TITOLO:Terapia precoce nelle MICI

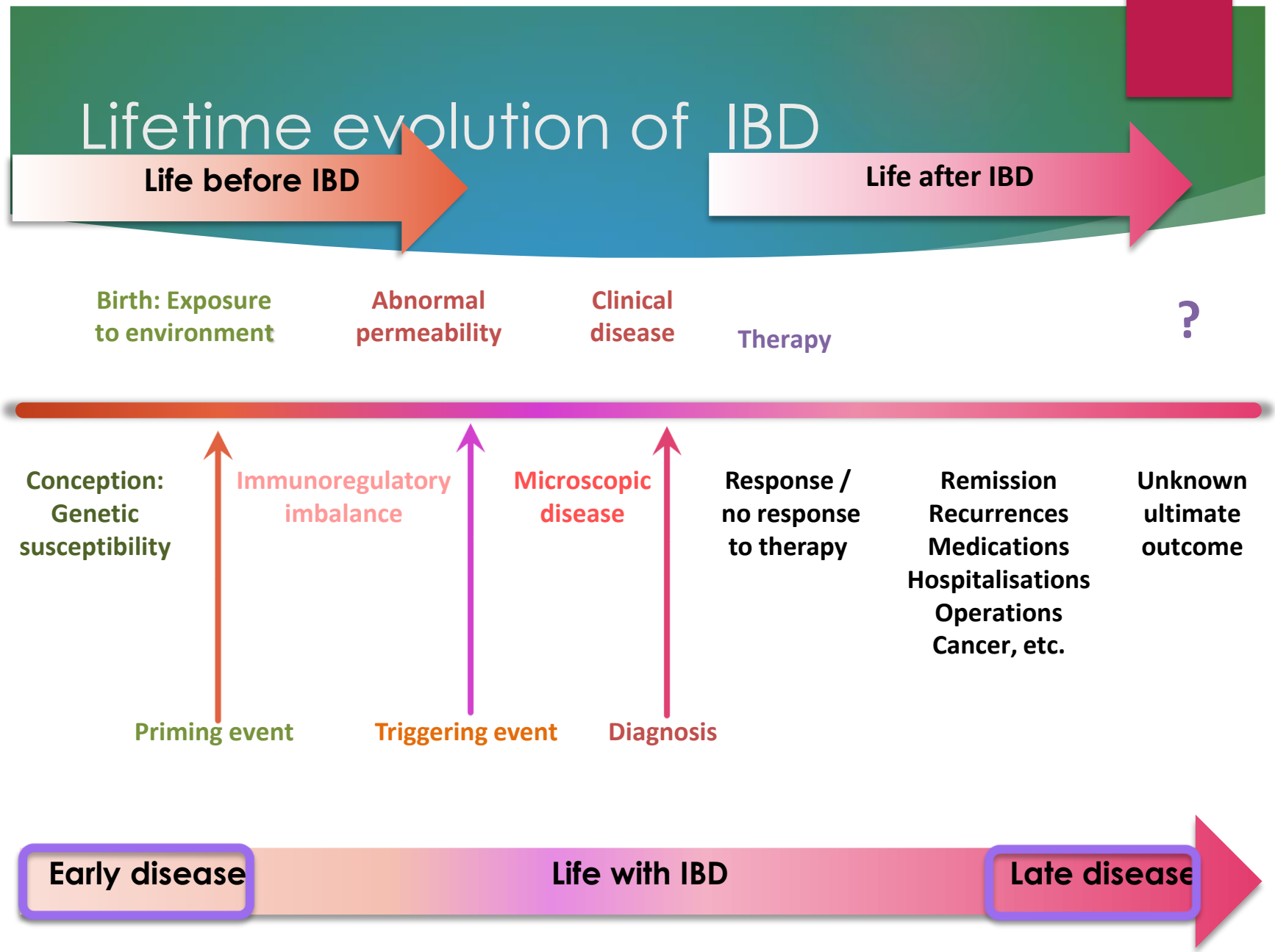
RELATORE: Nicola Gennarelli

Link
profitable solutions

Rational

Recent studies suggest that early biologic therapy improves patient outcomes and can prevent disease progression. While an early intervention strategy has accumulating evidence in Crohn's disease, there is less evidence supporting its impact in ulcerative colitis.

Lifetime evolution of IBD



G. Fiorino

Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease

Methods: Mucosal biopsies and T-cell clones were derived from children experiencing the first attack of Crohn's disease, children with long-standing Crohn's disease, infectious colitis, and children without gut inflammation.

Results: As in acute infectious colitis, interleukin (IL) 12 induced T cells from early Crohn's disease to acquire a strongly polarised T helper (Th) type 1 response characterised by high IFN-gamma production and IL12Rbeta2 chain expression. Th1 polarisation was not induced in clones from late Crohn's disease. Mucosal levels of IL12p40 and IL12Rbeta2 messenger RNA were significantly higher in children with early than late Crohn's disease. These results demonstrate that susceptibility to IL12-mediated modulation is strongly dependent on the stage of Crohn's disease.

