Current Therapeutic Challenges in IBD Therapy

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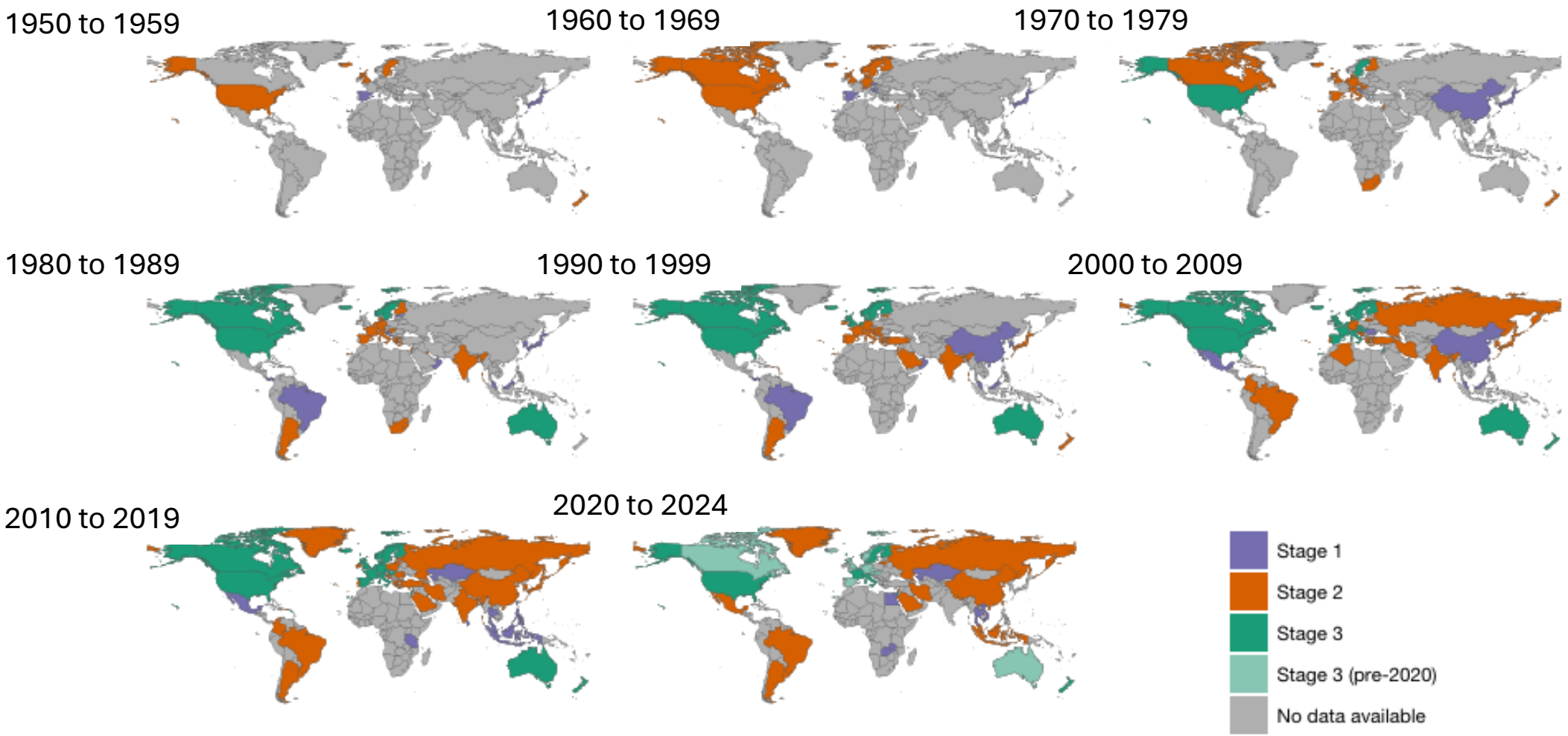
Disclosures

- Presenter's Name: Gerhard Rogler

- **Consulting** to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pierre Fabre, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller;
- **Speaker's honoraria** from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pierre Fabre, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor and Zeller;
- **Educational grants and research grants** from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB and Zeller.
- **Co-founder and Head of Scientific AdBoard:** PharmaBiome

Increasing prevalence of IBD worldwide



Hracs L, Windsor JW, Gorospe J, …..Ng SC, Kaplan GG; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group. Global evolution of inflammatory bowel disease across epidemiologic stages. Nature. 2025 Jun;642(8067):458-466

Previous Therapeutic Challenges in IBD Therapy

- Limited treatment options (limited clinical trials in pediatric IBD)
- No convenient method to monitor treatment success
- Psychosocial burden
- High rates of surgery in Crohn’s disease
- Fibrosis and Fistula development in CD patients

Problems of the Past: Limited Therapeutic Options

- Reliance on (topical???) corticosteroids
- Lack of acceptance of rectal therapies
- Few maintenance therapies
- Steroid dependence and side effects common

20 years ago: Biologics were introduced in IBD therapy.....

LEADING ARTICLE

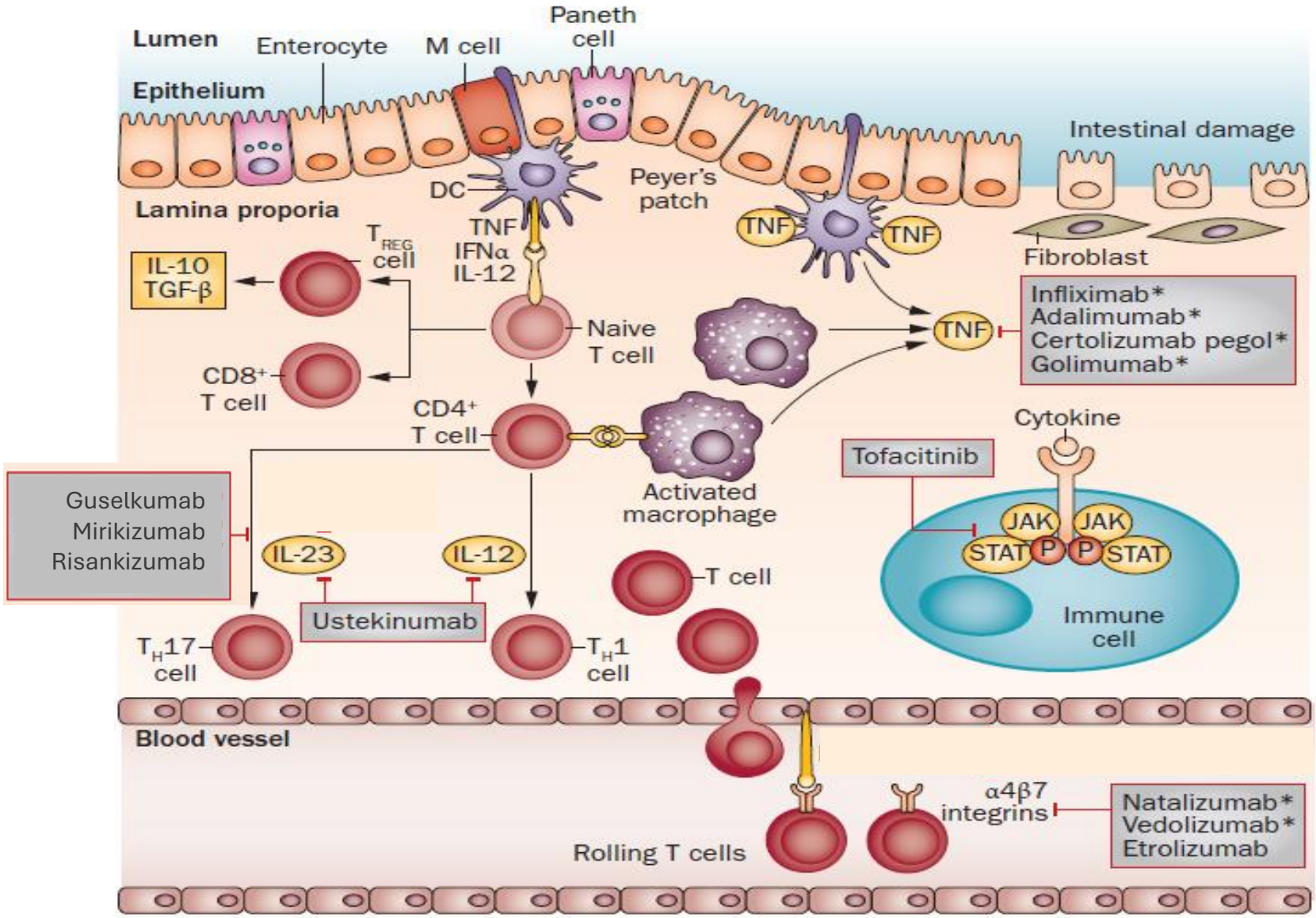
Drugs R&D 1999 Mar; 1 (3): 237-244
1174-5886/99/0003-0237/$04.00/0

Promising New Agents for the Treatment of Inflammatory Bowel Disorders

Kevin A. Lang[1,2] and *Mark A. Peppercorn*[3,4]

