



XXXV Congrés de la
Societat Catalana de Digestologia

TRATAMIENTO PRECOZ EN LA ENFERMEDAD DE CROHN

Simposium Abbvie. Reus, 29 de Enero de 2016

Dra Mercè Navarro Llavat
Hospital de Sant Joan Despí Moisès Broggi

Sumario

1. Introducción
2. ¿Existe una ventana de oportunidad terapéutica en el curso de la enfermedad?
3. ¿Cuáles son los factores predictivos de riesgo de progresión de la EC?
4. ¿Cuál es el impacto del uso precoz de inmunosupresores o anti-TNFs?
5. Conclusiones

Objetivos



Too late ... too late ...

Too late ... too late ...

Tratamiento precoz en la EC

Aprendiendo de la Artritis Reumatoide...

944

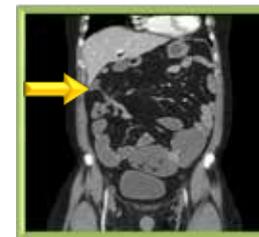
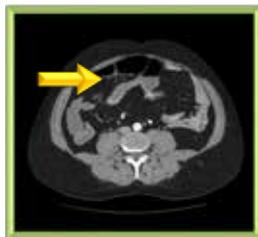
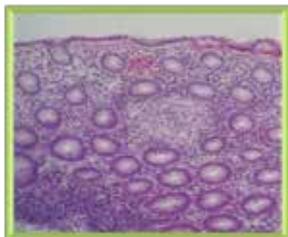
Annals of the Rheumatic Diseases 1995; 54: 944-947

VIEWPOINTS on more definitive treatment of rheumatoid arthritis

Early rheumatoid arthritis: time to aim for remission?

Paul Emery, Michael Salmon

Tratamiento precoz en la EC



Preclinical phase

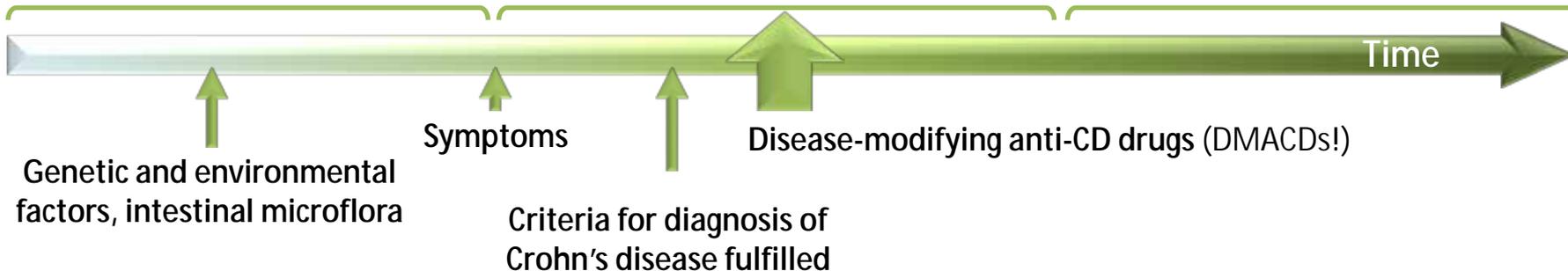
- Subclinical inflammation (immune response and histologic lesions)

Early Crohn's disease

- Inflammation (clinical, biological, endoscopic, radiologic evidence of disease activity)
- No fistula, abscess or stricture

Late Crohn's disease

- Bowel damage (fistula, abscess, stricture)
- Impairment of GI functioning
- Colorectal cancer



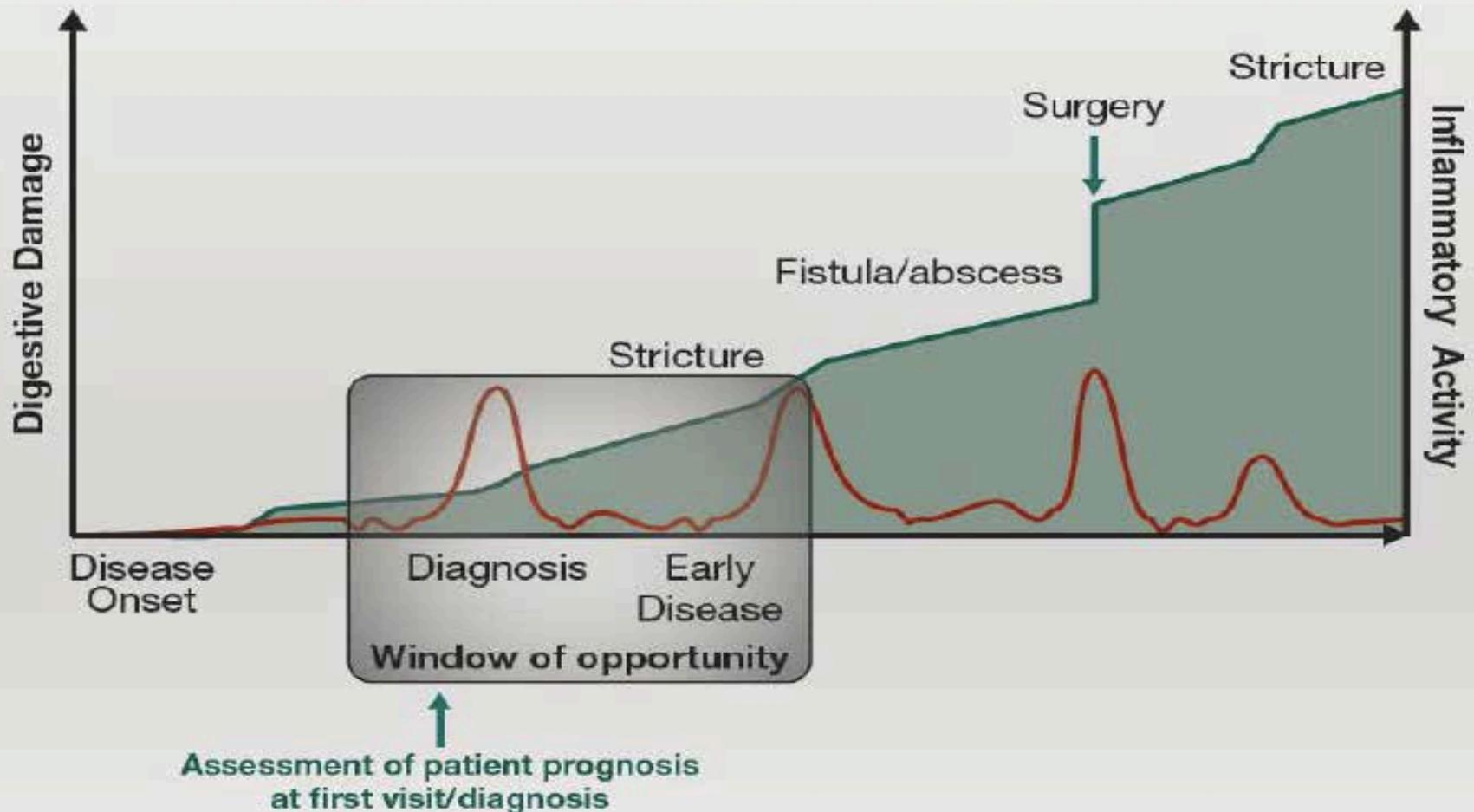
Adapted from Peyrin-Biroulet L *et al.* *Gut* 2010

