborators in the Stop Infliximab Treatment (STOP-IT) Study Group is provided in the Supplementary Appendix, available at evidence.nejm.org.*

*The author affiliations are listed at the end of the article.*

*Dr. Ainsworth can be contacted at mark.ainsworth@rsyd.dk or at Department of Medical Gastroenterology S, Odense University Hospital, 5000 Odense C, Denmark.*





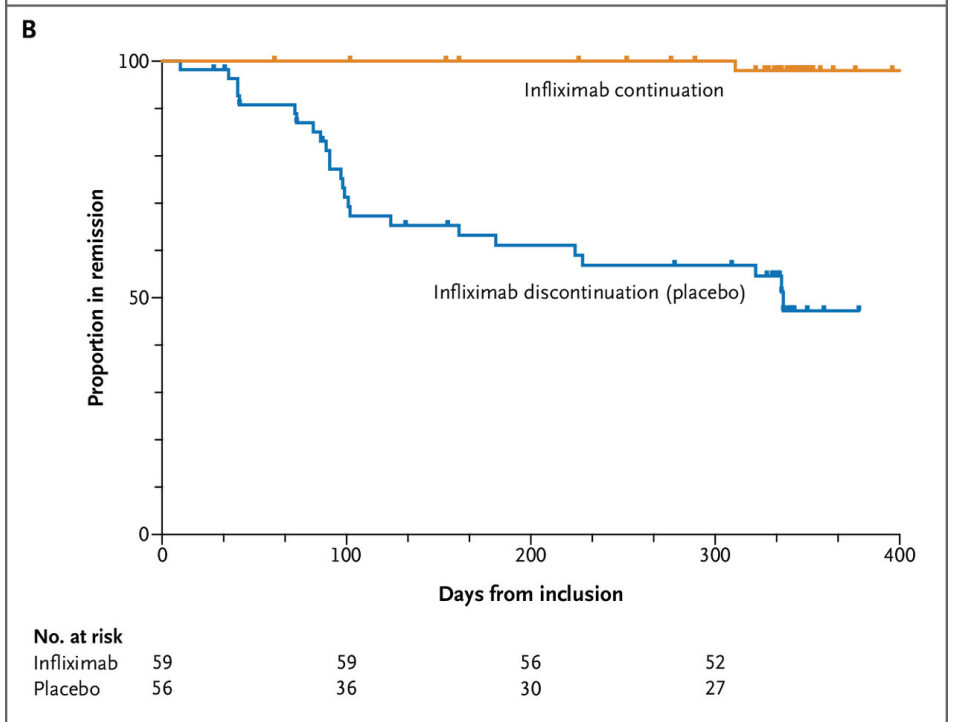
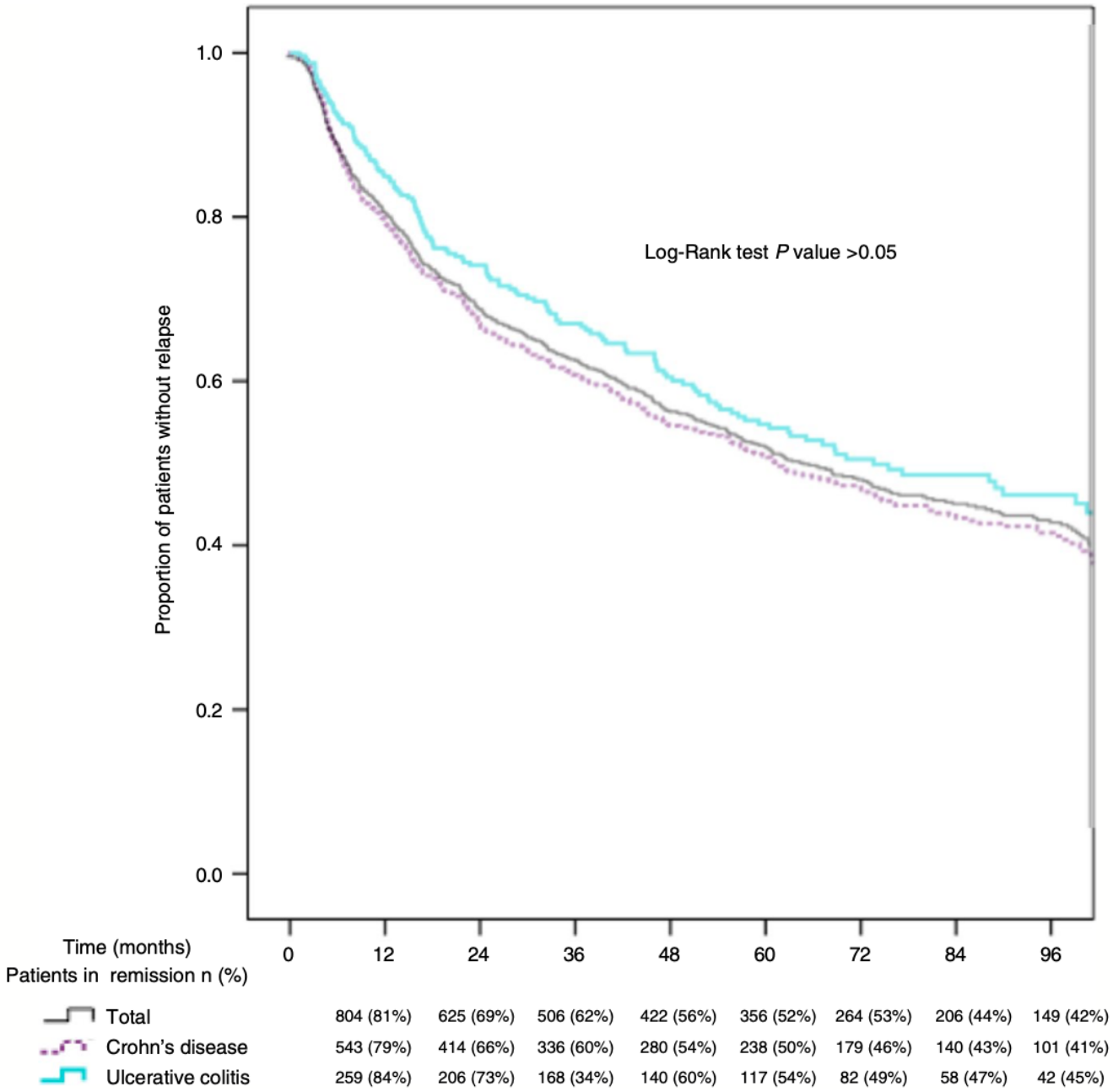