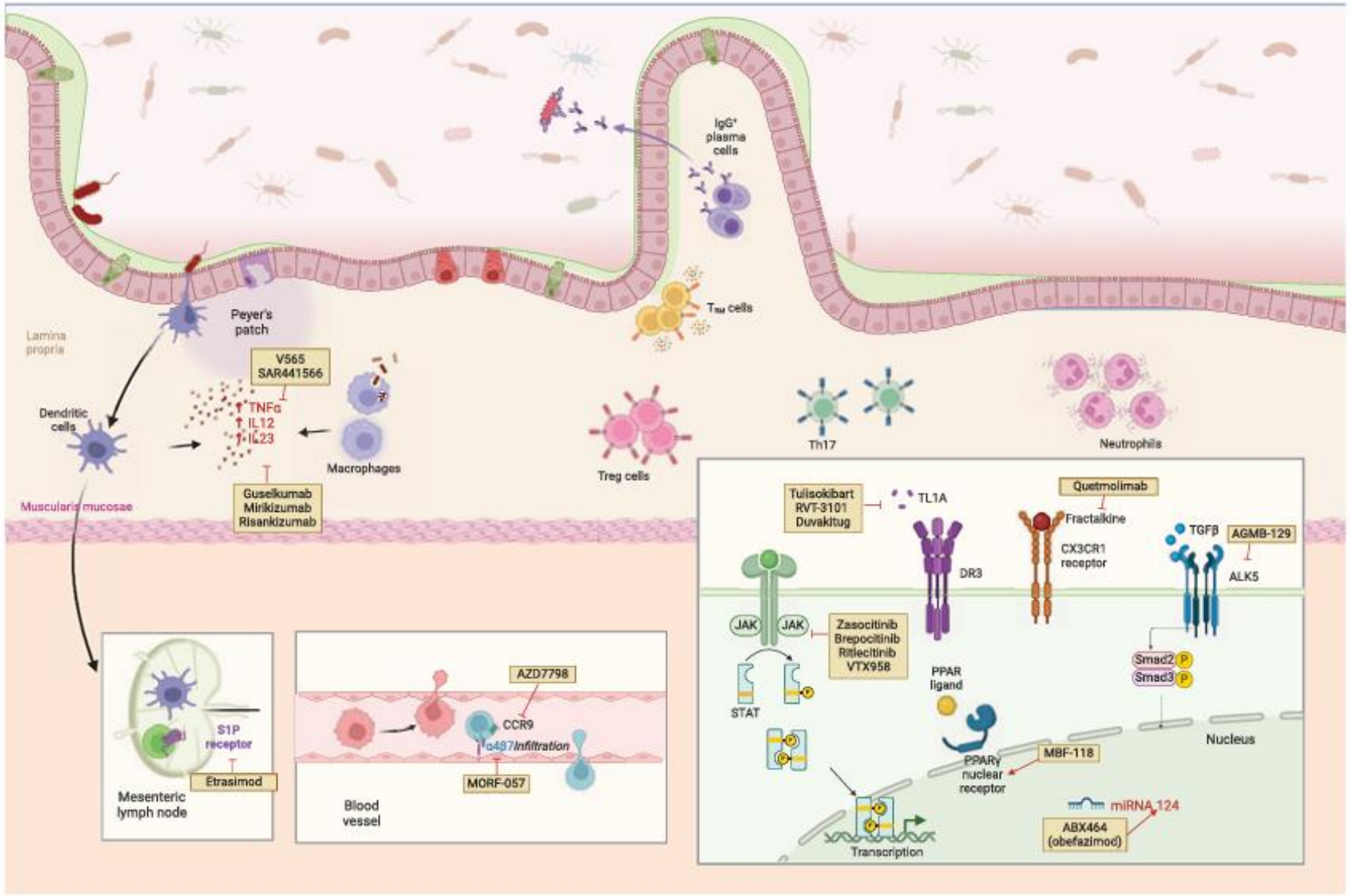
"A groundswell of therapeutic modalities is presently sweeping through the field of inflammatory bowel disease (IBD), revolutionising the treatment and management of these disorders. At the forefront of newer agents are biological therapies, also referred to as 'biologics'. These include infliximab (cA2), CDP 571, rhIL-10, ICAM-1 antisense oligonucleotide (ISIS 2302) and opreleukin (rhIL-11)."

Biologics and small molecules established in IBD therapy



mod acc to Danese, S. et al. Nat. Rev. Gastroenterol. Hepatol. 12, 537–545 (2015)

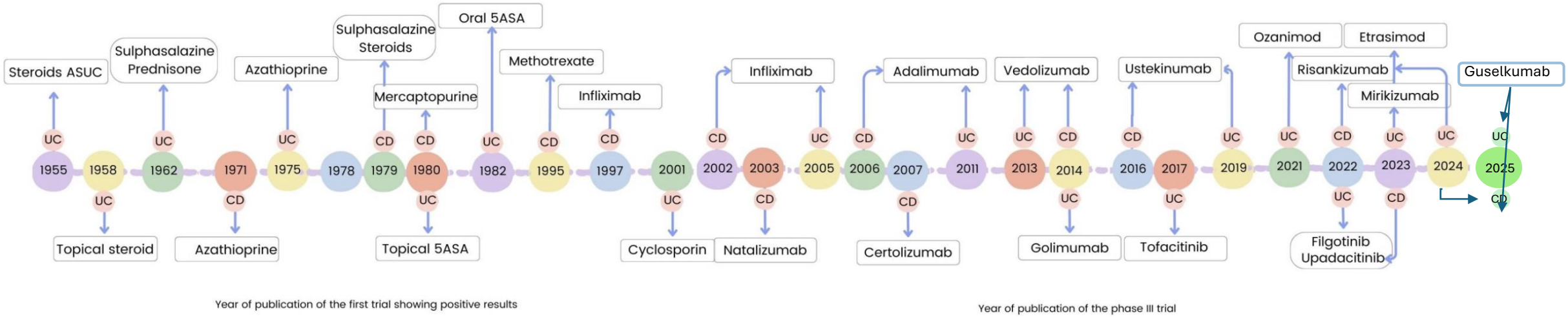
Mechanisms of action of emerging therapies



Bertin L, Crepaldi M, Zanconato M, Lorenzon G, Maniero D, de Barba C, Bonazzi E, Facchin S, Scarpa M, Ruffolo C, Angriman I, Buda A, Zingone F, Barberio B, Savarino EV. Advancing therapeutic frontiers: a pipeline of novel drugs for luminal and perianal Crohn's disease management. Ther Adv Gastroenterol. 2024 Dec 19;17:17562848241303651

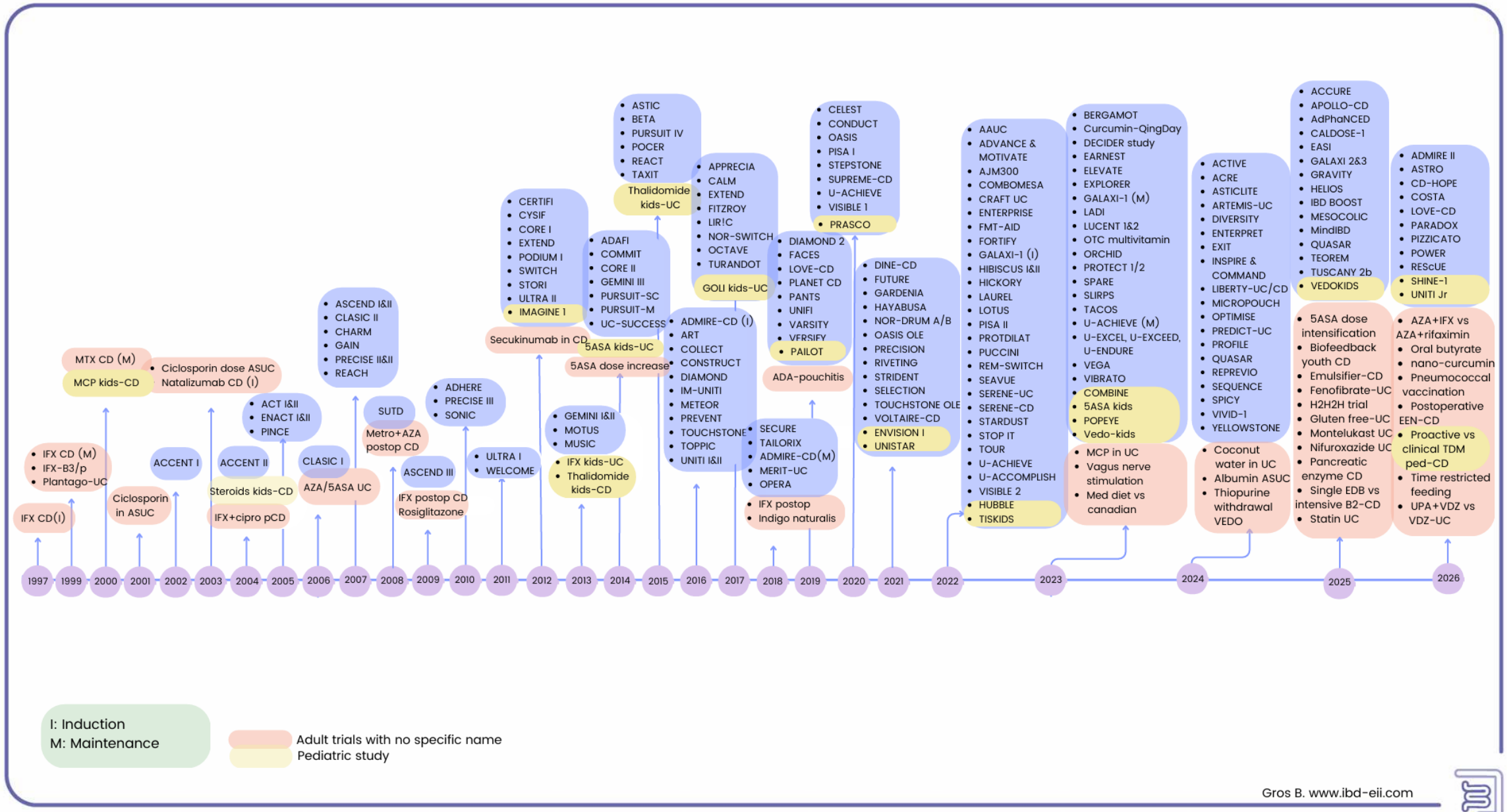
New Challenge – New therapies and monitoring