A cartoon illustration of Alice from 'Alice in Wonderland' standing in a doorway. She is looking at a door handle that has a large, round, orange nose and a face, resembling a character from the movie 'The Sandlot'. Alice has a surprised expression, with her hand to her mouth. The scene is set in a room with dark wood paneling and red curtains.

¿Existe una ventana de oportunidad
terapéutica en el curso de la enfermedad?

Ventana de oportunidad

Hypothetical Progression of Crohn's Disease



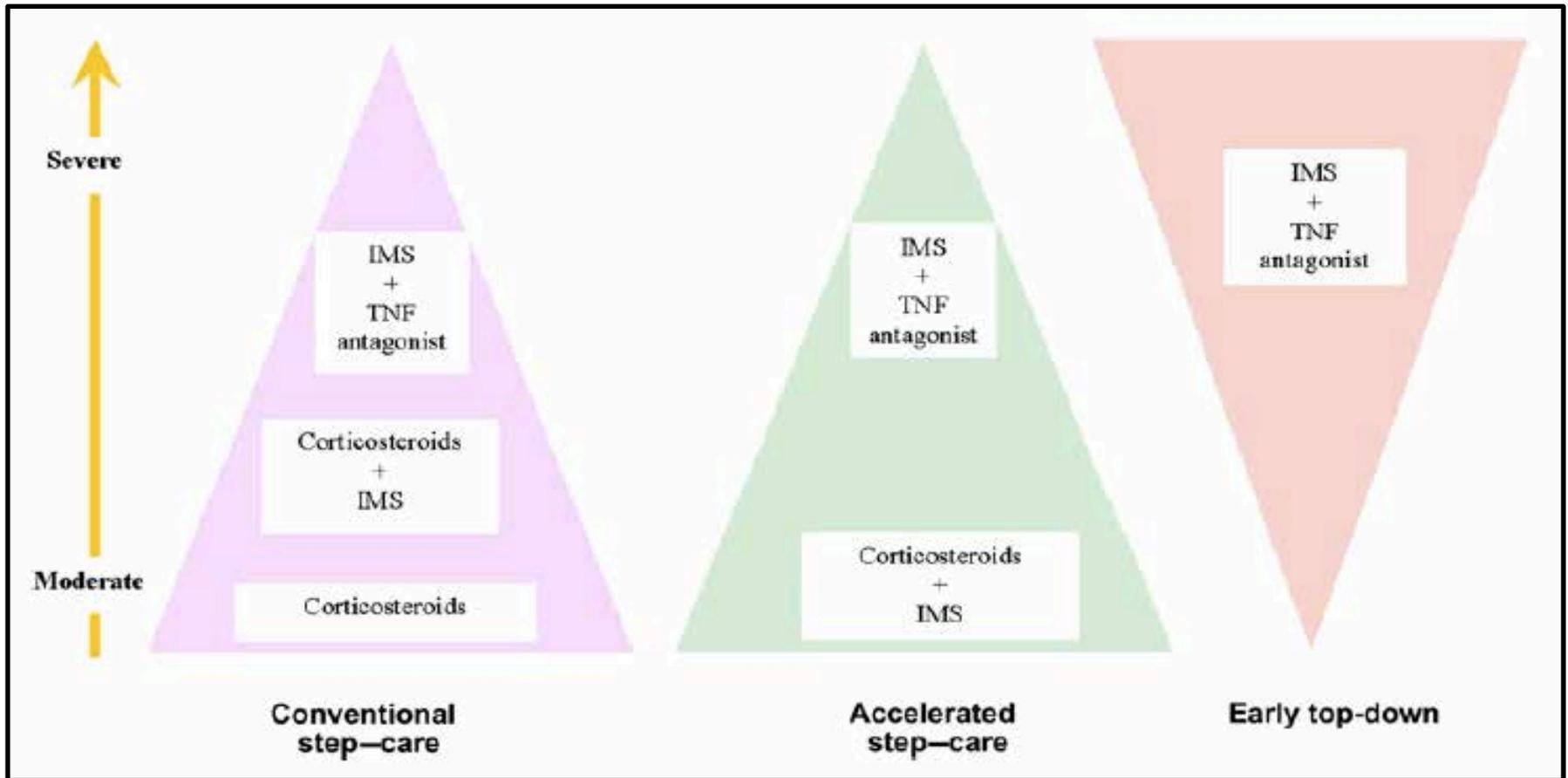
A cartoon illustration of Alice from 'Alice in Wonderland' standing in a doorway. She is looking at a large, anthropomorphic wooden door handle that has a very large, round nose. The scene is set in a room with dark wood paneling and red curtains.

¿Cuál es el impacto del uso precoz de INM o anti-TNFs ?

Objetivos del tratamiento precoz en la EC

1. Mantener la remisión libre de esteroides
2. Inducir y mantener la curación mucosa: $\hat{=}$ hospitalización, $\hat{=}$ CIR.
3. Evitar la progresión a complicaciones: modificar el curso de la enf.