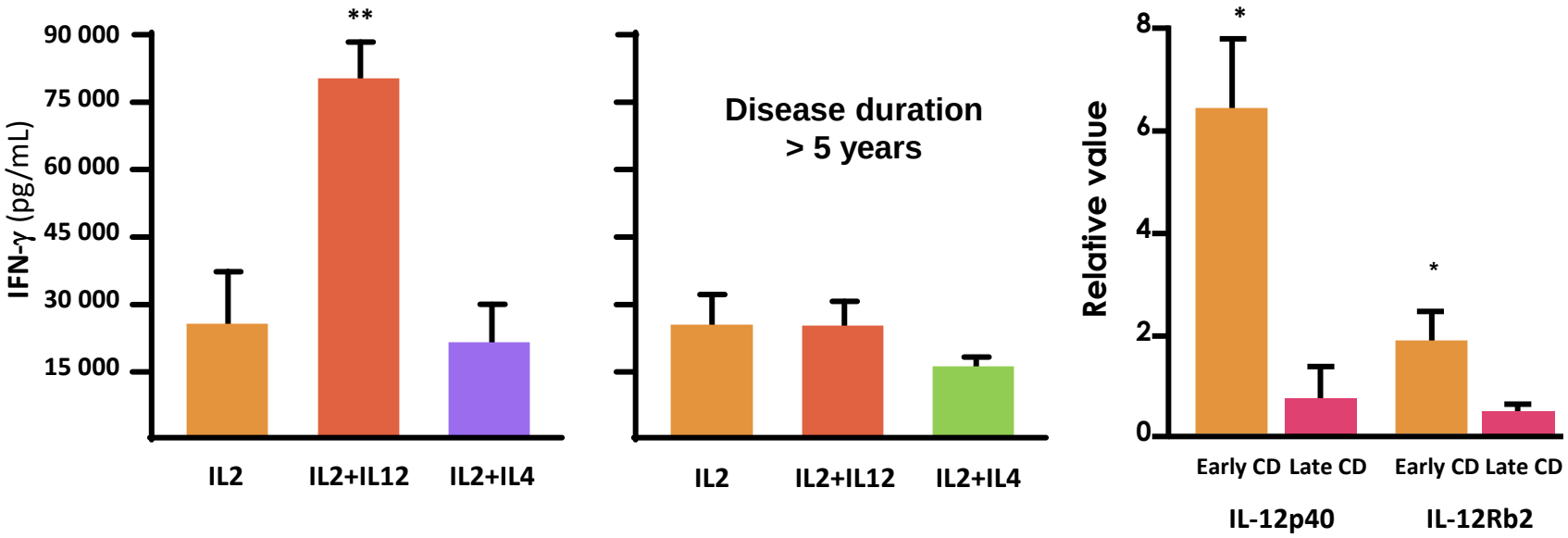
Conclusions: At the onset of Crohn's disease mucosal T cells appear to mount a typical Th1 response that resembles an acute infectious process, and is lost with progression to late Crohn's disease. This suggests that mucosal T-cell immunoregulation varies with the course of human IBD. Patients with the initial manifestations of IBD may represent an ideal population in which immunomodulation may have optimal therapeutic efficacy.

Kugathasan S, et al. Gut. 2007;56:1696–1705

Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease

Early Crohn's disease

Late Crohn's disease



- IFNγ production no longer upregulated by exposure to IL-12 in late disease
  - Increased mucosal levels of IL12p40 mRNA in early vs late CD