- **Problem:** Need for: Right drug, right time



Gros B. www.ibd-eii.com

Number of clinical trials in IBD since 1997



Gros B. www.ibd-eii.com

New Challenges

- Biologic therapies & monitoring
- How to choose the right therapy
- Therapeutic ceiling
- Mental health focus
- Integration of precision medicine
- Access & health equity

TREATMENT PIPELINE FOR IBD THERAPY

A step-up approach tailored to disease severity, patient factors, and treatment goals

LOWER INTENSITY
LOWER RISK

HIGHER INTENSITY
HIGHER EFFICACY

1 5-ASA / Topical Therapy

- Mild disease
- Induction & maintenance of remission in mild UC
- Rectal or oral 5-ASA (± topical steroids)

Examples

Mesalamine (oral)
Mesalamine suppository/ enema
Budesonide MMX*

2 Corticosteroids

- Induction of remission in moderate disease
- Short-term use for active flares
- Not for maintenance

Examples

Budesonide (mild–moderate ileocecal CD)
Prednisone/Prednisolone
IV steroids (severe flare)

3 Immunomodulators

- Steroid-sparing
- Maintenance of remission
- Onset: slow (8–12 weeks)
- Monitor for toxicity

Examples

Azathioprine
6-Mercaptopurine
Methotrexate

4 Biologic Therapies

- Moderate–severe disease
- Induction & maintenance of remission
- Mucosal healing
- Steroid-sparing

Examples

Anti–TNF: Infliximab, Adalimumab, Golimumab
Anti–integrin: Vedolizumab
Anti–IL-12/23: Ustekinumab

5 Small Molecule Therapies

- Oral targeted options
- For moderate–severe disease
- Alternative or complement to biologics

Examples

JAK inhibitors: Tofacitinib, Upadacitinib, Filgotinib
S1P receptor modulator: Ozanimod*

Refractory / Advanced Disease

- Loss of response or intolerance to prior therapies
- Optimize, switch mechanism, or combination therapy
- Consider clinical trials
- Surgery when indicated

Options

Switch within/outside class
Combination therapy
Clinical trials
Surgical intervention

TREATMENT GOALS

- ✓ Clinical remission
- ✓ Endoscopic healing
- ✓ Steroid-free remission
- ✓ Improved quality of life

ASSESS & MONITOR

- Symptoms & biomarkers (CRP, fecal calprotectin)
- Endoscopy
- Therapeutic drug monitoring (TDM)
- Safety monitoring

INDIVIDUALIZE CARE

- Disease type & severity
- Prior treatment response
- Risk factors & comorbidities
- Patient preferences & goals

KEY PRINCIPLES

Right drug, right patient, right time, right target

UC: Ulcerative Colitis; CD: Crohn's Disease; 5-ASA: 5-Aminosalicylate; JAK: Janus Kinase; S1P: Sphingosine-1-Phosphate

*Not approved in all regions/indications. Follow local guidelines.

What could be treatment targets in IBD?

- **Short term**

- Clinical remission and minimising risk (side effects)
  - PRO2 and beyond!
  - Quality of Life (including fatigue, pain, productivity etc.)
  - Integrated decision making
- Normalisation of biomarkers values and mucosal (or histological) healing

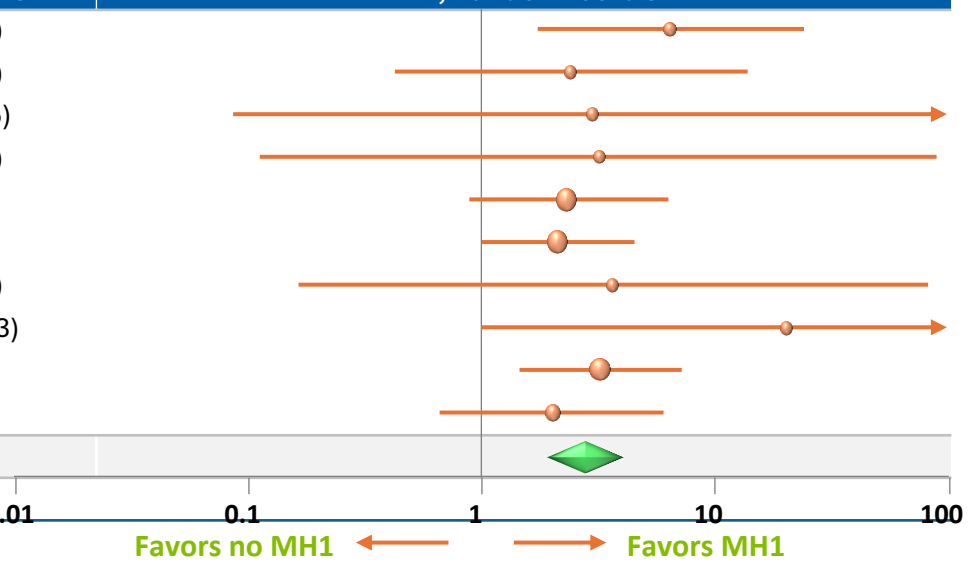
- **Long(er) term**

- Avoid disease progression (CD+UC)
- Avoid complications serious adverse events
  +
  For UC: Cancer and colectomy
  For CD: (Repeated) surgery in patients with extensive small bowel disease

Impact of mucosal healing for long-term outcomes in CD: Meta-analysis

Association of MH at first endoscopic assessment (MH1) with long-term clinical remission (CR)

Study or subgroup	MH 1		No MH 1		Weight	Odds Ratio M–H, Random. 95% CI
	Events	Total	Events	Total		
Baert 2010	17	24	6	22	8.9%	**6.48** (1.79, 23.44)
Bjorkesten 2013	8	10	20	32	5.0%	**2.40** (0.44, 13.23)
Cohen 2014	3	3	3	4	1.2%	**3.00** (0.09, 102.05)
Czaja-Bulsa 2012	2	2	5	8	1.3%	**3.18** (0.12, 87.92)
Dai 2014	65	78	21	31	15.9%	**2.38** (0.91, 6.22)
Froslie 2007	22	53	22	88	27.6%	**2.13** (1.03, 4.41)
Fukuchi 2014	5	5	13	17	1.5%	**3.67** (0.17, 80.21)
Grover 2014	7	15	10	11	1.6%	**20.29** (1.01, 406.33)
Reinisch 2015	54	70	27	53	24.4%	**3.25** (1.50, 7.06)
Rutgeerts 2010	10	20	14	42	12.4%	**2.00** (0.67, 5.93)
Total (95% CI)		280		308	100.0%	**2.80** (1.91, 4.10)
Total events	193		131			



Heterogeneity. τ^2=0.00; χ^2=4.57; df=9 (p=0.87); I^2=0%; **Test for overall effect: *Z*=5.26** (p<0.00001)

Association of MH1 with CD-related surgery-free rate

Study or subgroup	MH 1		No MH 1		Weight	Odds Ratio M–H, Random. 95% CI
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Baert 2010	24	24	22	22		Not estimable
Bjorkesten 2013	10	10	26	32	10.0%	**5.15** (0.27, 99.79)
Froslie 2007	47	53	70	88	89.9%	**2.01** (0.74, 5.45)
Total (95% CI)		87	118	142	100.0%	**2.22** (0.86, 5.69)
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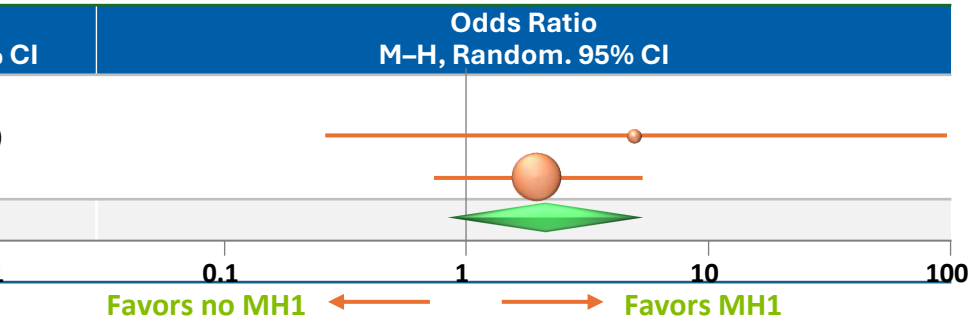