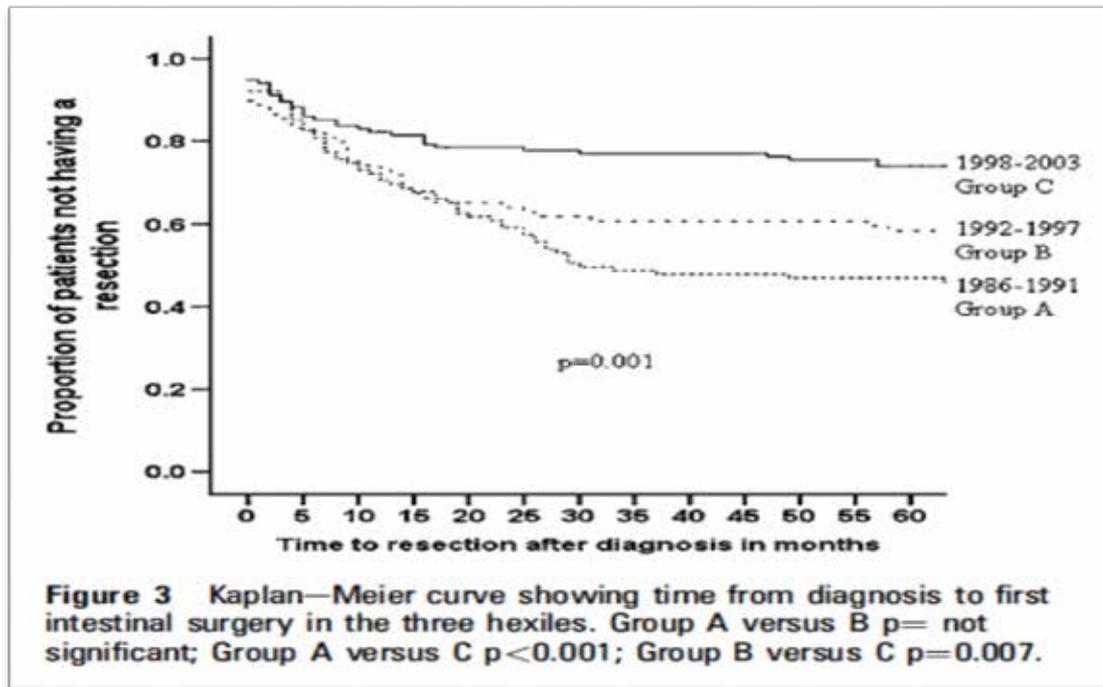
Estrategias de tratamiento en la EC precoz



Ordás I. Gut 2011;60:1754-1763

Uso precoz de inmunosupresores

Estudios retrospectivos:
Beneficio en la REDUCCIÓN de las tasas de CIRUGÍA.



1. Ramadas AV. Gut 2010;59:1200-6
2. Peyrin-Biroulet L. Gut 2011;60:930-6
3. Kariyawasam VC. IBD 2014 aug;20(8),1382-90
4. Kim B.J Gastroenterol Hepatol 2016 Jan; 31(1):126-32

Uso precoz de inmunosupresores

Gastroenterology. 2013 Oct;145(4):758-65.e2; quiz e14-5. doi: 10.1053/j.gastro.2013.04.048. Epub 2013 Apr 30.

Early administration of azathioprine vs conventional management of Crohn's Disease: a randomized controlled trial.

Cosnes J¹, Bourrier A, Laharie D, Nahon S, Bouhnik Y, Carbonnel F, Allez M, Dupas JL, Reimund JM, Savoye G, Jouet P, Moreau J, Mary JY, Colombel JF; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID).

CONCLUSIONS: Based on results from a clinical trial, administration of azathioprine within 6 months of diagnosis of CD was no more effective than conventional management in increasing time of clinical remission. Clinicaltrials.gov, Number [NCT00546546](#).

Gastroenterology. 2013 Oct;145(4):766-74.e1. doi: 10.1053/j.gastro.2013.06.009. Epub 2013 Jun 13.

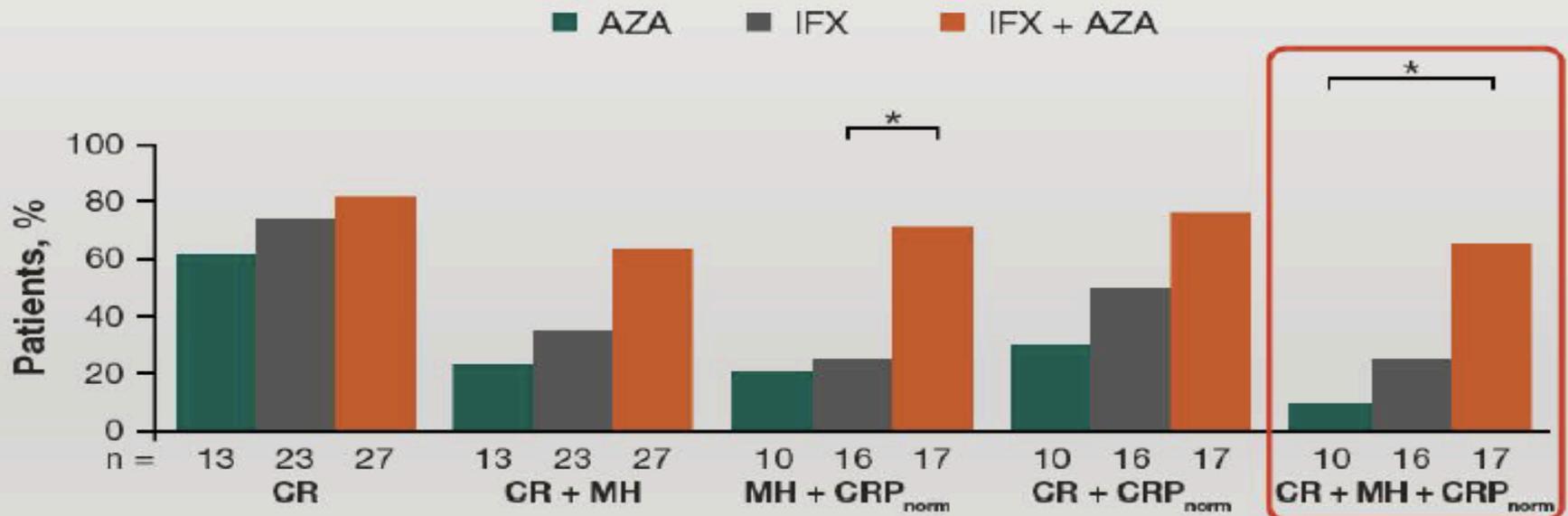
Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease.

Panés J¹, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, Torres Y, Domènech E, Piqueras M, Gomez-García M, Gutiérrez A, Taxonera C, Sans M; AZTEC Study Group.

CONCLUSIONS: In a study of adults with Crohn's disease, early azathioprine therapy was no more effective than placebo to achieve sustained corticosteroid-free remission but was more effective in preventing moderate to severe relapse in a post hoc analysis. EudraCT 2005-001186-34.

Uso precoz de anti-TNFs

SONIC Trial Post-hoc Subanalysis: Remission Outcomes at Week 26 for Patients With Early Crohn's Disease (N = 63)^{1a}



* $P \leq .016$. Note statistical significance based Bonferroni correction for multiple comparisons ($P \leq .016$).