**FIGURE 1** Kaplan–Meier curve showing the probability of relapse-free survival after discontinuation of antitumour necrosis factor alpha (anti-TNF) therapy in all patients and by type of inflammatory bowel disease (IBD)




Relapse rate similar in UC and CD

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AP&T Alimentary Pharmacology & Therapeutics WILEY

# Clinical outcome after anti-tumour necrosis factor therapy discontinuation in 1000 patients with inflammatory bowel disease: the EVODIS long-term study

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# Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial

Edouard Louis, Matthieu Resche-Rigon*, David Laharie*, Jack Satsangi*, Nik Ding, Britta Siegmund, Geert D'Haens, Laurence Picon, Peter Bossuyt, Lucine Vuitton, Peter Irving, Stephanie Viennot, Christopher A Lamb, Richard Pollok, Filip Baert, Maria Nachury, Mathurin Fumery, Cyrielle Gilletta, Sven Almer, Shomron Ben-Horin, Yoram Bouhnik, Jean-Frederic Colombel†, Erik Hertervig†, GETAID and the SPARE-Biocycle research group

## Summary

**Background** The combination of infliximab and immunosuppressant therapy is a standard management strategy for patients with Crohn's disease. Concerns regarding the implications of long-term combination therapy provided the rationale for a formal clinical trial of treatment de-escalation. Our aim was to compare the relapse rate and the time spent in remission over 2 years between patients continuing combination therapy and those stopping infliximab or immunosuppressant therapy.

**Methods** This multicentre, open-label, randomised controlled trial was performed in 64 hospitals in seven countries in Europe and Australia. Adult patients with Crohn's disease in steroid-free clinical remission for more than 6 months, on combination therapy of infliximab and immunosuppressant therapy for at least 8 months were randomly assigned (1:1:1) to either continue combination therapy (combination group), discontinue infliximab (infliximab withdrawal group), or discontinue immunosuppressant therapy (immunosuppressant withdrawal group). Randomisation was stratified according to disease duration before start of first anti-TNF treatment (≤2 or >2 years), failure of immunosuppressant therapy before start of infliximab, and presence of ulcers at baseline endoscopy. The patient number and group of each stratum were assigned by a central online randomisation website. Treatment was optimised or resumed in case of relapse in all groups. Participants, those assessing outcomes, and those analysing the data were not masked to group assignment. The coprimary endpoints were the relapse rate (superiority analysis) and time in remission over 2 years (non-inferiority analysis, non-inferiority margin 35 days). Analyses were done on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, NCT02177071, and with EU Clinical Trials Register, EUDRACT 2014-002311-41. The trial was completed in April, 2021.

**Findings** Between Nov 2, 2015, and April 24, 2019, 254 patients were screened. Of these, 211 were randomised and 207 were included in the final analysis (n=67 in the combination group, n=71 in the infliximab withdrawal group, and n=69 in the immunosuppressant withdrawal group). 39 patients had a relapse (eight [12%] of 67 in the combination group, 25 [35%] of 71 in the infliximab withdrawal group, six [9%] of 69 in the immunosuppressant withdrawal group). 2-year relapse rates were 14% (95% CI 4–23) in the combination group, 36% (24–47) in the infliximab withdrawal group, and 10% (2–18) in the immunosuppressant withdrawal group (hazard ratio [HR] 3·45 [95% CI 1·56–7·69], p=0·003, for infliximab withdrawal *vs* combination, and 4·76 [1·92–11·11], p=0·0004, for infliximab withdrawal *vs* immunosuppressant withdrawal). Of 28 patients who had a relapse and were retreated or optimised according to protocol, remission was achieved in 25 patients (one of two in the combination group, 22 of 23 in the infliximab withdrawal group, and two of three in the immunosuppressant withdrawal group). The mean time spent in remission over 2 years was 698 days (95% CI 668–727) in the combination group, 684 days (651–717) in the infliximab withdrawal group, and 706 days (682–730) in the immunosuppressant withdrawal group. The difference in restricted mean survival time in remission was −14 days (95% CI −56 to 27) between the infliximab withdrawal group and the combination group and −22 days (−62 to 16) between the infliximab withdrawal group and the immunosuppressant withdrawal group. The 95% CIs contained the non-inferiority threshold (−35 days). We recorded 31 serious adverse events, in 20 patients, with no difference in frequency between groups. The most frequent serious adverse events were infections (four in the combination group, two in the infliximab withdrawal group, and one in the immunosuppressant withdrawal group) and Crohn's disease exacerbation (three in the combination group, four in the infliximab withdrawal group, and one in the immunosuppressant withdrawal group). No death nor malignancy was recorded.