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Shah SC, *et al.* Aliment Pharmacol Ther 2016:43(3):317–33

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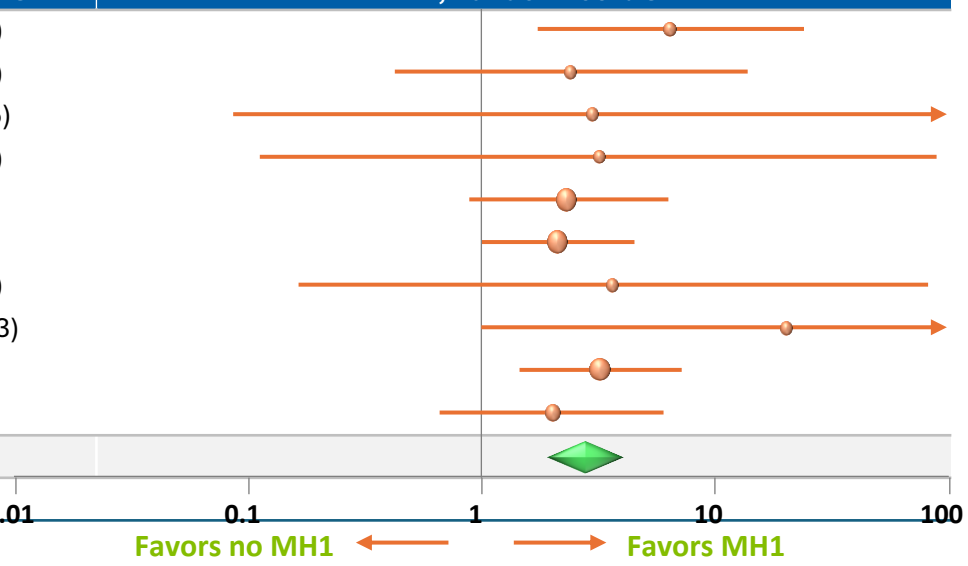

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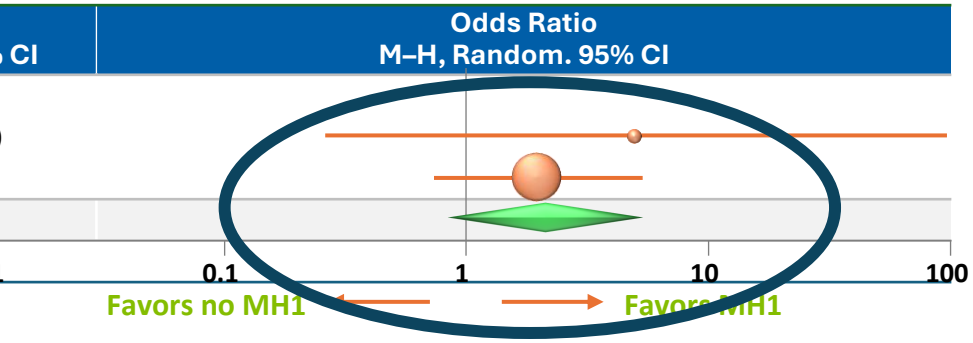

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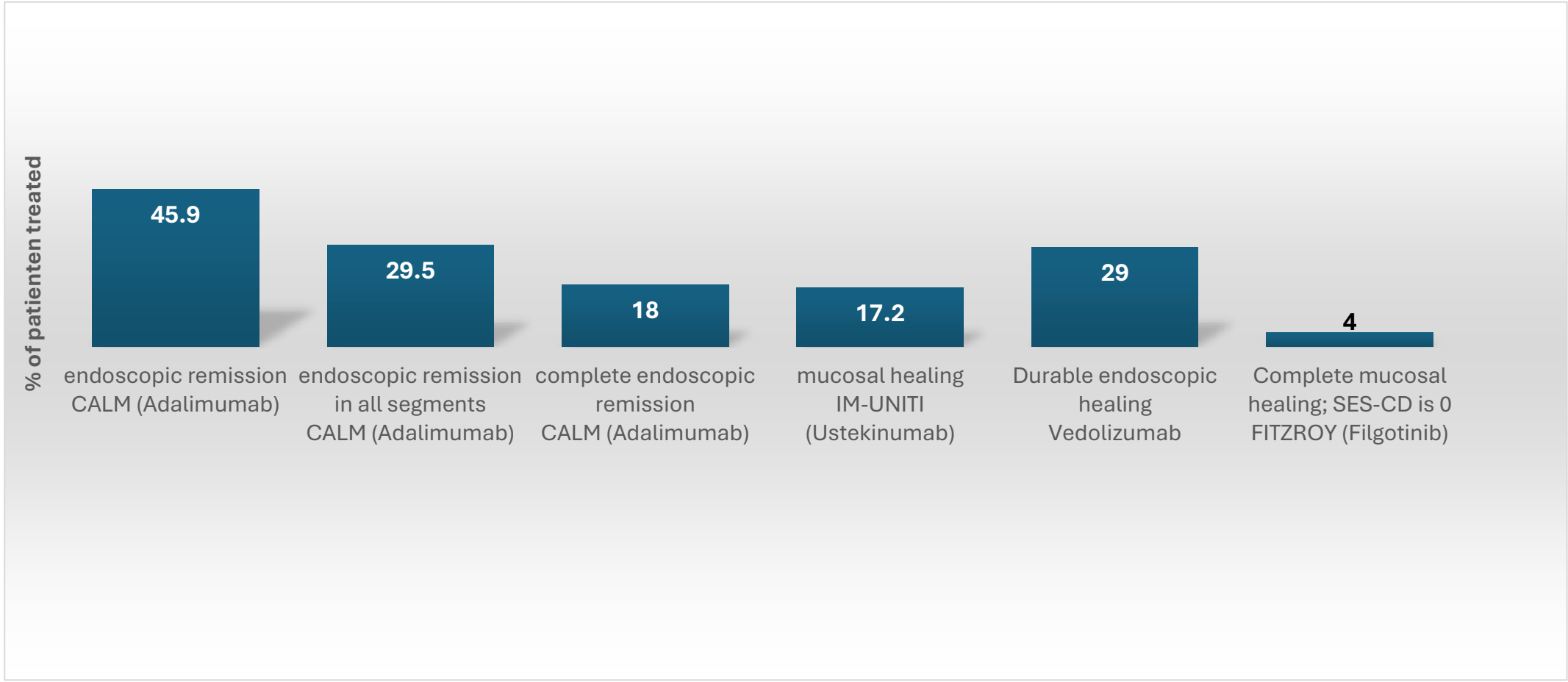
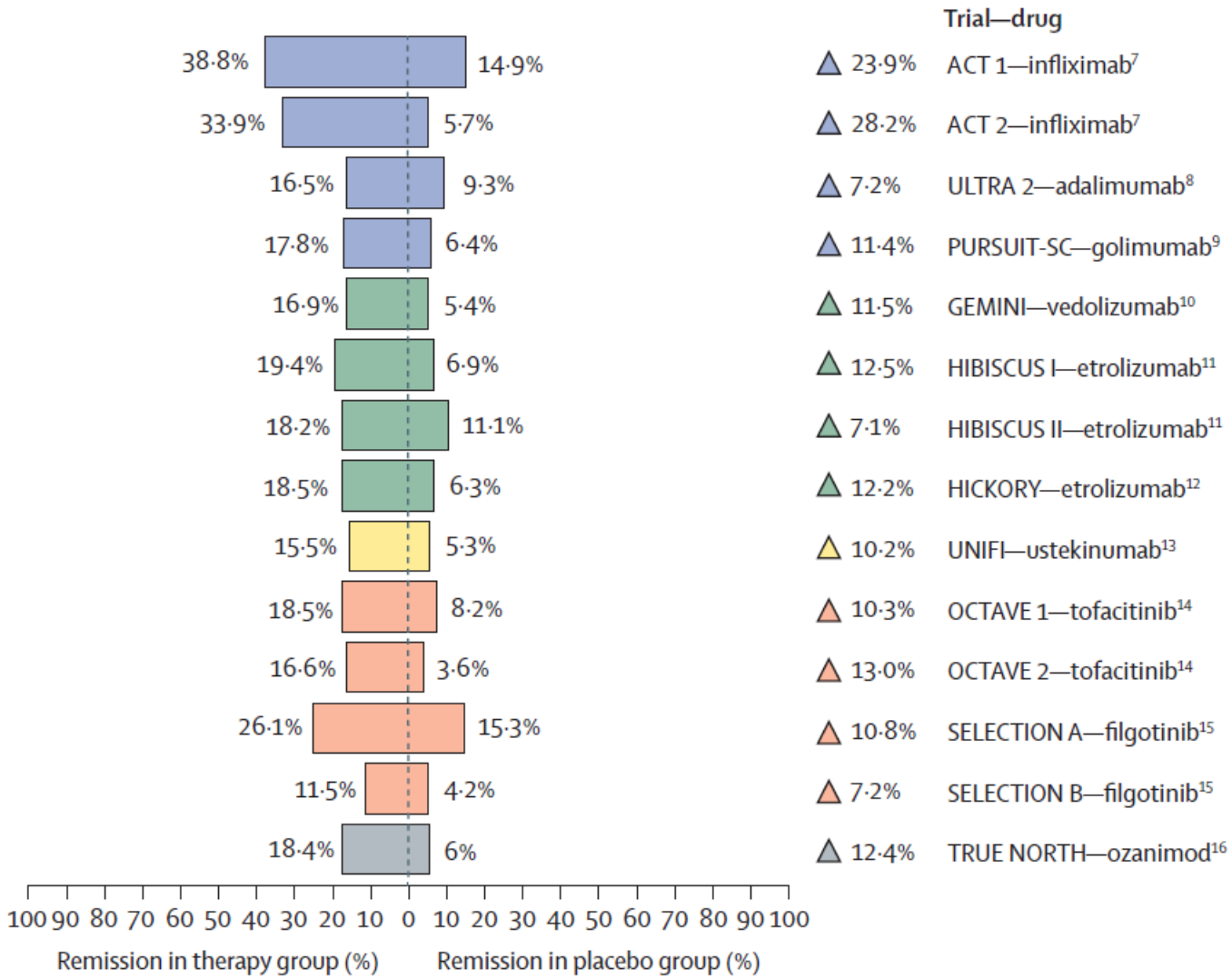
Mucosal healing rates in clinical trials in CD