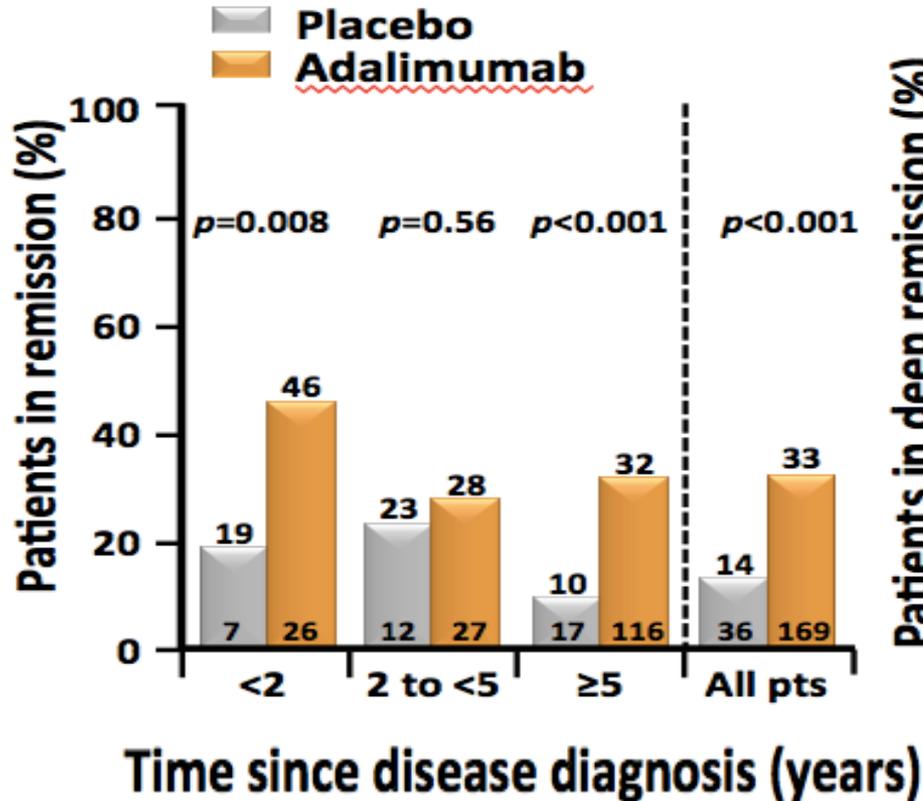
^a Early CD defined as disease duration ≤ 18 mo after diagnosis, and no previous use of immunosuppressants or biologics.² Note that although this analysis reports clinical remission at week 26, the primary endpoint of SONIC was corticosteroid-free clinical remission at week 26.

AZA: azathioprine; CR: clinical remission; CRP: C-reactive protein; IFX: infliximab; MH: mucosal healing; TNF: tumour necrosis factor.

Uso precoz de anti-TNFs

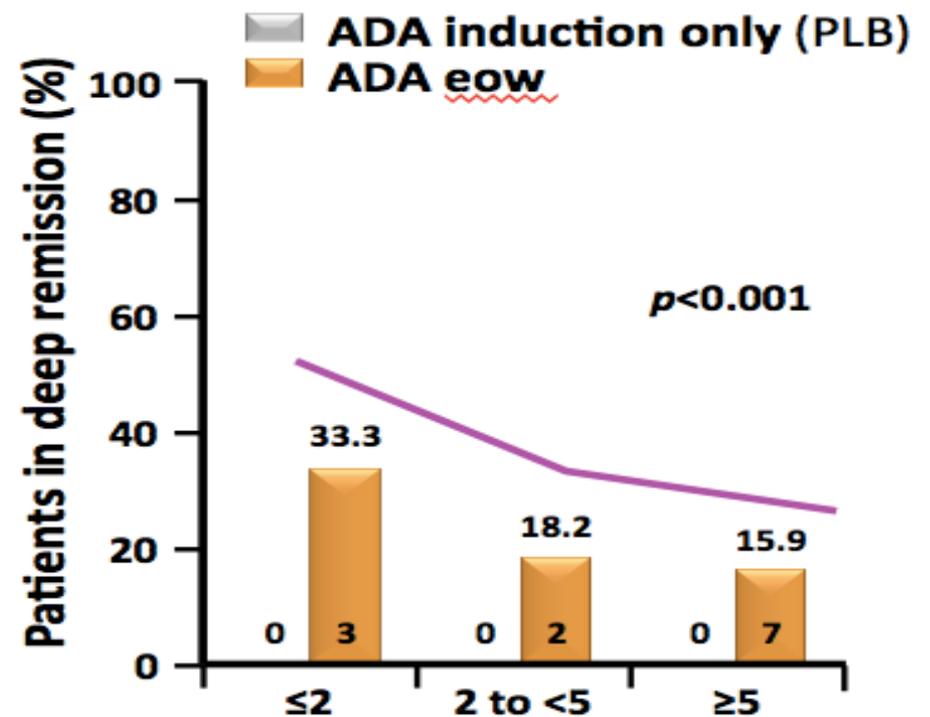
CHARM Week 26¹

Patients in remission (ITT population)



EXTEND Week 52²

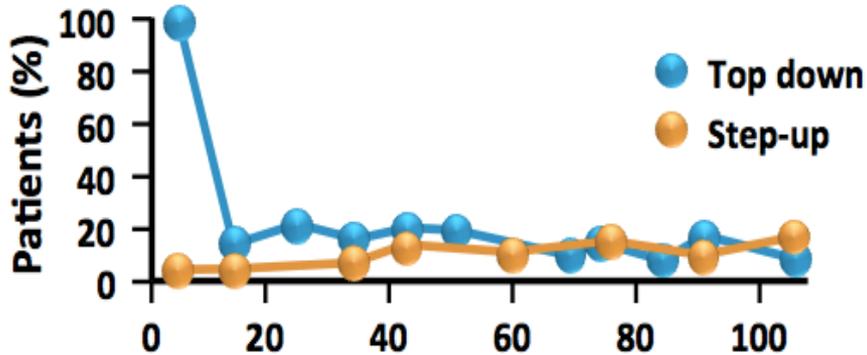
Patients in "deep" remission (ITT population)



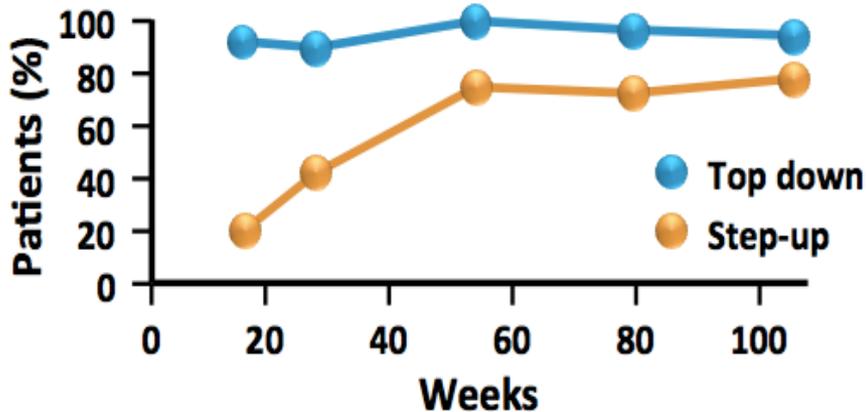
Note: The data are exploratory, as the primary efficacy endpoint of mucosal healing at Week 12 was not reached ($p=0.056$)