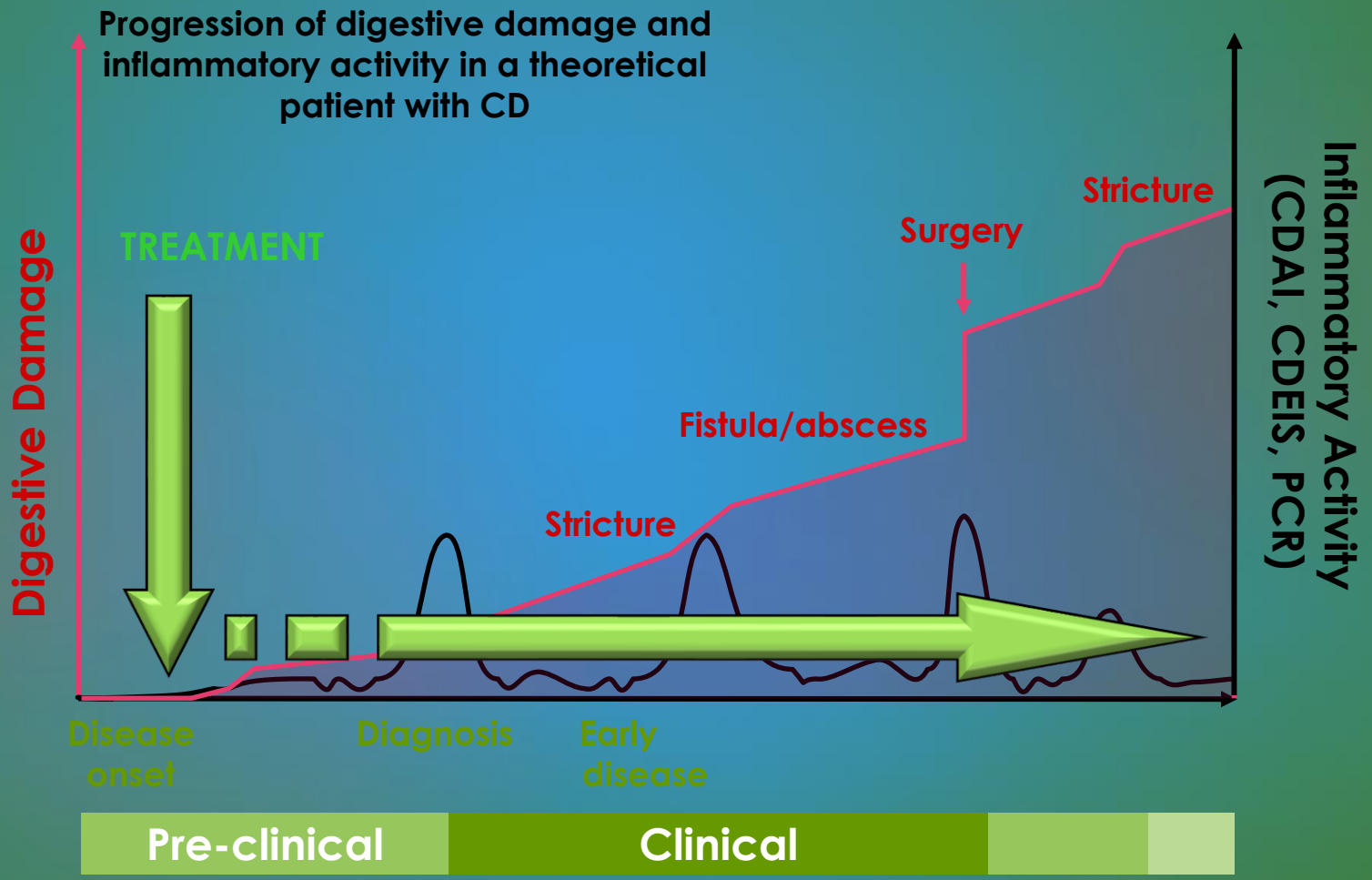
*P=0.05
**P=0.0001

Kugathasan S, et al. Gut. 2007;56:1696–1705

Lémann score

- Crohn's Disease Digestive Damage Score (the Lémann score), should take into account damage location, severity, extent, progression, and reversibility, as measured by diagnostic imaging modalities and the history of surgical resection. It should not be "diagnostic modality driven": for each lesion and location, a modality appropriate for the anatomic site
- computed tomography
- magnetic resonance imaging enterography
- colonoscopy

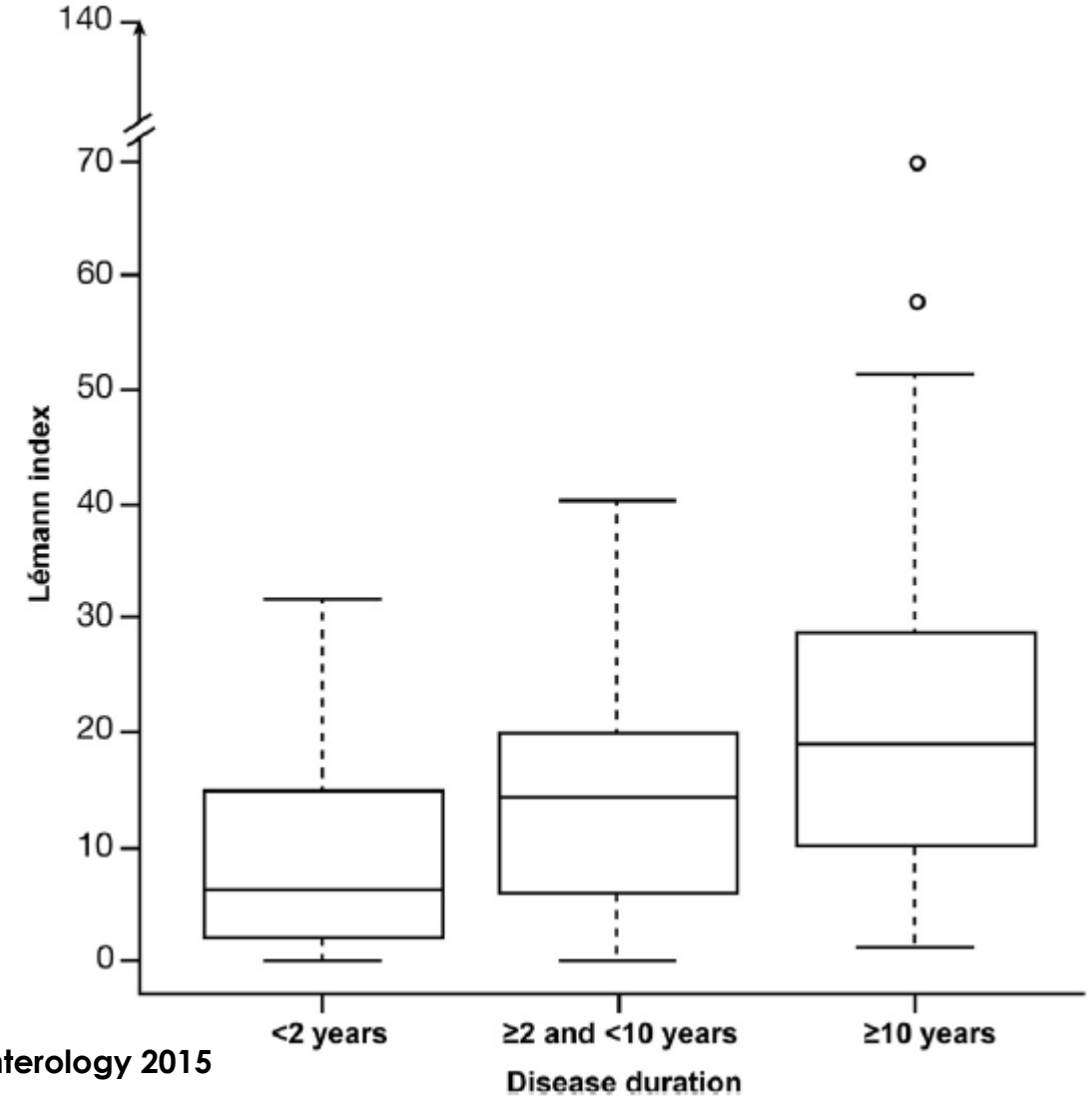
Progression of digestive disease damage and inflammation