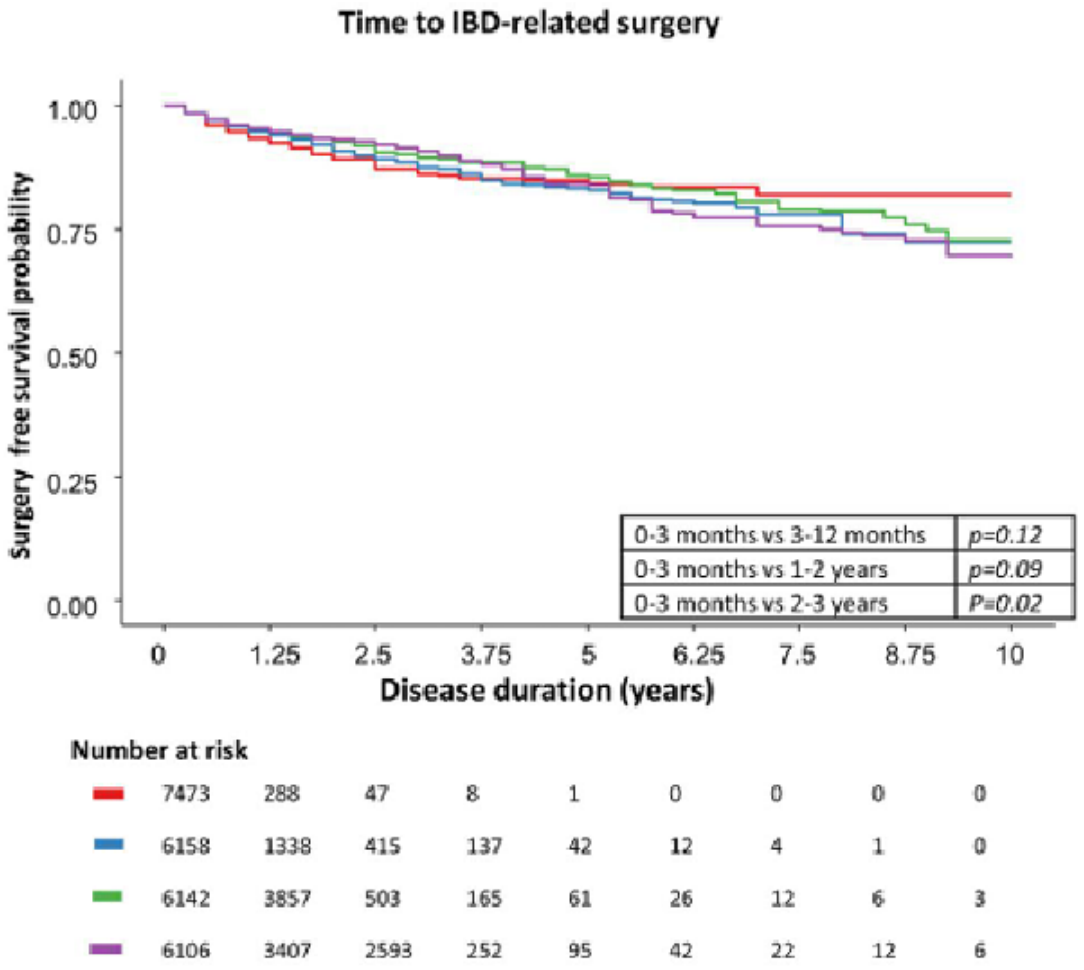
Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Rutgeerts P et al. UEGW 2016 #OP 104
Noman et al, J Crohns Colitis. 2017 Sep 1;11(9):1085-1089.
Vermeire S, et al. Lancet. 2017 Jan 21;389(10066):266-275.

Remission rates in induction trials for ulcerative colitis



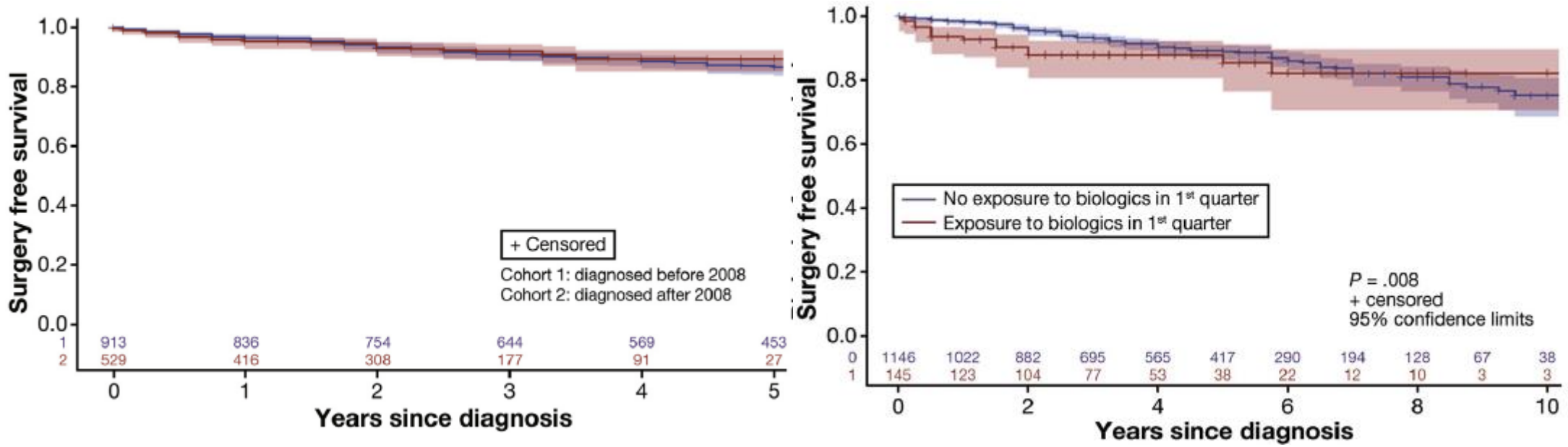
Alsoud D, Verstockt B, Fiocchi C, Vermeire S. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol. 2021 Jul;6(7):589-595

Early start of biologics is not associated with a significantly reduced risk of surgery in CD



Lujan R, Buchuk R, Focht G, Yogev D, Greenfeld S, Ben-Tov A, Weisband YL, Lederman N, Matz E, Ben Horin S, Dotan I, Nevo D, Turner D. Early Initiation of Biologics and Disease Outcomes in Adults and Children With Inflammatory Bowel Diseases: Results From the Epidemiology Group of the Nationwide Israeli Inflammatory Bowel Disease Research Nucleus Cohort. Gastroenterology. 2024 Feb 6:S0016-5085(24)00128-8

Biologics Delay Progression of Crohn's Disease, but Not Early Surgery, in Children



- Data from the Pediatric Inflammatory Bowel Disease Collaborative Research Group registry on 1442 children (age, <16 y) diagnosed with CD from January 2002 through December 2014.
- The 5-year risk of bowel surgery did not change from 2002 through 2014, and remained between 13% and 14%.