**Interpretation** In patients with Crohn's disease in sustained steroid-free remission under combination therapy with infliximab and immunosuppressant therapy, withdrawal of infliximab should only be considered after careful assessment of risks and benefits for each patient, whereas withdrawal of immunosuppressant therapy could generally represent a preferable strategy when considering treatment de-escalation.

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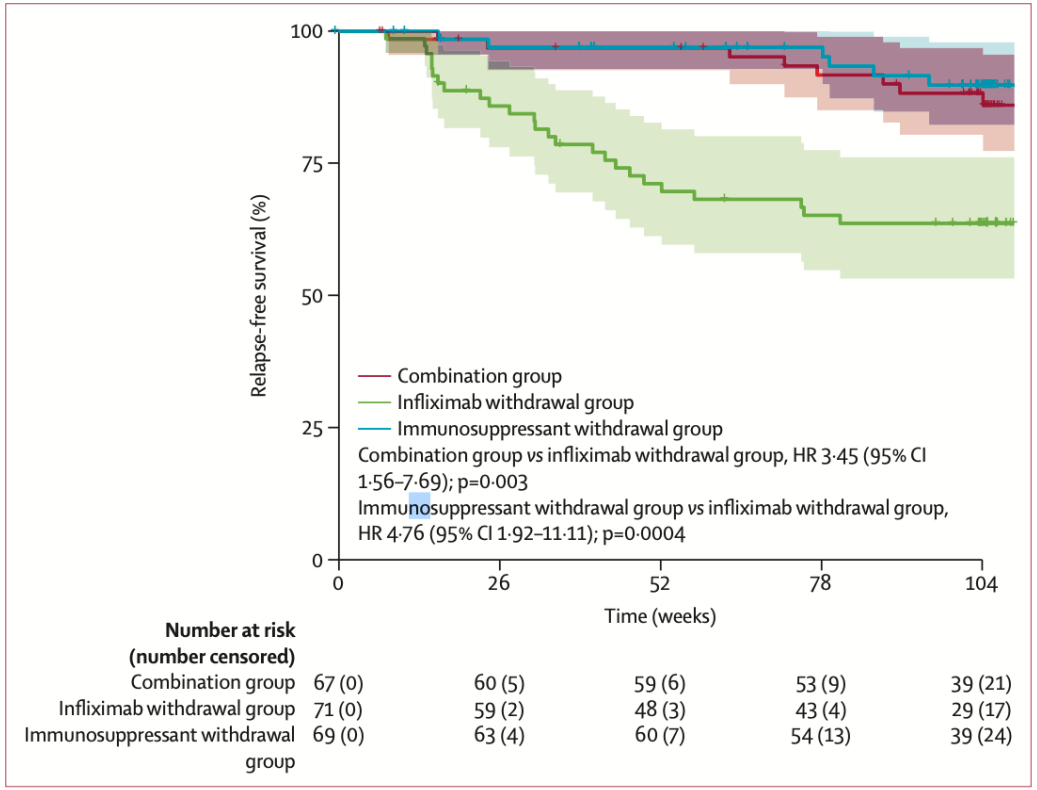



| Number at risk (number censored) | | | | | |
|---|---|---|---|---|---|
| Combination group | 67 (0) | 60 (5) | 59 (6) | 53 (9) | 39 (21) |
| Infliximab withdrawal group | 71 (0) | 59 (2) | 48 (3) | 43 (4) | 29 (17) |
| Immunosuppressant withdrawal group | 69 (0) | 63 (4) | 60 (7) | 54 (13) | 39 (24) |

***Figure 3*: Relapse-free survival**
Relapse-free survival was estimated by Kaplan–Meier estimators with their 95% CIs in the three groups, over 104 weeks.