CDAI : *Crohn's disease activity index*, indice d'activité de la maladie de Crohn ; CDEIS : *Crohn's disease endoscopic index of severity*, indice de gravité endoscopique de la maladie de Crohn ; PCR : protéine C réactive

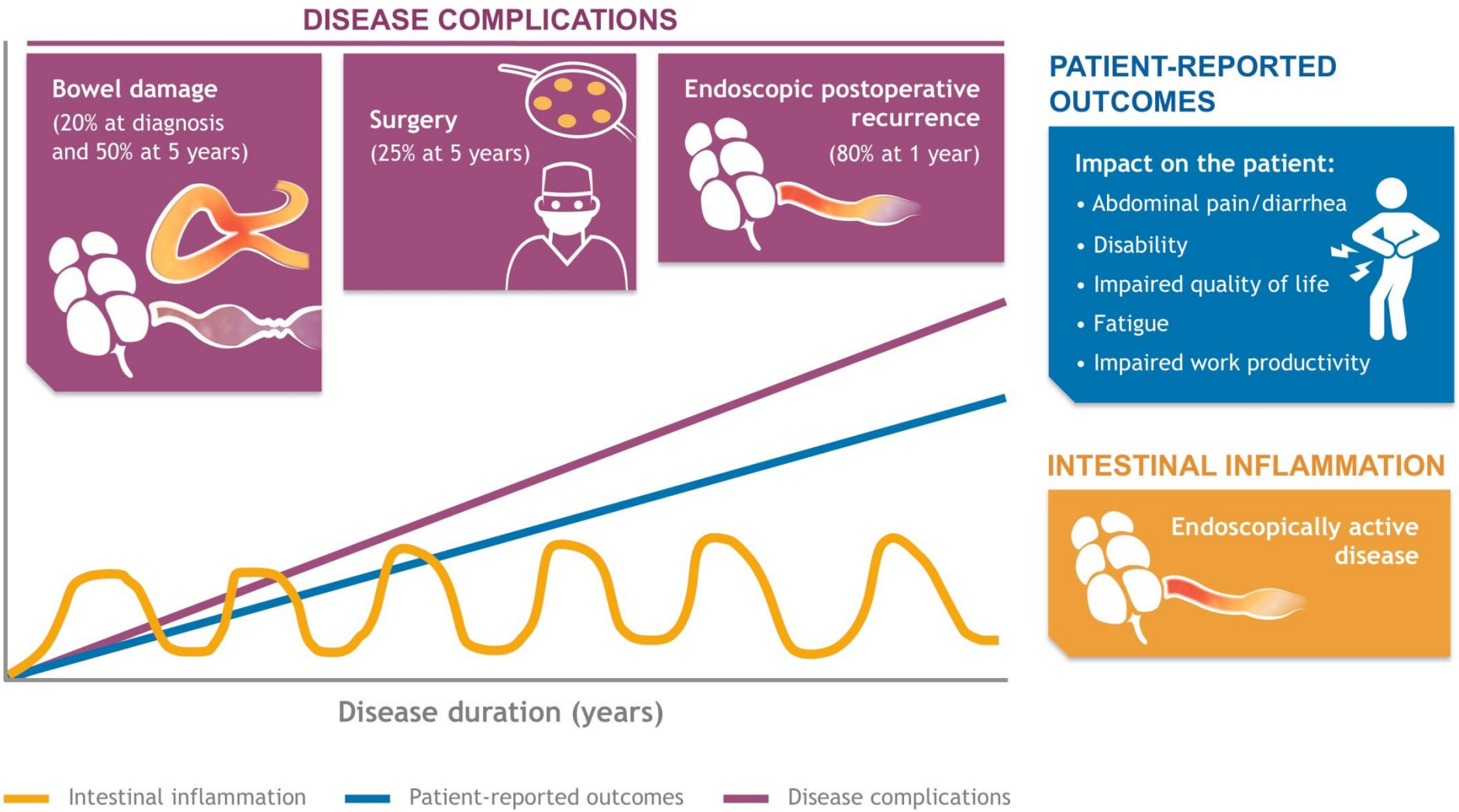
Pariente B et al. Inflamm Bowel Dis 2011 Jun;17(6):1415-22