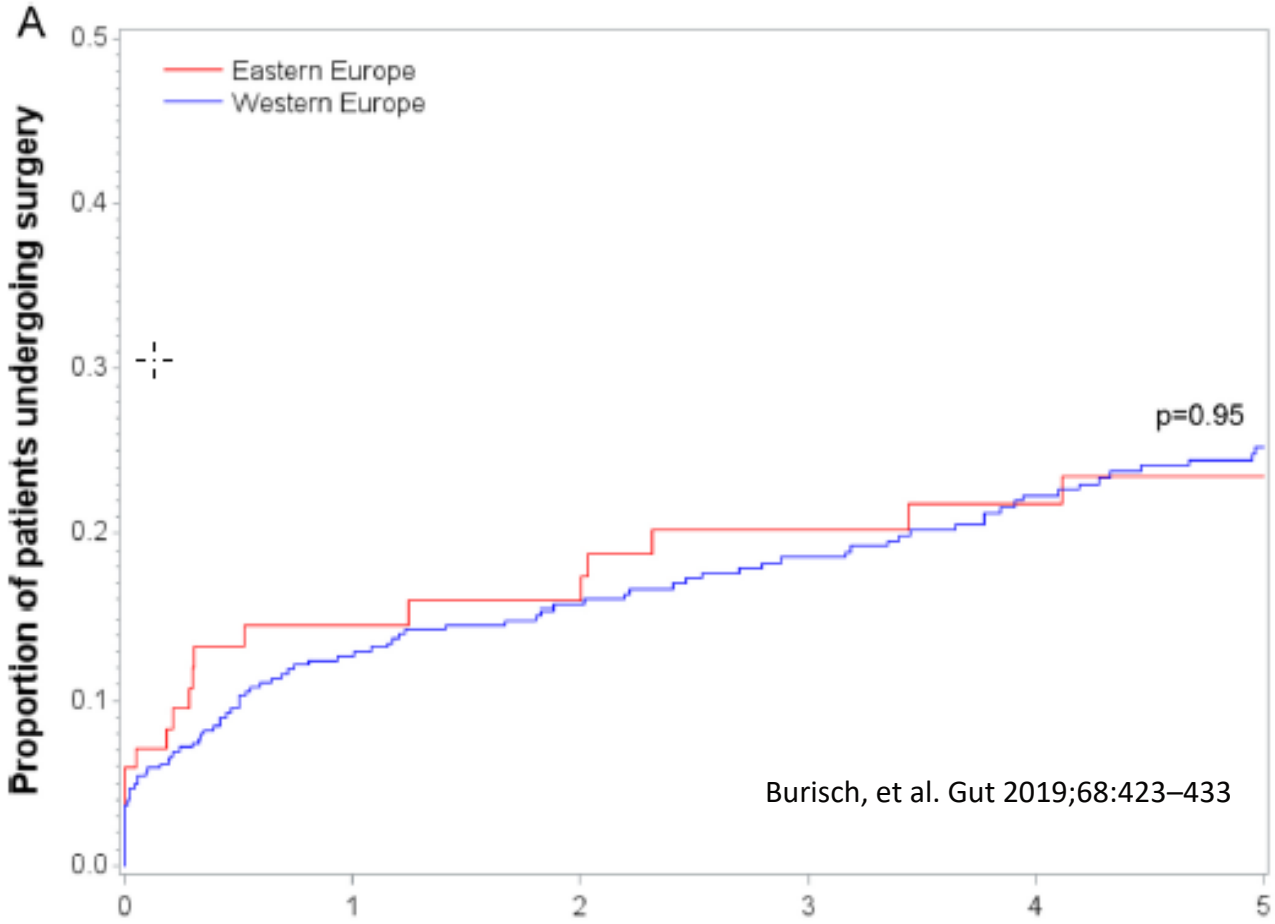
Kerur, et al. Clinical Gastroenterology and Hepatology 2018;16:1467–1473

Natural disease course of Crohn's disease in a European population-based inception cohort (Epi-IBD)

Epi-IBD cohort: A prospective population-based inception cohort of unselected patients with IBD from 29 European centres

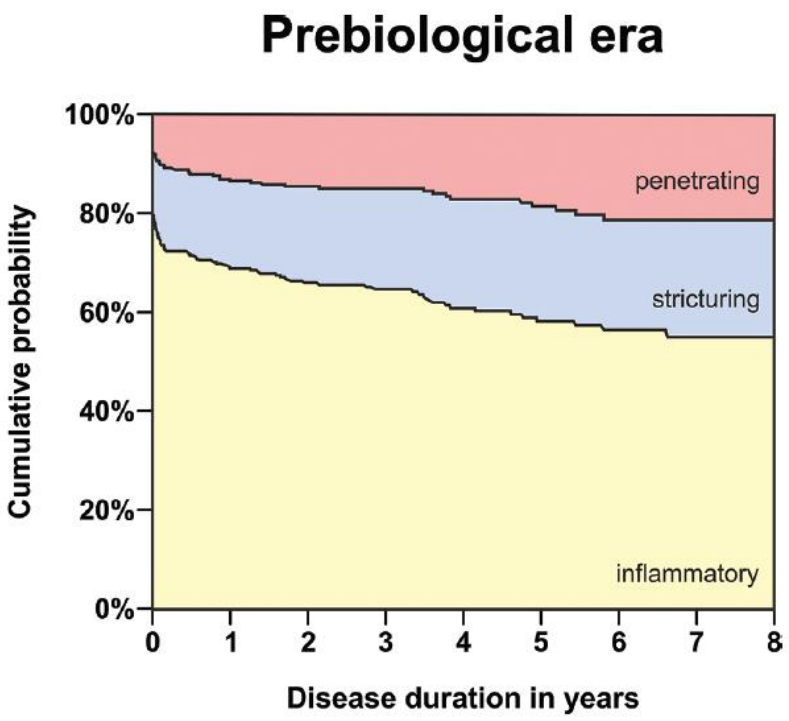
Despite geographic differences in treatment, the disease-course **did not differ** between Western and Eastern European patients.

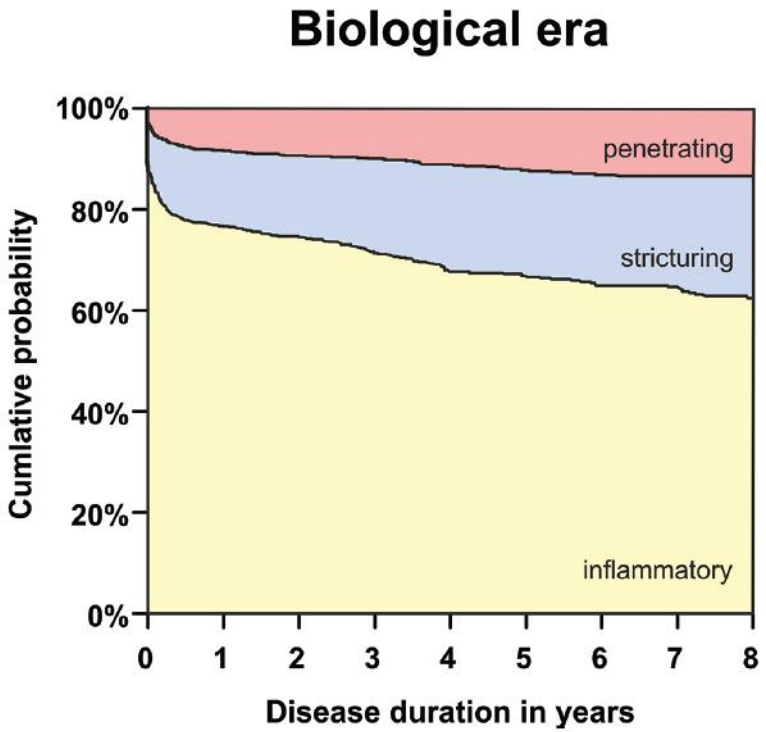
Five-year surgery, hospitalization and phenotype progression rates **are similar to cohorts from 20 years ago.**



Burisch, et al. Gut 2019;68:423–433

Does current medical therapy prevent intestinal damage?