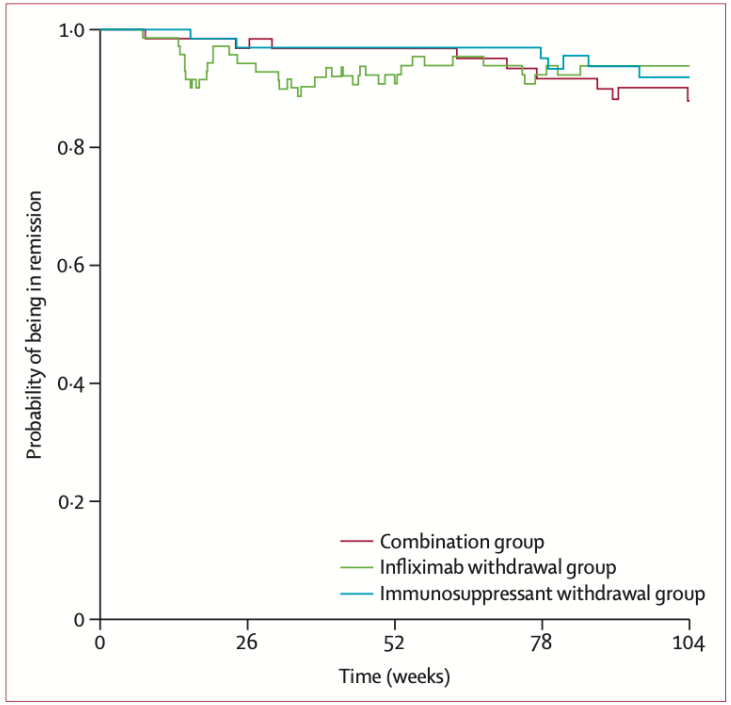



***Figure 4*: Probability of being in remission by time**
Patients who had a relapse, were considered not to be in remission until subsequent regained remissions (CDAI <150). Patients for whom remission was not achieved or who met other definitions of treatment failure terminated the trial and were considered not to be in remission for the remainder of the study (except for the treatment failures linked to treatment side-effects who were censored at the time of treatment failure).

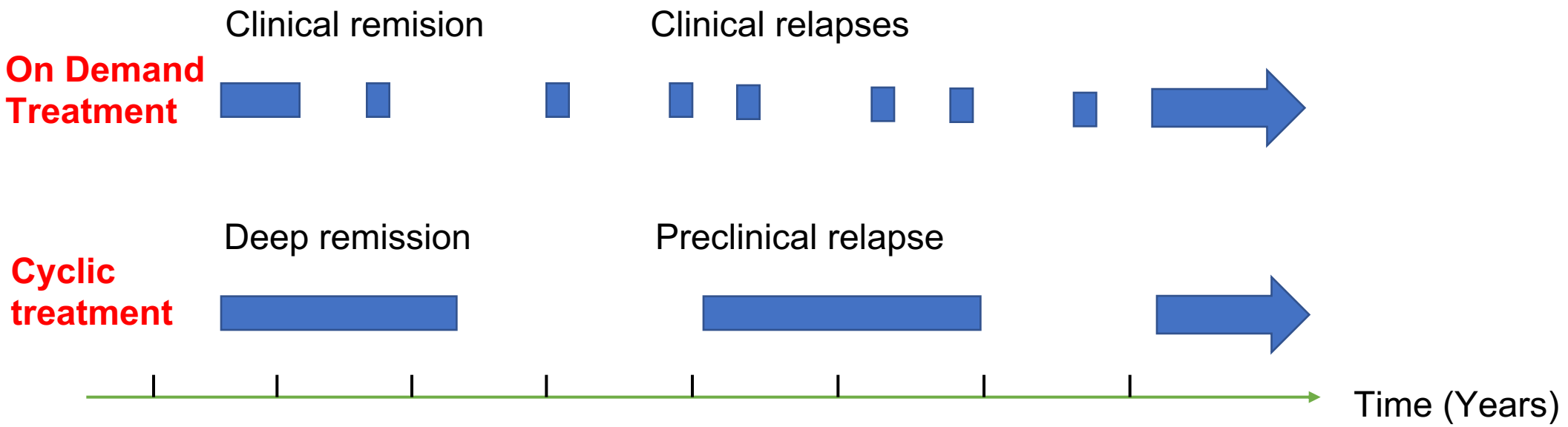
# personalised, risks, crude,  very small minority, deep remission,……..

Taken together, these findings highlight that stopping anti-TNF therapy is a highly personalized treatment decision, and one that carries considerable risks. The clinical decision support tool developed by the CEASE group emphasizes that our current measures for predicting relapse risk remain relatively crude and that we still do not have discriminative predictors of maintaining remission after treatment cessation. In the absence of individualized risk prediction, therapeutic discontinuation of TNF antagonists should be reserved for the very small minority of patients who are in deep remission, have a strong desire to stop treatment, have no (or very few) characteristics of high-risk CD, can tolerate a substantial disease flare, and are fully informed of the risks of therapeutic withdrawal, recognizing that there remains a paucity of high-quality data to guide treatment decisions in this space.