Bowel damage increases with disease duration



Pariente et al. Gastroenterology 2015

Diagnosis of Crohn's disease



[1]Thia et al. Gastroenterology 2010; [2]Fiorino, Zallot et al. JCC 2016

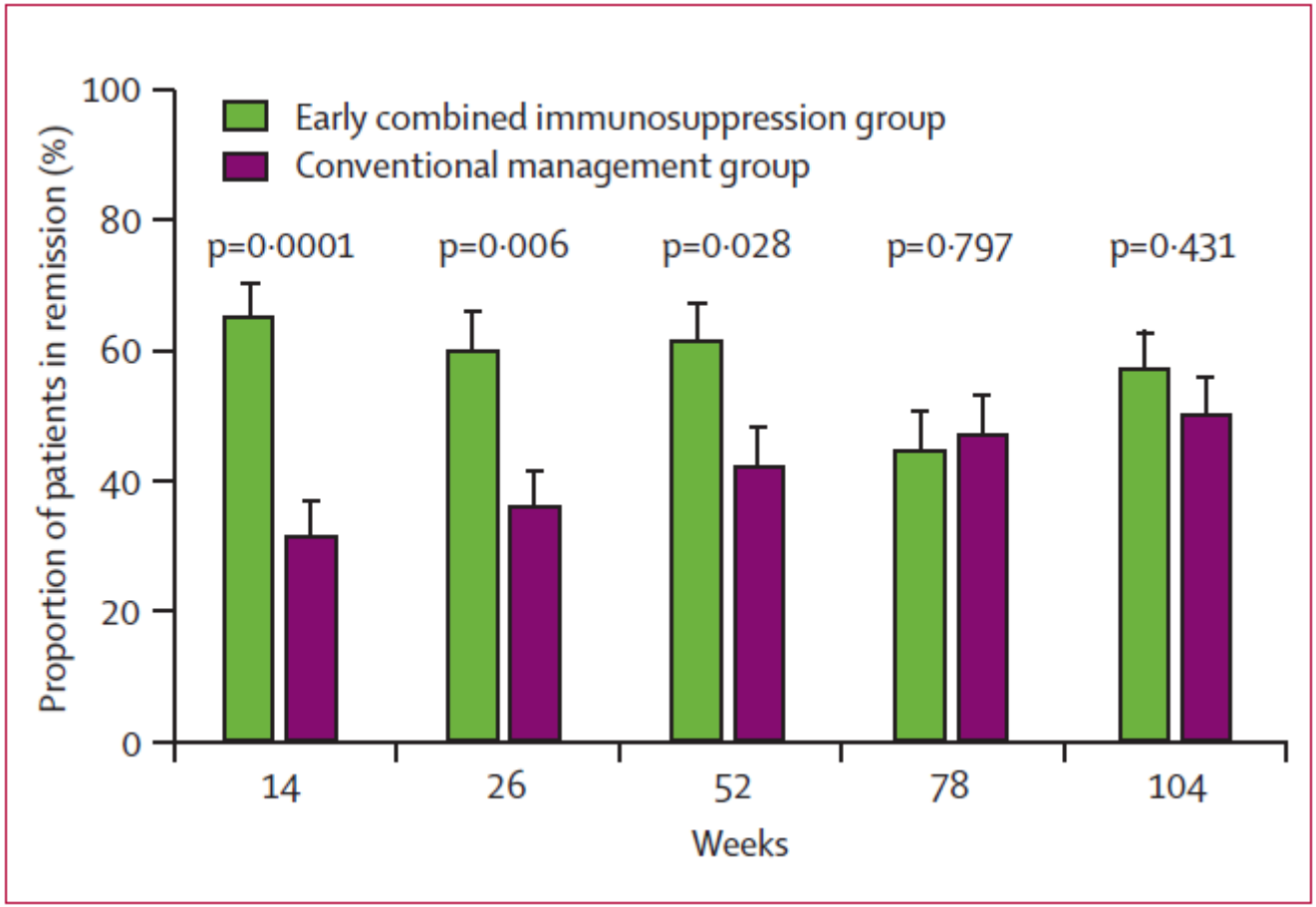
- The goals for treatment of inflammatory bowel diseases (IBDs) are changing from elimination of symptoms toward complete disease control—a process that demands both clinical and endoscopic remission.

- This new IBD treatment paradigm has been shifting from a conventional "step-up" approach toward a more "top-down" early intervention treatment strategy.

- Recent studies suggest that the use of biologic agents, specifically those targeting tumor necrosis factor alpha, earlier in the treatment course improves patient outcomes and can prevent progression to irreversible bowel damage.