Estrategia "Top-down vs Step-up"

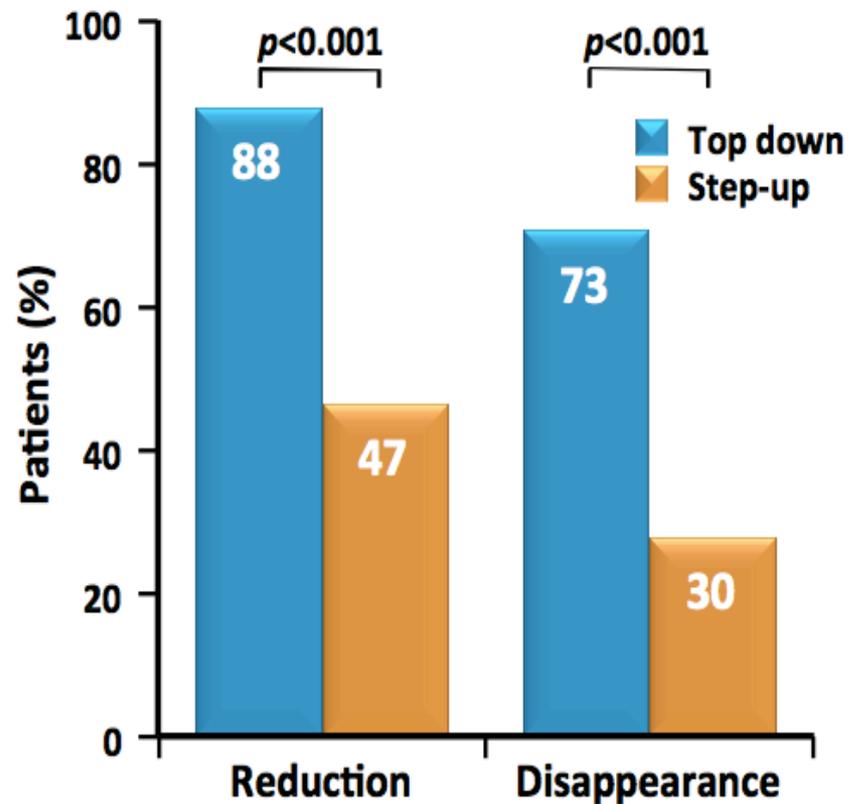
Patients receiving infliximab



Patients receiving immunosuppressants



Reduction and disappearance of ulcers

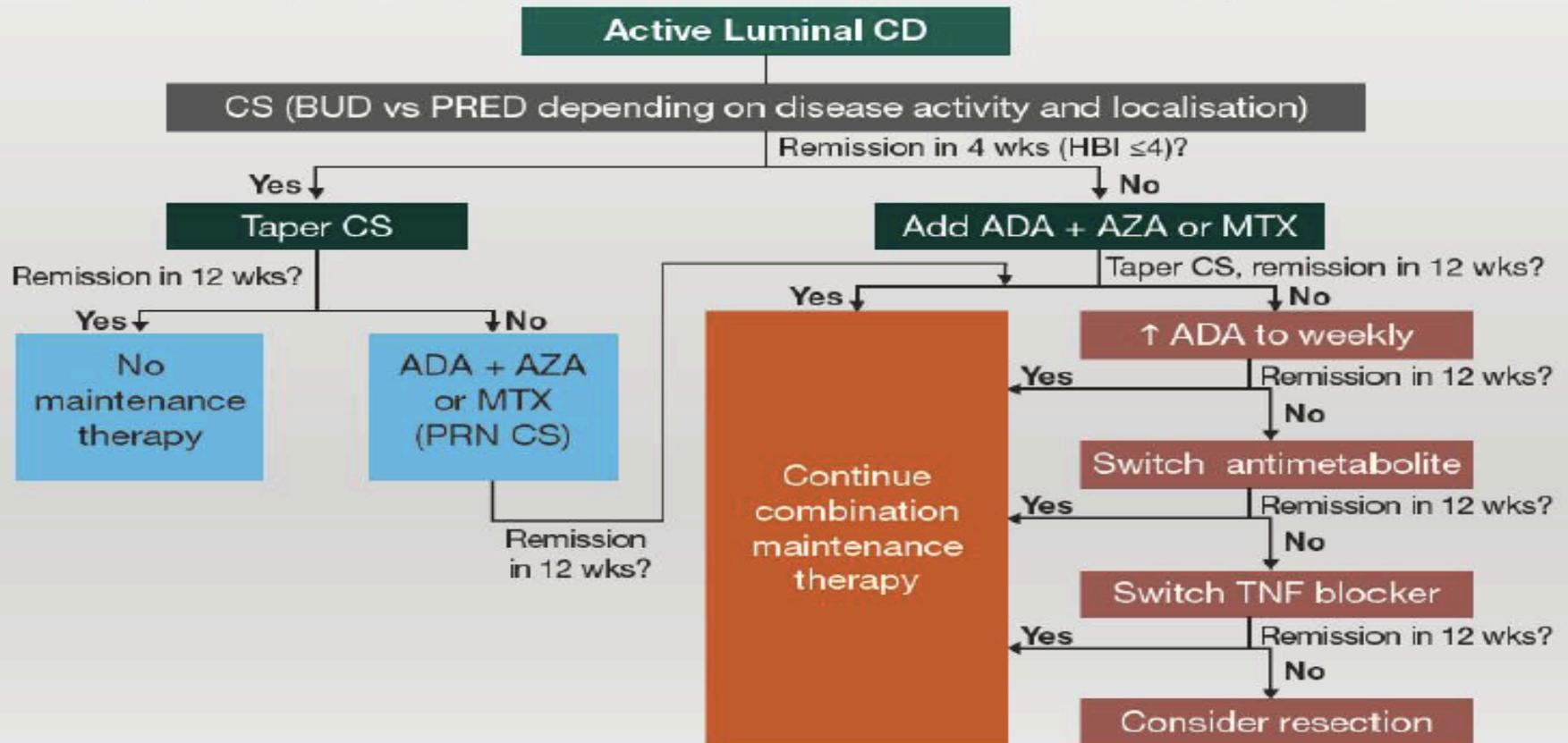


D'Haens G et al. *Lancet* 2008;371:660-667

Estudio REACT

REACT Study: A 'Treat to Target' Algorithm

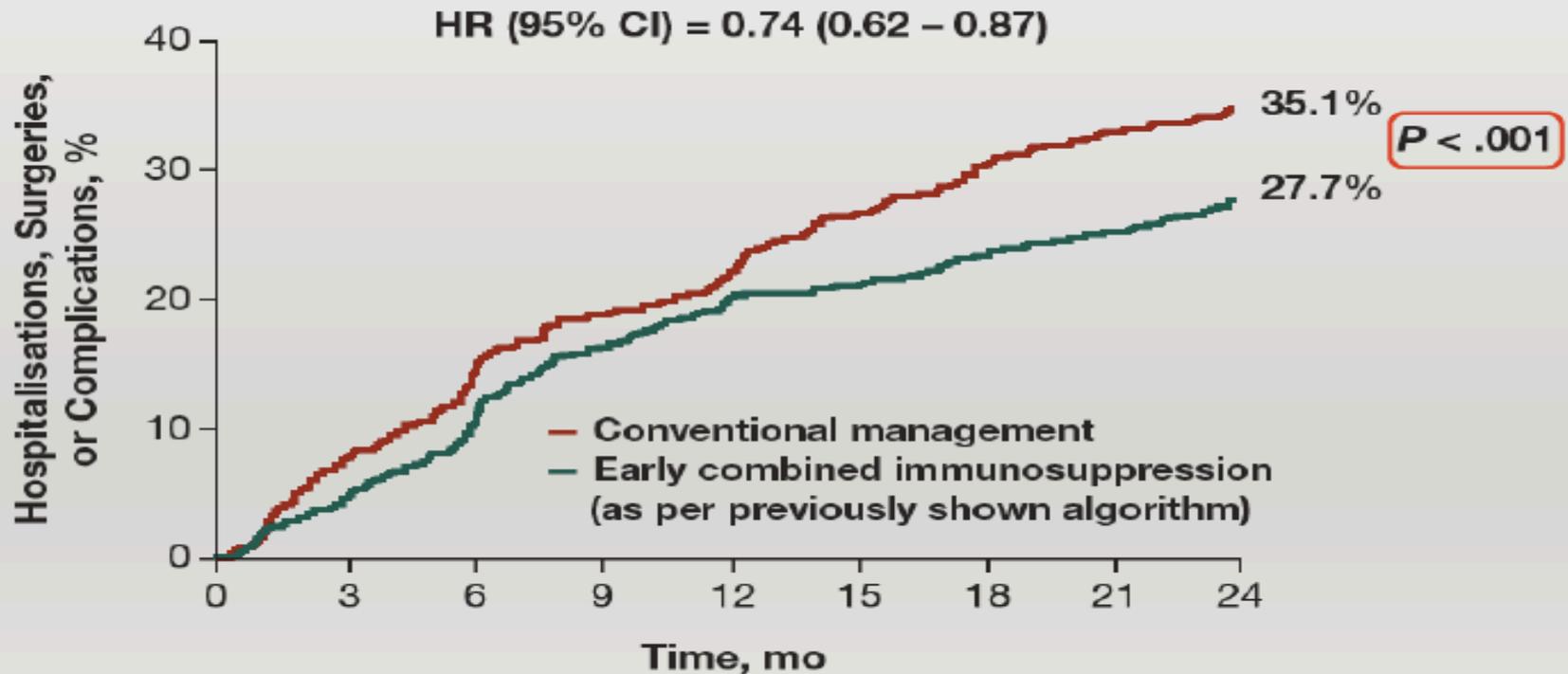
Therapeutic Algorithm Utilised for Patients in the Early Combined Immunosuppression Group



ADA: adalimumab; BUD: budesonide; CS: corticosteroids; HBI: Harvey-Bradshaw Index; MTX: methotrexate; PRED: prednisone; PRN: *pro re nata* (as needed).

Estudio REACT

REACT Study^a: Composite Secondary Endpoint of Time to First Hospitalisation, Surgery, or Complication