Ma Ch. To stop or not to stop? Predicting relapse after anti-TNF cessation in patients with Crohn's disease. Clin Gastroenterol Hepatol 2021 (in press)

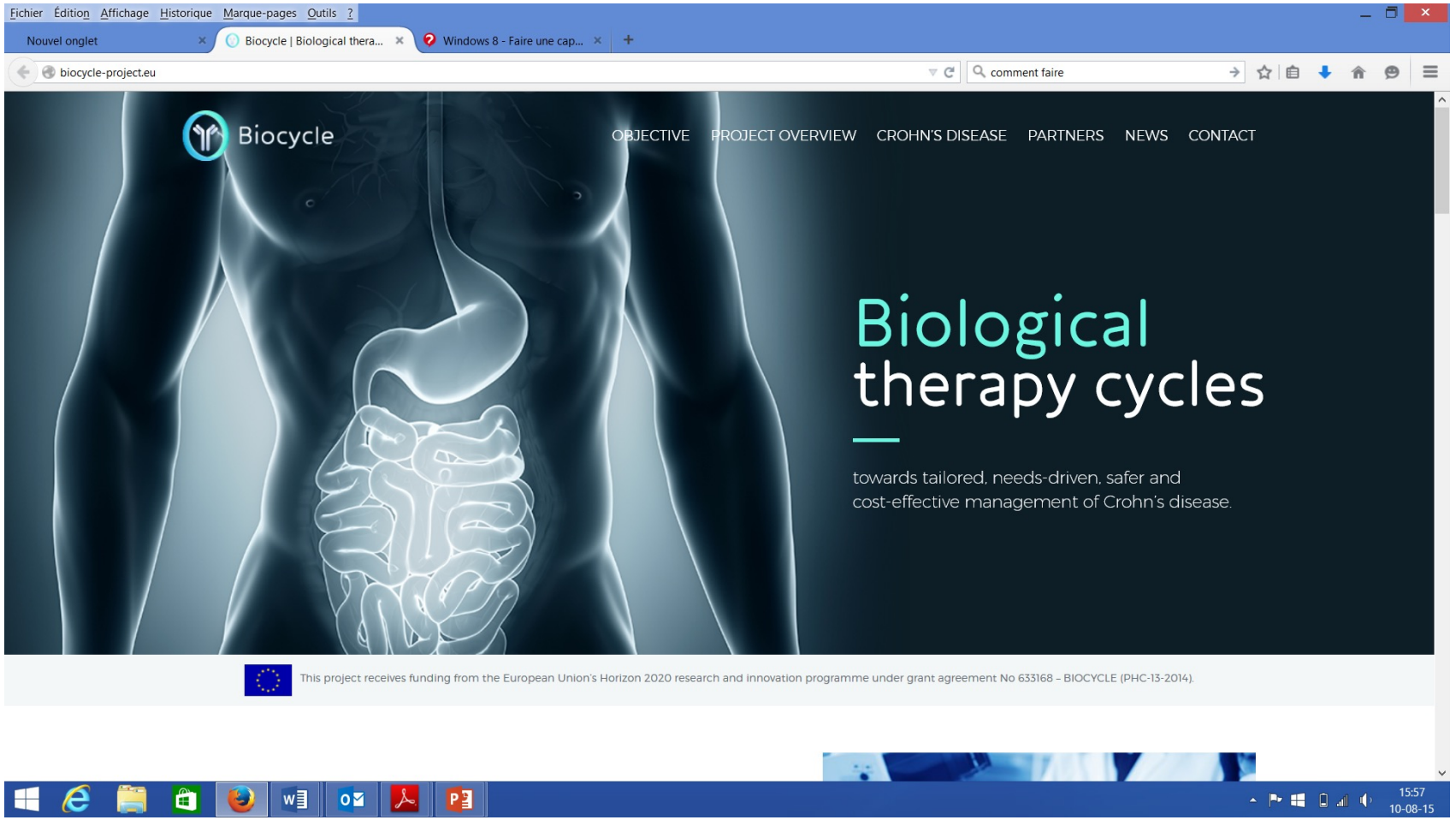
# Cyclic treatment **is not** on demand treatment

- First and undisputable aim of IBD treatment is **full disease control**
- The idea of the Cyclic treatment is to aim at the **lowest IS/biological use** still compatible with full disease control