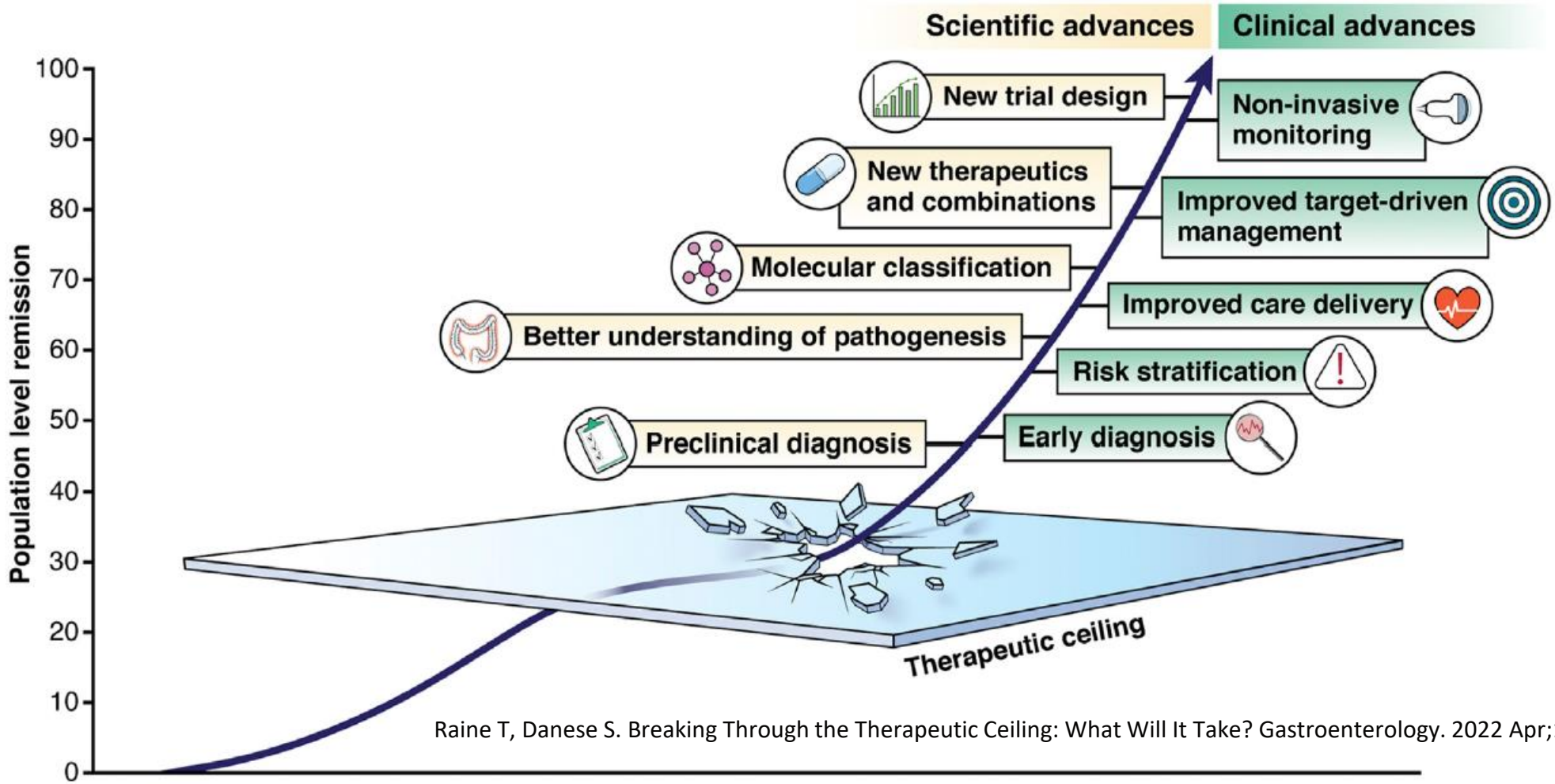


- Incident IBD cases South-Limburg Area; Population-based IBD cohort with >93% coverage
- «Pre-biological cohort»: 1991-1998
- «Biologic cohort»: 1999 – 2011 (Follow up until 2014)

➔ **Similar risk to develop fibrosis in the pre- and biological era**

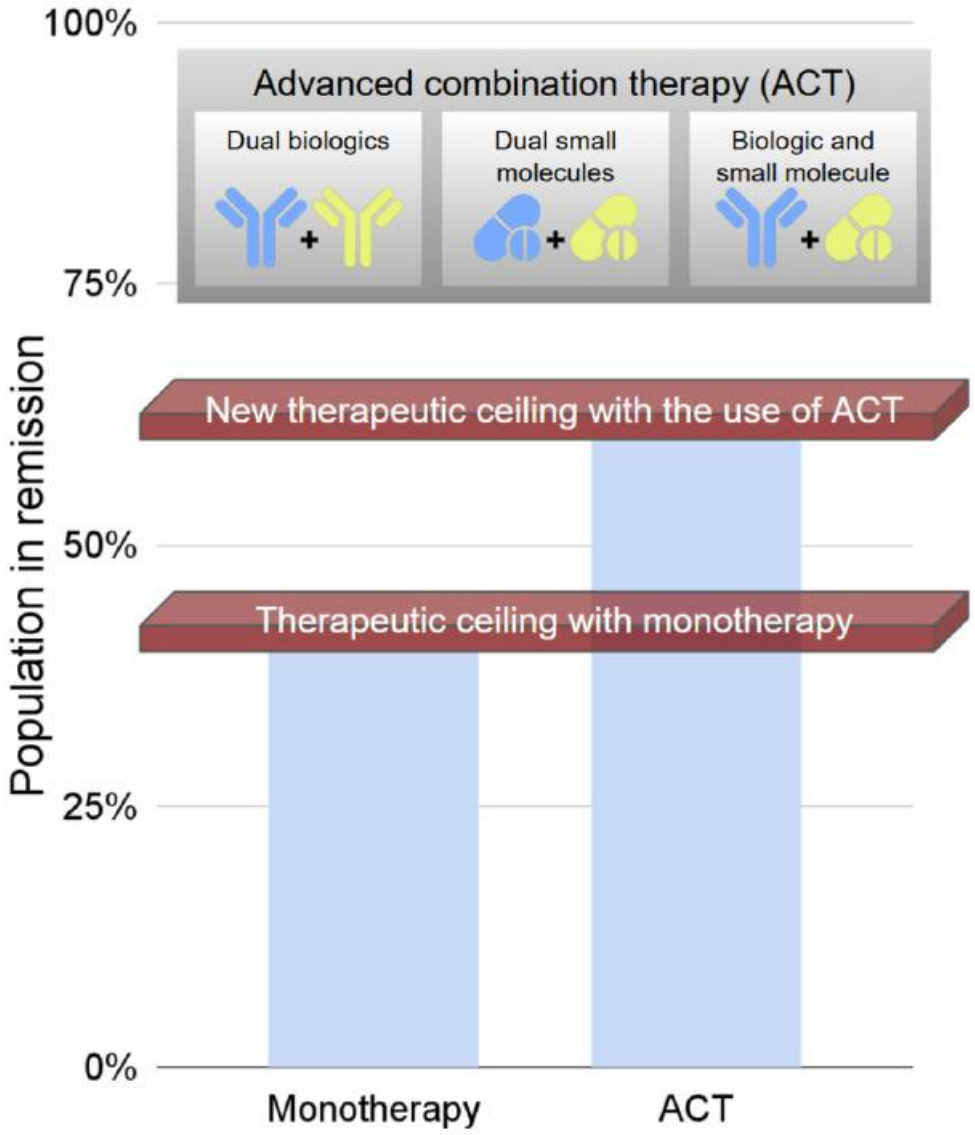
Steuring, et al. DDW2015, #79 (Oral)

Suggested solutions to break the “therapeutic ceiling”



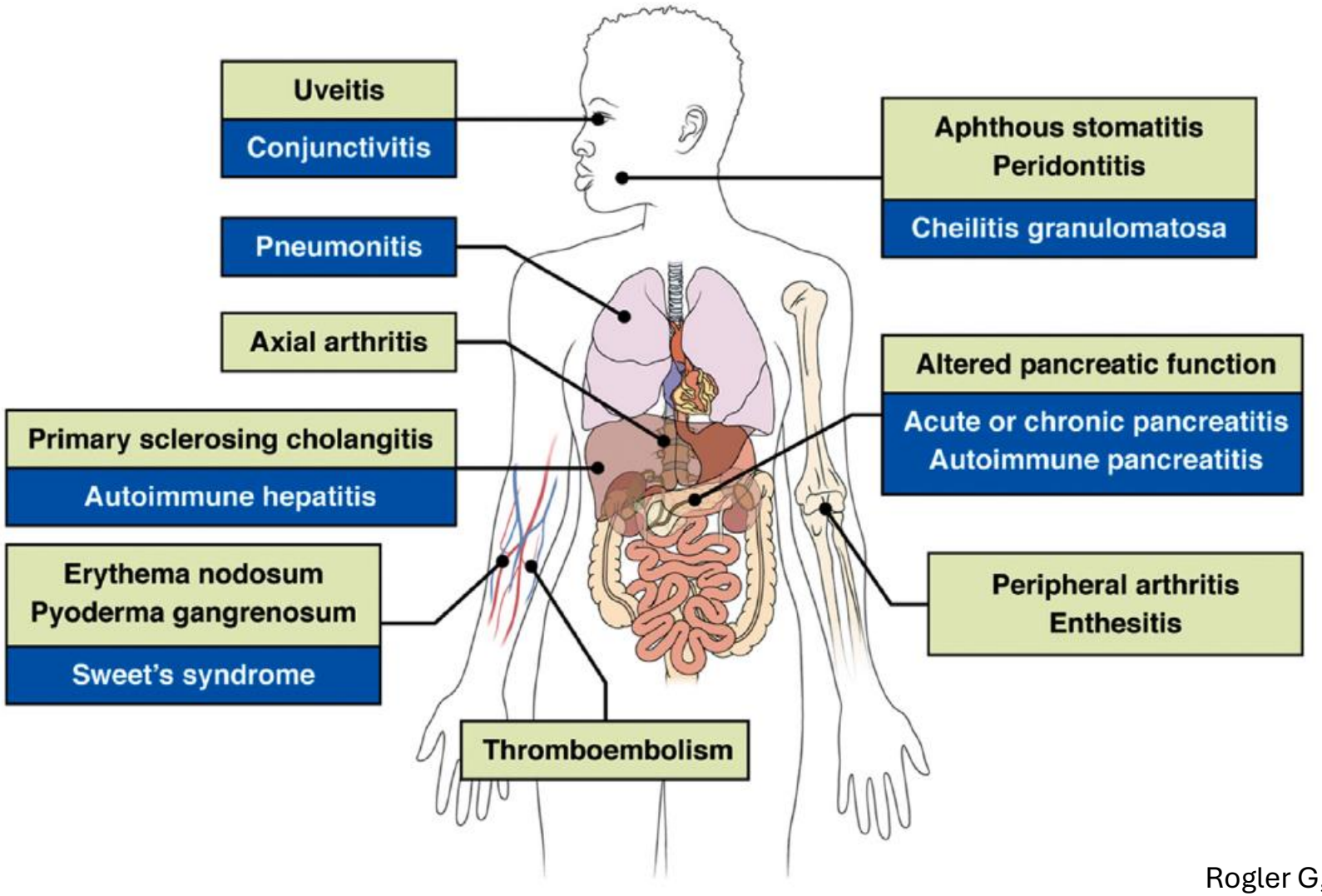
Raine T, Danese S. Breaking Through the Therapeutic Ceiling: What Will It Take? Gastroenterology. 2022 Apr;162(5):1507-1511