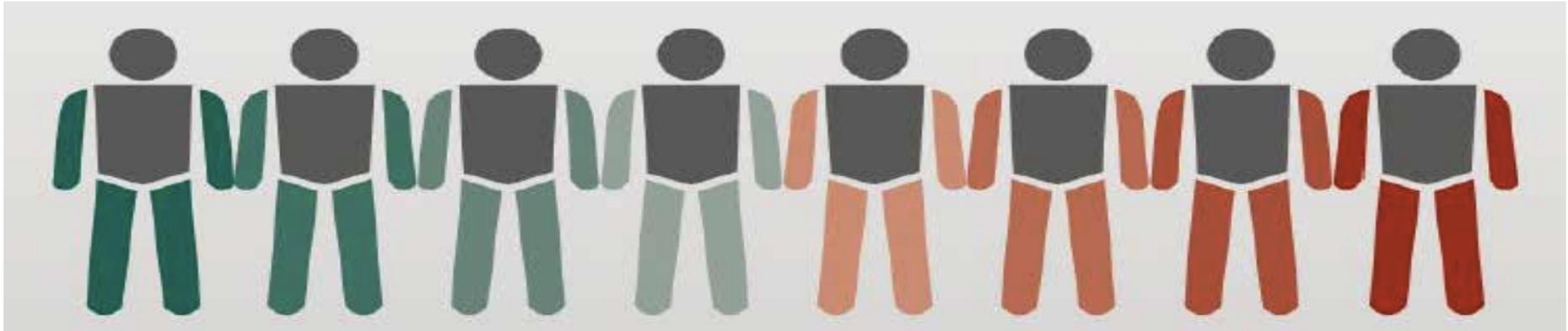
^a When evaluating these individual endpoints, there was a significant reduction in surgeries and in complications for the early combined immunosuppression group, but only a nonsignificant trend for reduced hospitalisation.

CI: confidence interval; HR: hazard ratio.

A cartoon illustration of Alice from 'Alice in Wonderland' with long blonde hair, wearing a blue dress with a white apron and a black headband. She is looking at the Cheshire Cat, a grinning orange cat with a large yellow nose, who is sitting on a wooden ledge. The background is a dark grey wall with a wooden door handle and a red curtain on the left.

¿Cuáles son los factores predictivos de riesgo de progresión de la EC?