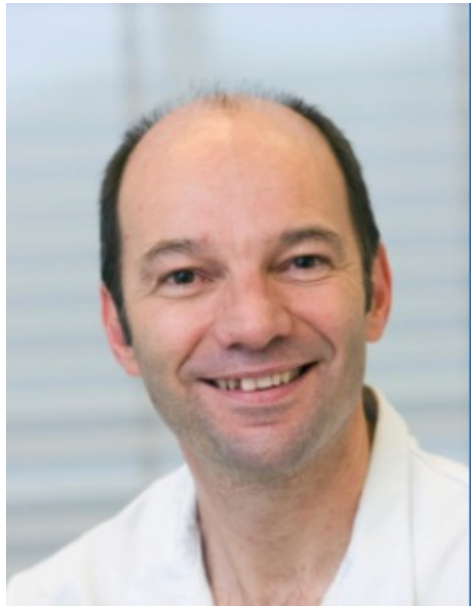



*Louis E. Inflamm Bowel Dis* 2018;24:725-731

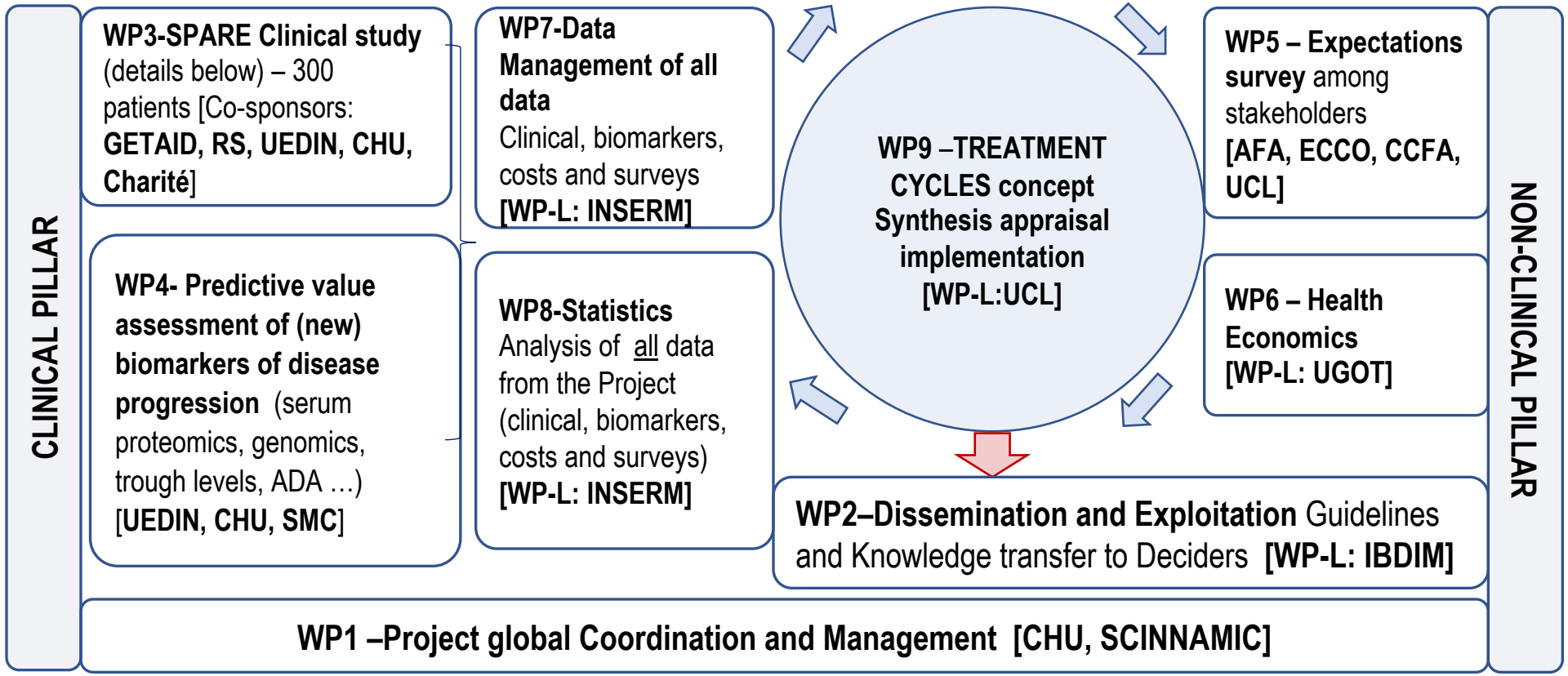
# Biocycle Website: http://biocycle-project.eu/



# The BIOCYCLE Project



Edouard Louis



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https://doi.org/10.1093/ecco-jcc/jjad001
Advance access publication 10 January 2023
**ECCO Topical Review**

# ECCO Topical Review on Biological Treatment Cycles in Crohn's Disease

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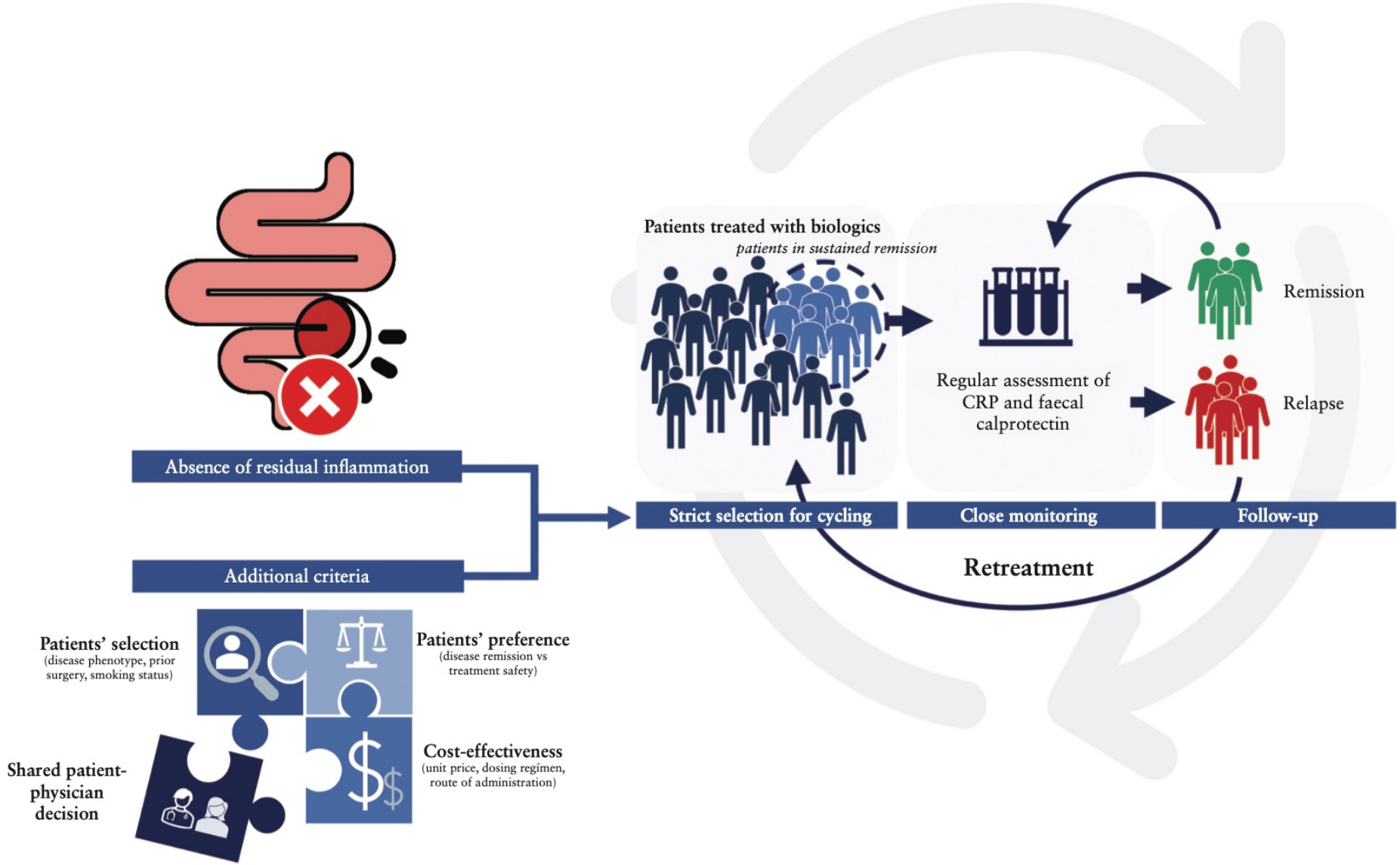