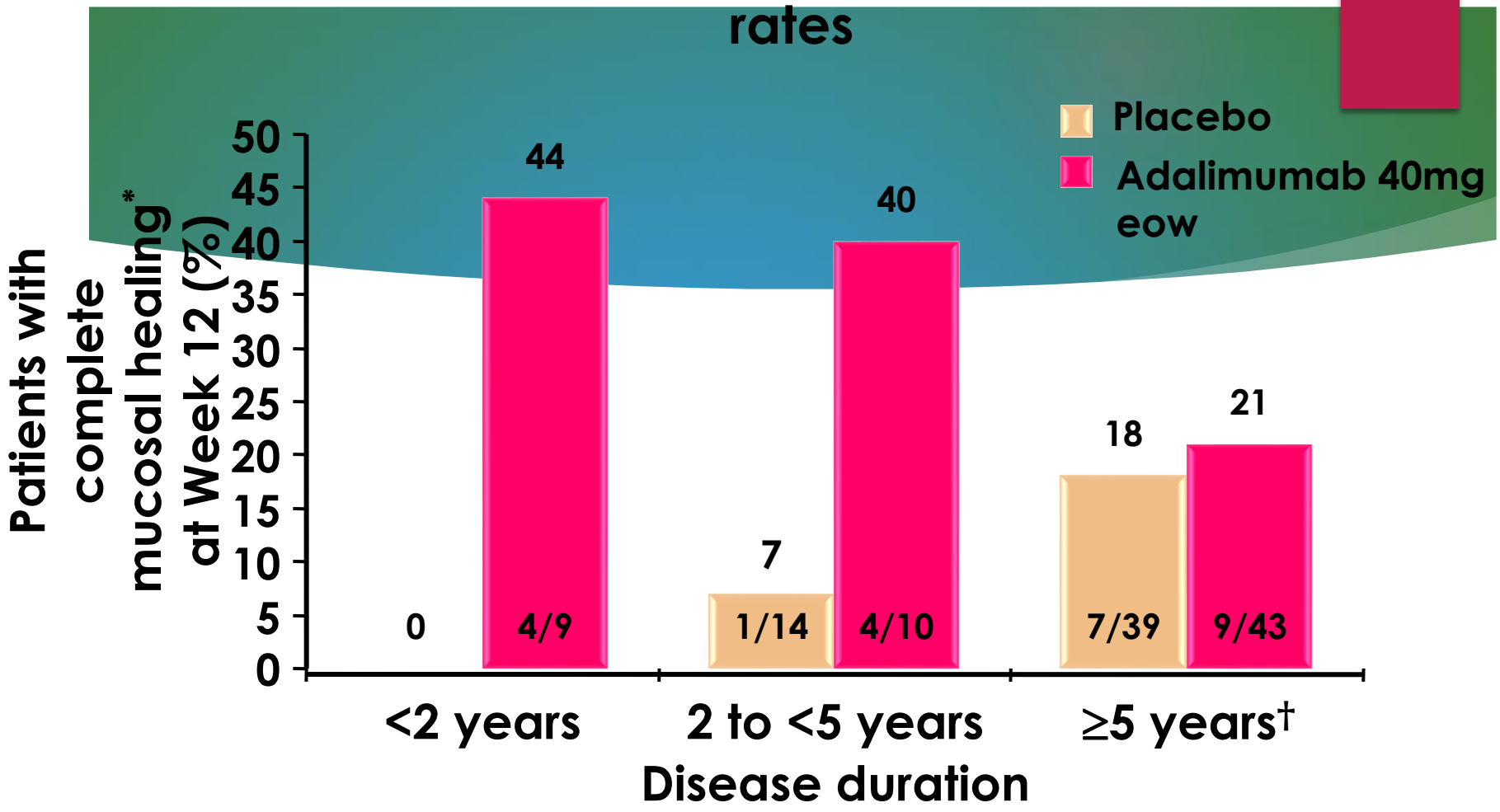
- Although the strategy of early intervention has accumulating evidence in Crohn's disease, there is less evidence supporting its impact in ulcerative colitis.

Step-up vs. top-down approach



D'Haens Lancet 2008

EXTEND: disease duration and complete mucosal healing* rates



* Complete mucosal healing was defined as absence of mucosal ulceration on endoscopic exam

† *p*=0.029 for adalimumab vs placebo for disease duration <5 years vs ≥5years

All patients (n=135) received adalimumab 160/80mg induction therapy, before randomisation (n=129) to adalimumab 40mg eow or to placebo; data for patients with ulceration at baseline (n=123) : eow: every other week