Factores pronóstico en EC



Indolente \longrightarrow Agresivo

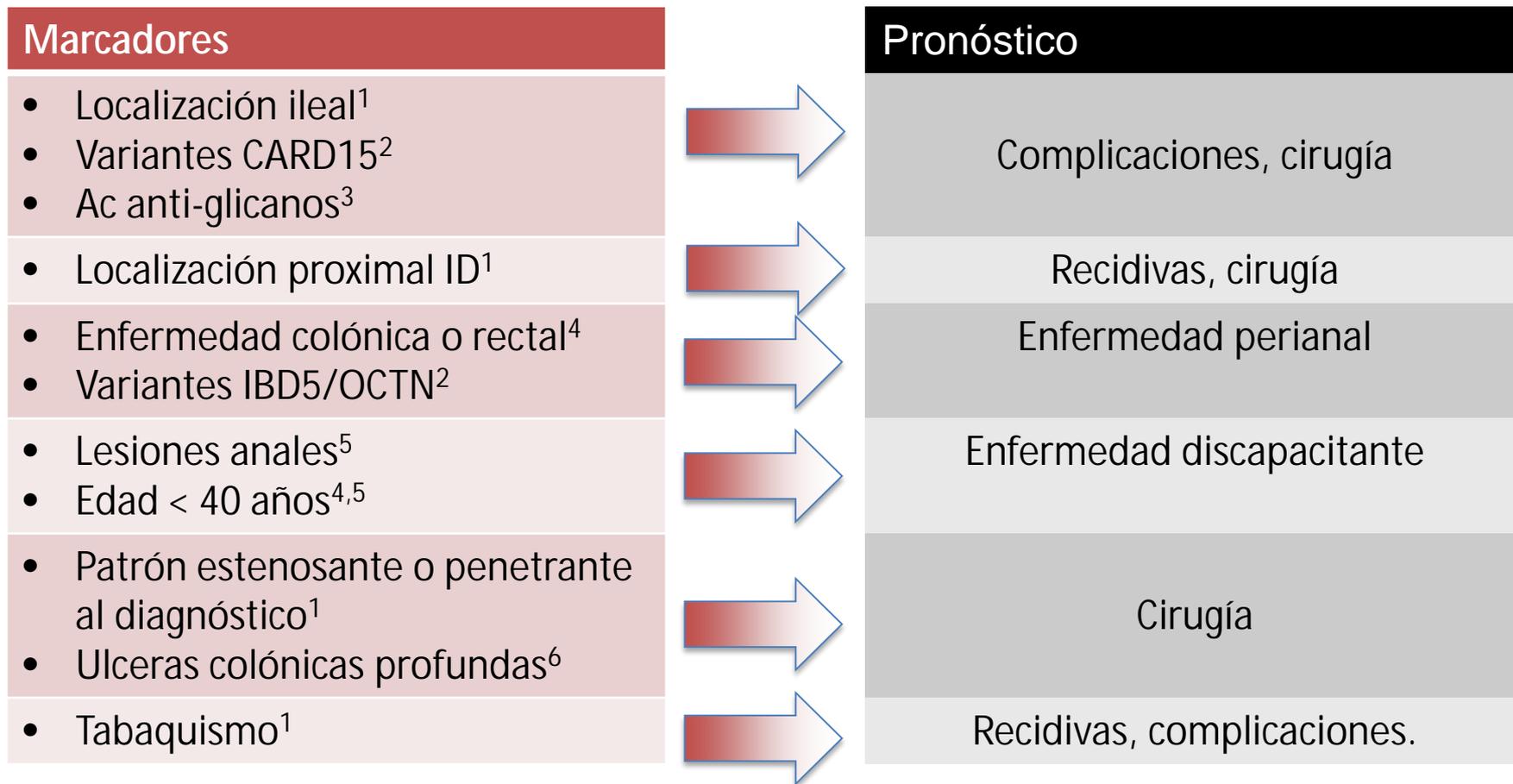
Step-up

Evita terapias intensivas,
inmunodepresión,
efectos adv

Top-down

Asegura una terapia
intensiva precoz para
evitar complicaciones

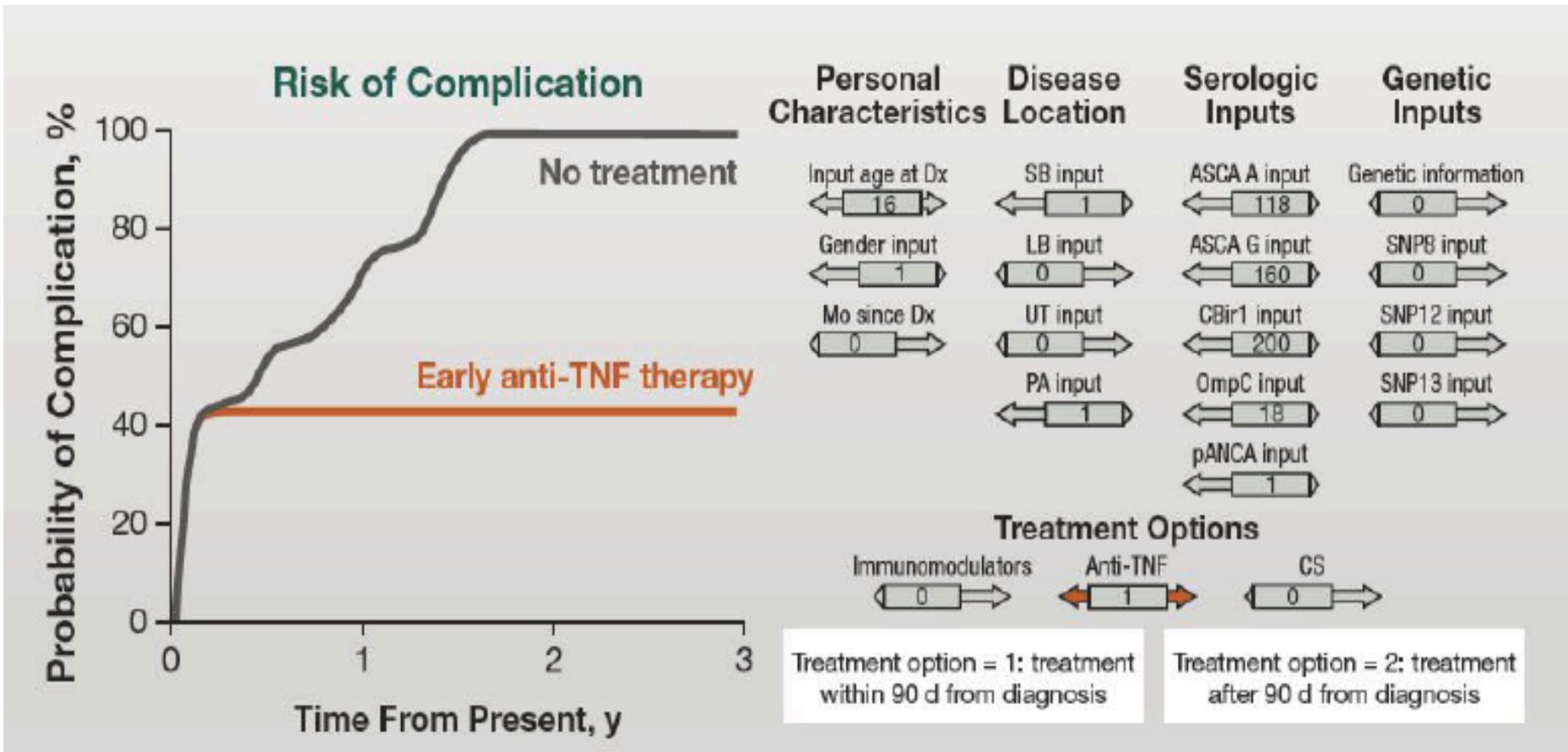
Factores pronóstico en EC



CARD: caspase-activating recruitment domain; OCTN:organic cation/l-carnitine transporter

1.Louis E. Gut 2003;52:552-57. 2.Henckaerts L. Clin Gastroenterol Hepatol 2009;7:972-80. 3.Rieder F.IBD 2010;16:1367-75. 4.Romberg-Camps MJ. Am J Gastroenterol 2009;104:371-83. 5.Beaugerie L. Gastroenterology 2006;130:650-56. 6.Allez M. Am J Gastroenterol 2002;97:947-53.

En el futuro...

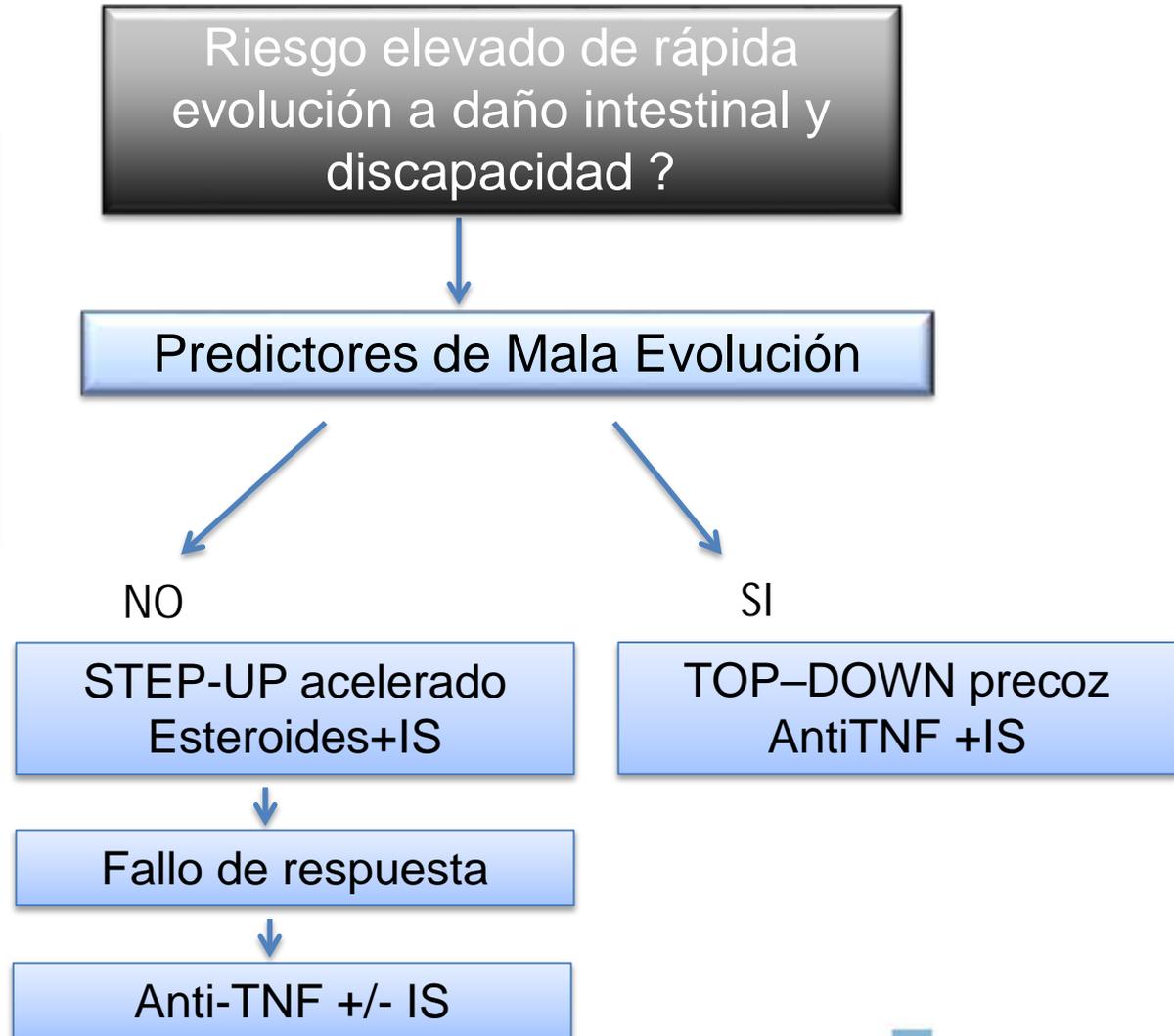


1. Siegel CA. *Inflamm Bowel Dis* 2011;17:30-38

2. Siegel CA. *Gastroenterology* 2014;146(suppl1):S433-434

E. de Crohn precoz moderada-severa: Propuesta de Algoritmo de tratamiento

- Edad < 40 a
- ID
- Enf perianal
- Lesiones endoscópicas graves
- B2, B3



Conclusiones

1. El objetivo del tratamiento precoz en la E.de Crohn es evitar el daño intestinal irreversible y sus complicaciones.
2. Debemos valorar el grado de actividad de la enfermedad así como la presencia de factores de riesgo desde la primera visita e instaurar el tratamiento adecuado lo antes posible.
3. La terapia anti-TNF (+/-IS) en la EC precoz en los pacientes con alto riesgo de progresión podría ser la mejor estrategia para conseguir una buena evolución

Conclusiones

4. Son necesarios estudios prospectivos para validar los marcadores predictivos actuales y definir nuevos (serológicos, genéticos, biomarcadores).
5. Son necesarios estudios prospectivos a largo plazo para establecer si la terapia precoz con anti-TNF +/-IS modifica el curso de la enfermedad.