**Figure 1.** Biological treatment cycles in Crohn's disease. Biological treatment discontinuation and cycling for patients, involving re-treatment with the same biologic agent to achieve remission. Demonstration of the need to carefully consider patient selection, patient preferences and pharmacoeconomic costs.

# Mi paciente

**Table 4.** Score Chart for Prediction of the Individual Risk of Relapse Based on the Biochemical Model

| Predictor | Points |
|---|---|
| Clinical symptoms[a] | 4 |
| Smoking | 2 |
| Age at cessation, *y* | |
| <40 | 3 |
| 40–60 | 2 |
| 61–80 | 1 |
| >80 | 0 |
| Age at diagnosis ≤16 y (A1) | 2 |
| No immunosuppressant | 2 |
| Steroid use 6–12 mo before cessation | 2 |
| Disease location including L4 | 1 |
| Second-line anti-TNF | 1 |
| Adalimumab | 1 |
| Infliximab | 0 |
| Disease duration, *y* | |
| 0–15 | 0 |
| 15–30 | 1 |
| 30–40 | 2 |
| >40 | 3 |
| CRP, *mg/L* | |
| ≤5 | 0 |
| >5 | 1 |

A, age; L, location; CRP, C-reactive protein; TNF, tumor necrosis factor.
[a]Defined as Crohn's Disease Activity Index of 150 or more, Harvey Bradshaw Index of 5 or more, Physicians' Global Assessment greater than 0.

**Supplementary Table 6.** Relapse Rates Based on the Allocated Points From the Simple Score Chart to Each Patient (According to the Biochemical Model)

| Allocated points from the score chart | Sensitivity, % | Specificity, % | Patients above, n (%) | Patients below, n (%) | Relapse rate above threshold, % | Relapse rate at and below threshold, % |
|---|---|---|---|---|---|---|
| 1[a] | 99 | 3 | 1292 (98) | 25 (2) | 33 | 13 |
| 2 | 95 | 11 | 1205 (91) | 112 (9) | 34 | 21 |
| 3 | 79 | 39 | 903 (69) | 414 (31) | 37 | 22 |
| 4 | 60 | 59 | 645 (49) | 672 (51) | 40 | 26 |
| 5 | 37 | 78 | 372 (28) | 945 (72) | 42 | 29 |
| 6 | 20 | 89 | 200 (15) | 1117 (85) | 43 | 31 |
| 7 | 11 | 96 | 100 (8) | 1217 (92) | 45 | 32 |
| ≥8 | 4 | 99 | 36 (3) | 1281 (97) | 53 | 32 |

[a]No patients with less than 1 point were identified in the individual participant data meta-analysis cohort.

**The best model had a c-statistic of 0.63**

# A Treat-to-Target Strategy Guided by Pan-Enteric Evaluation in Children With Crohn's Disease Improves Outcomes at 2 Years

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**Background and Aims:** It is uncertain whether a treat-to-target approach could be an effective strategy for improving outcomes in children with Crohn's disease (CD). Previously, we reported mucosal healing (MH) and deep remission rates throughout the intestinal tract by performing 3 pan-enteric capsule assessments and using a treat-to-target strategy over 52 weeks in children with CD. This report describes the outcomes of this approach at 104 weeks.