Sandborn WJ, *et al. J Crohn's Colitis* 2010; 4:S36

The CALM trial

Randomized clinical trial

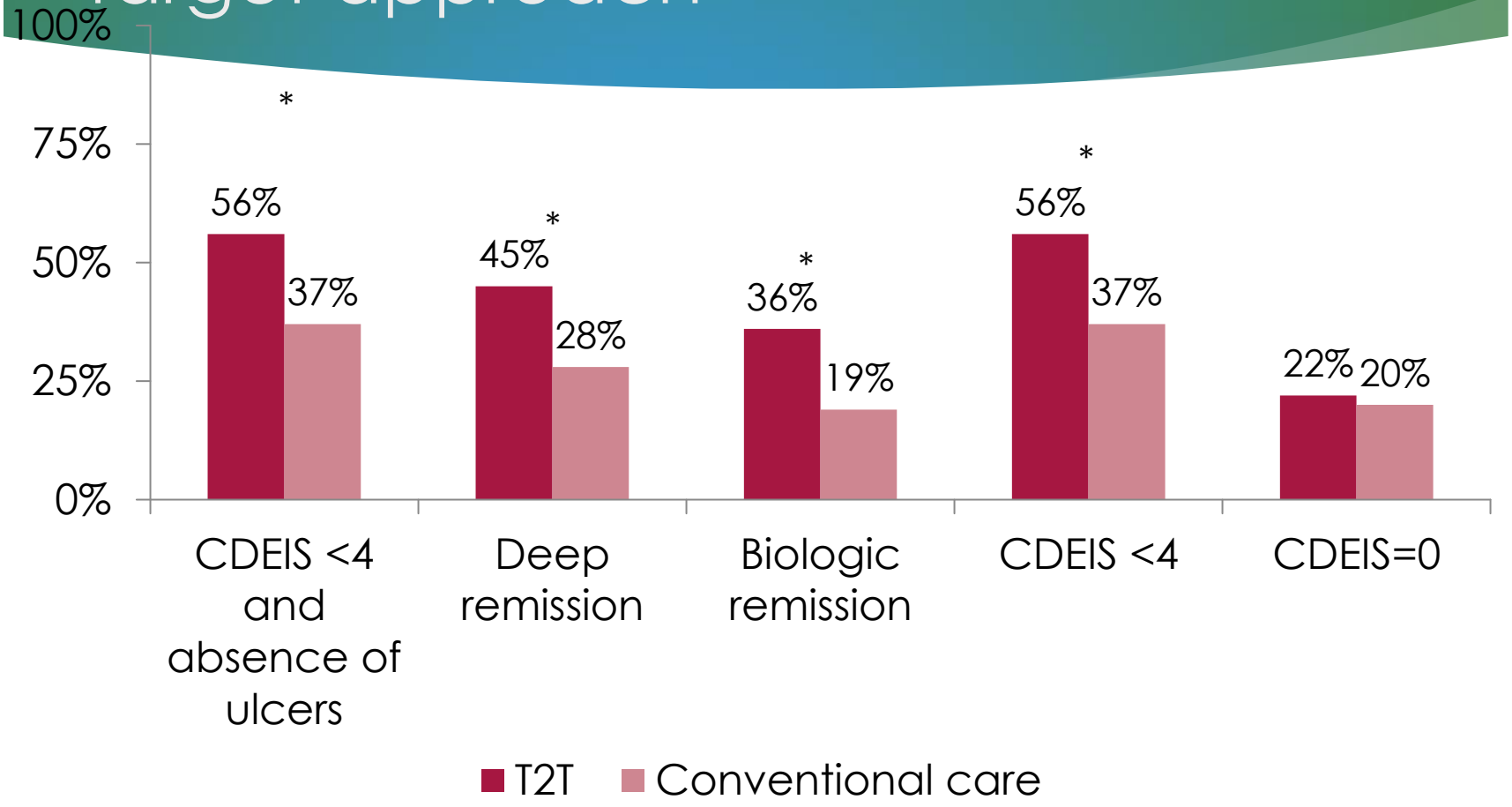
Tight control vs. Clinically-driven approach

Tight control: Accelerated step-up approach based on CRP and calpro levels

Clinically driven: Accelerated step-up based on clinical score (CDAI)

Colombel et al. CALM trial 2017

Early treatment and Treat-to-target approach



Colombel et al. CALM trial 2017

Anti-integrins (Vedolizumab)

In the GEMINI 2 and GEMINI 3 trials for vedolizumab, clinical response and remission rates were higher among anti-TNF-naïve patients, providing indirect evidence for possible improved response with shorter disease duration; however, this question was not specifically analyzed.

More recently, in a real-world observational cohort of vedolizumab-treated patients, CD disease duration <2 years was significantly associated with higher rates of steroid-free clinical remission and endoscopic healing at 6 months.

Is there an optimal sequence of biologic therapies for inflammatory bowel disease?

Table 2. Endoscopic remission in CD with and without prior use of anti-TNF therapy.*

	Overall			TNF naive			TNF exposed		
	Drug	Placebo	Difference	Drug	Placebo	Difference	Drug	Placebo	Difference
Drugs that show lower endoscopic remission rates after anti-TNF therapy									
Vedolizumab (VERSIFY)[a]									
26 weeks	11.9%	–	–	19.6%	–	–	5.5%	–	–
52 weeks	17.9%			25.0%			8.3%		
Adalimumab (EXTEND)[b]									
12 weeks	27.0%	13.0.0%	14.0	31.3%	11.5%	9.0	31.3%	11.5%	19.8
52 weeks	24.0%	0%	24.0	25.0%	0%	25.0	23.3%	0%	23.3
Drugs that show similar endoscopic remission rates before and after anti-TNF therapy									
Ustekinumab (IM-UNITI)[c]									
12 weeks	47.7%	29.9%	17.8	43.9%	17.1%	26.8			
44 weeks	37.0%	25.0%	12.0	–	–	–			
Risankizumab (FORTIFY)[d]									
180 mg dose	47.1%			63.6%			40.7%		
360 mg dose	46.8%	22.0%	~25	53.8%	26.8%	~32	44.1%	20.3%	~22

B Bressler Therap Adv Gastroenterol. Apr. 2023

Is there an optimal sequence of biologic therapies for inflammatory bowel disease?

Table 3. Clinical effectiveness in EVOLVE.

	UC			CD		
First-line vedolizumab or first-line anti-TNF over 24 months						
	First-line vedolizumab	**First-line anti-TNF**	***p* Value**	**First-line vedolizumab**	**First-line anti-TNF**	***p* Value**
Clinical remission	65.9%	48.6%	0.09	76.6%	68.5%	0.10
Clinical response	88.3%	86.2%	0.64	84.0%	72.1%	0.27
Mucosal healing	86.6%	80.6%	0.66	100%	90.4%	0.12
First-line anti-TNF or second-line anti-TNF at 3 or 6 months						
	First-line anti-TNF	**Second-line anti-TNF**	***p* Value**	**First-line anti-TNF**	**Second-line anti-TNF**	***p* Value**
Clinical remission at 3 months	9.7%	11.0%	0.92	22.9%	49.2%	***0.02***
Clinical response at 3 months	38.4%	44.8%	0.54	30.1%	41.3%	0.52
Clinical remission at 6 months	19.6%	14.7%	0.69	36.2%	74.6%	***<0.01***
Clinical response at 6 months	57.1%	61.1%	0.58	43.5%	74.8%	0.13

p Values in bold italics are statistically significant.
CD, Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

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Is there an optimal sequence of biologic therapies for inflammatory bowel disease?

Table 4. Potential sequence of biologic agents.

	UC (considering magnitude of benefit for clinical remission)		CD (considering magnitude of benefit for endoscopic remission/mucosal healing)	
	Anti-TNF naïve	**Anti-TNF exposed**	**Anti-TNF naïve**	**Anti-TNF exposed**
First line*	Vedolizumab, ozanimod, or ustekinumab	Ustekinumab, tofacitinib, or upadacitinib	Risankizumab, ustekinumab, vedolizumab	Risankizumab or ustekinumab
Second line*	Tofacitinib or upadacitinib			
Third line	Anti-TNF			

*No sequence is recommended within each category.
CD, Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

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It is similarly unclear whether the above-mentioned "top-down" paradigm is equally valid in UC.

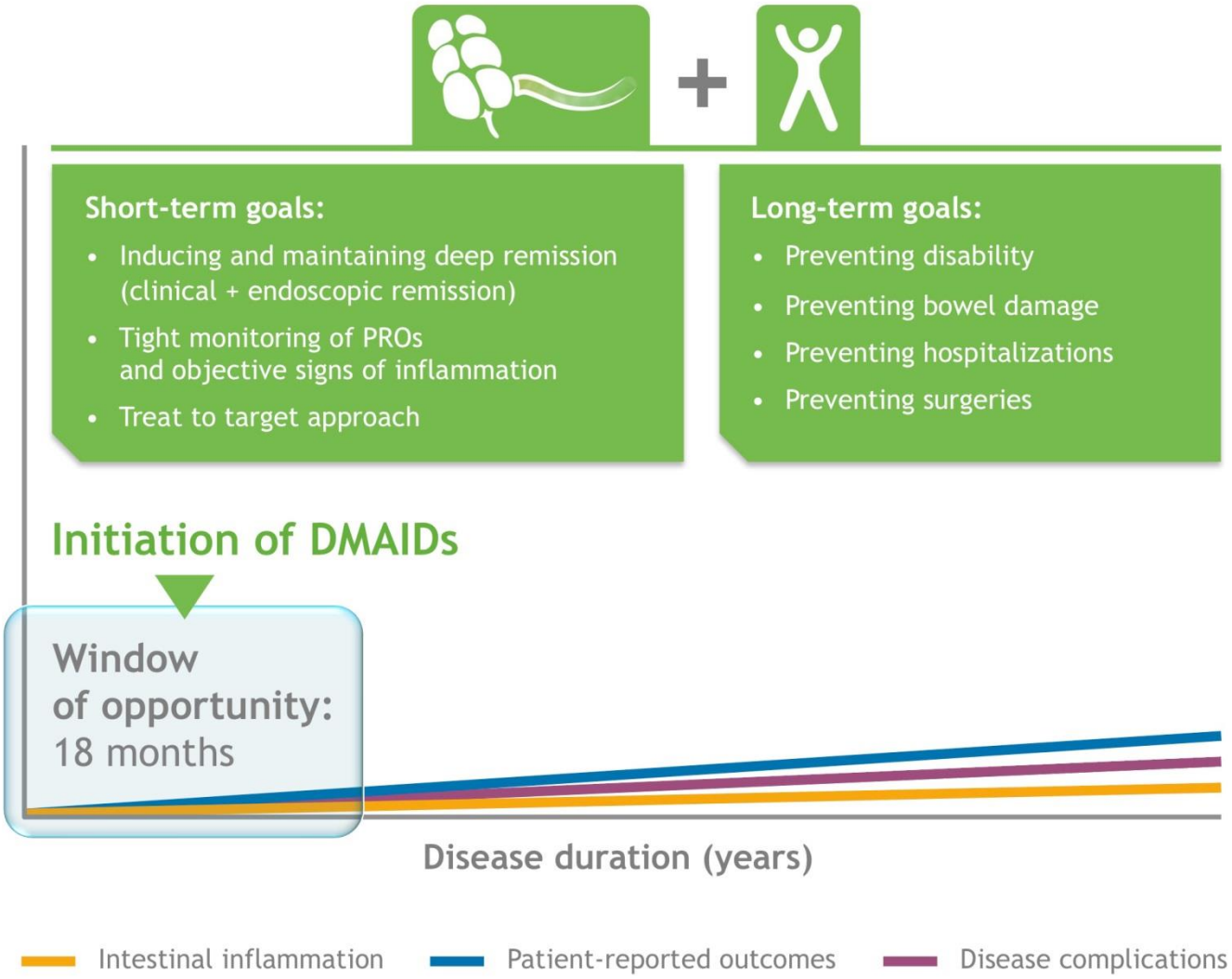
The data regarding utility of early biologic therapy in UC patients remain sparse.

There is, however, evidence that UC is also a progressive disease and can ultimately result in strictures, pseudopolyposis, bridging fibrosis,-dysmotility, and anorectal incontinence.

Additionally, 10 years after diagnosis, approximately 10% of UC patients will require a colectomy for management of disease-related complications.

Although surgery remains an important component of UC management and can allow patients to regain quality of life, it is not without risks, as nearly 30% of patients will have a postoperative complication.

Early treatment: which goals?



Danese Gut 2016