**Methods:** Children with known CD who completed the 52-week protocol repeated pan-enteric capsule endoscopy (PCE) at 104 weeks. Results at weeks 52 and 104 were compared, and long-term outcomes between patients, with and without MH, were calculated using an intention-to-treat analysis of clinical relapse, need for steroids, treatment escalation, hospitalization, and surgery.

**Results:** Of the previous study cohort of 48 patients, 46 (96%) were available for this extension study (28 [61%] of 46 with MH and 18 [39%] of 46 without MH at 52 weeks). When evaluated at 104 weeks, MH was maintained in 93% of patients with MH at 52 weeks. In the intention-to-treat analysis, complete MH at 52 weeks was associated with reduced risk of steroid use (log-rank $P < .0001$), treatment escalation (log-rank $P < .0001$), hospitalization (log-rank $P < .0001$), and clinical relapse (log-rank $P < .0001$).

**Conclusions:** When a PCE-based, treat-to-target strategy is employed, MH is sustainable (93%) over a 1-year period and is correlated with improved patient outcomes, including reduced need for steroids, treatment escalation, hospitalization, and clinical relapses at 104 weeks.

ClinicalTrials.gov number: NCT03161886.

**Key Words:** treat-to-target, Crohn's disease, mucosal healing, pan-enteric capsule endoscopy

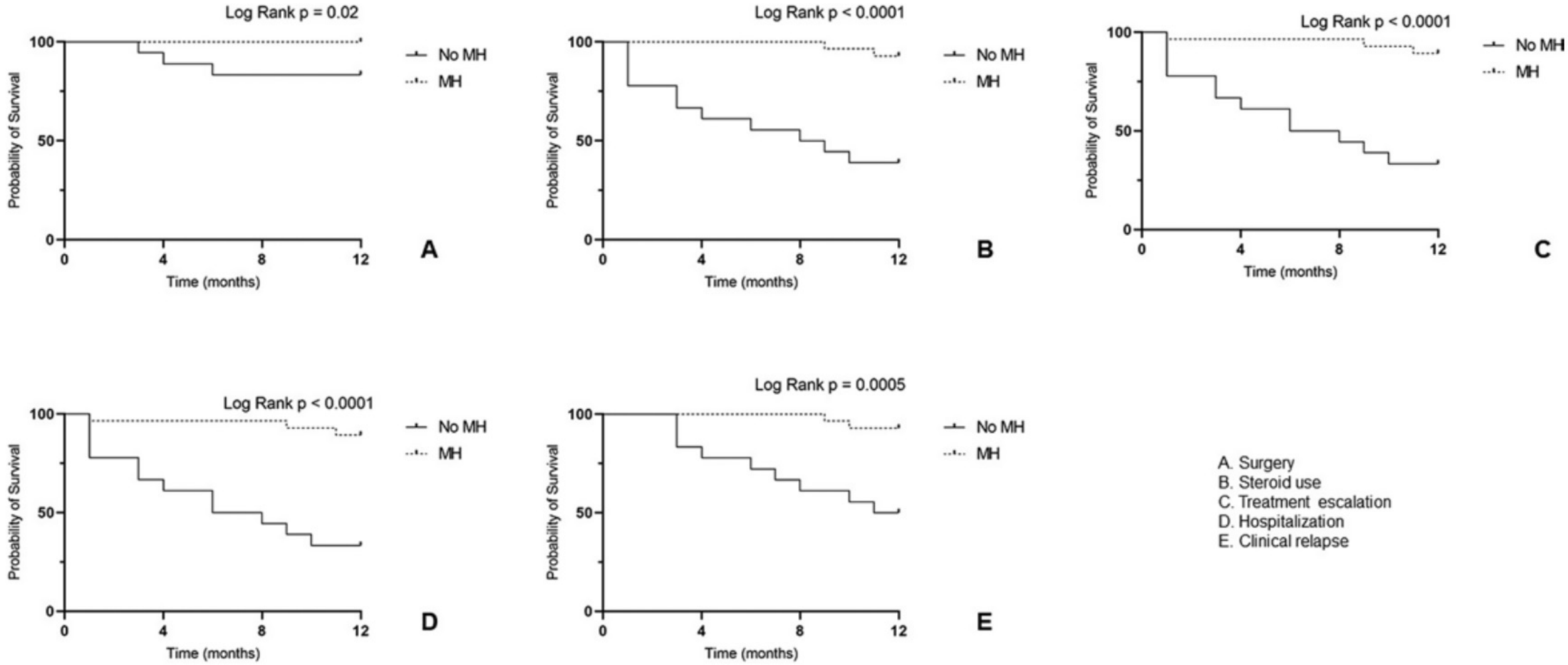


**Figure 3.** Kaplan-Meier survival analysis of (A) the risk of surgery, (B) need for steroids, (C) treatment escalation, (D) hospitalization, and (E) clinical relapse in the 2 groups. MH, mucosal healing.

## En pediatría *no* le veo sentido al tratamiento cíclico con antiTNF (ni con otros fármacos)

- No da tiempo real a plantearlo
- Curso individual imprevisible pero consecuencias irreversibles
- El coste va bajando cada año, más y más
- No hay señales nuevas de toxicidad en 20 años
- Seguros incluso en el embarazo
- Mucho tiempo por delante……