The Promise of Advanced Combination Treatment (ACT)?



Solitano V, Hanžel J, Estevinho MM, Sedano R, Massimino L, Ungaro F, Jairath V. Reaching the therapeutic ceiling in IBD: Can Advanced Combination Treatment (ACT) offer a solution? Best Pract Res Clin Gastroenterol. 2025 Aug;77:101981

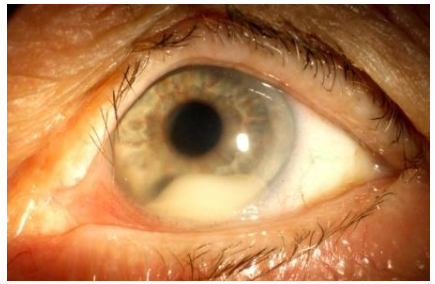
Extraintestinal manifestations

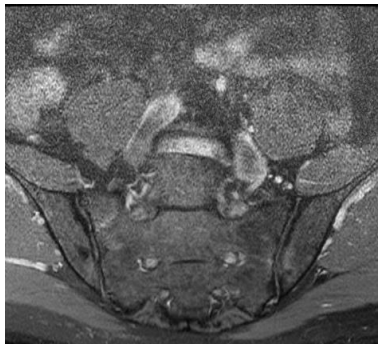


Rogler G, Singh A, Kavanaugh A, Rubin DT.
Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management.
Gastroenterology. 2021 Oct;161(4):1118-1132

Extraintestinal Manifestations of Inflammatory Bowel Disease

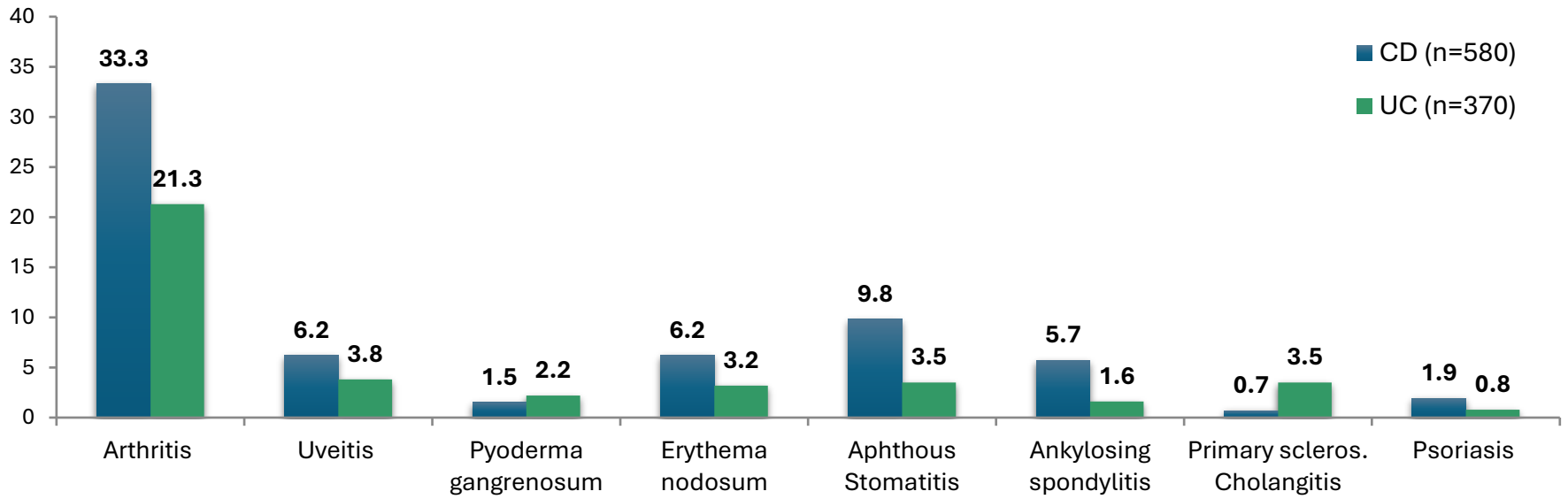
Stephan R. Vavricka, MD,[*,†] *Alain Schoepfer, MD,*[‡] *Michael Scharl, MD,*[*] *Peter L. Lakatos, MD,*[§] *Alexander Navarini, MD,*[‖] *and Gerhard Rogler, MD*[*]





Frequency and Risk Factors for Extraintestinal Manifestations in the Swiss Inflammatory Bowel Disease Cohort

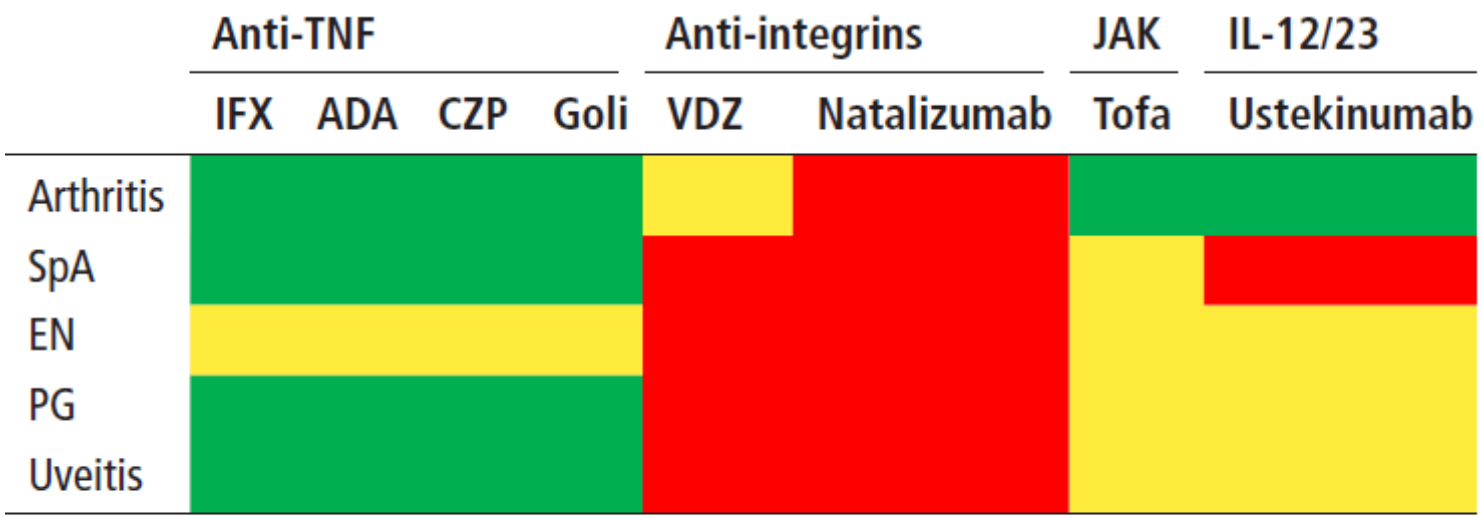
Stephan R. Vavricka, MD[1,6], Lionel Brun[1,6], Pierluigi Ballabeni[2], Valérie Pittet[2], Bettina Mareike Prinz Vavricka, MD[3], Jonas Zeitz, MD[1], Gerhard Rogler, MD[1], Alain M. Schoepfer, MD[4,5] and the Swiss IBD Cohort Study Group[7]



- CD patients with active disease were found to suffer significantly more frequently than patients with inactive disease from peripheral arthritis (45.1 vs. 31.3 % , P = 0.016), uveitis (12.2 vs. 5.2 % , P = 0.024), and aphthous stomatitis (17.1 vs. 8.6 % , P = 0.026).
- No difference in EIM frequency with regard to disease activity could be detected in UC patients.

Vavricka SR et al. Am J Gastroenterol. 2011 Jan;106(1):110-9

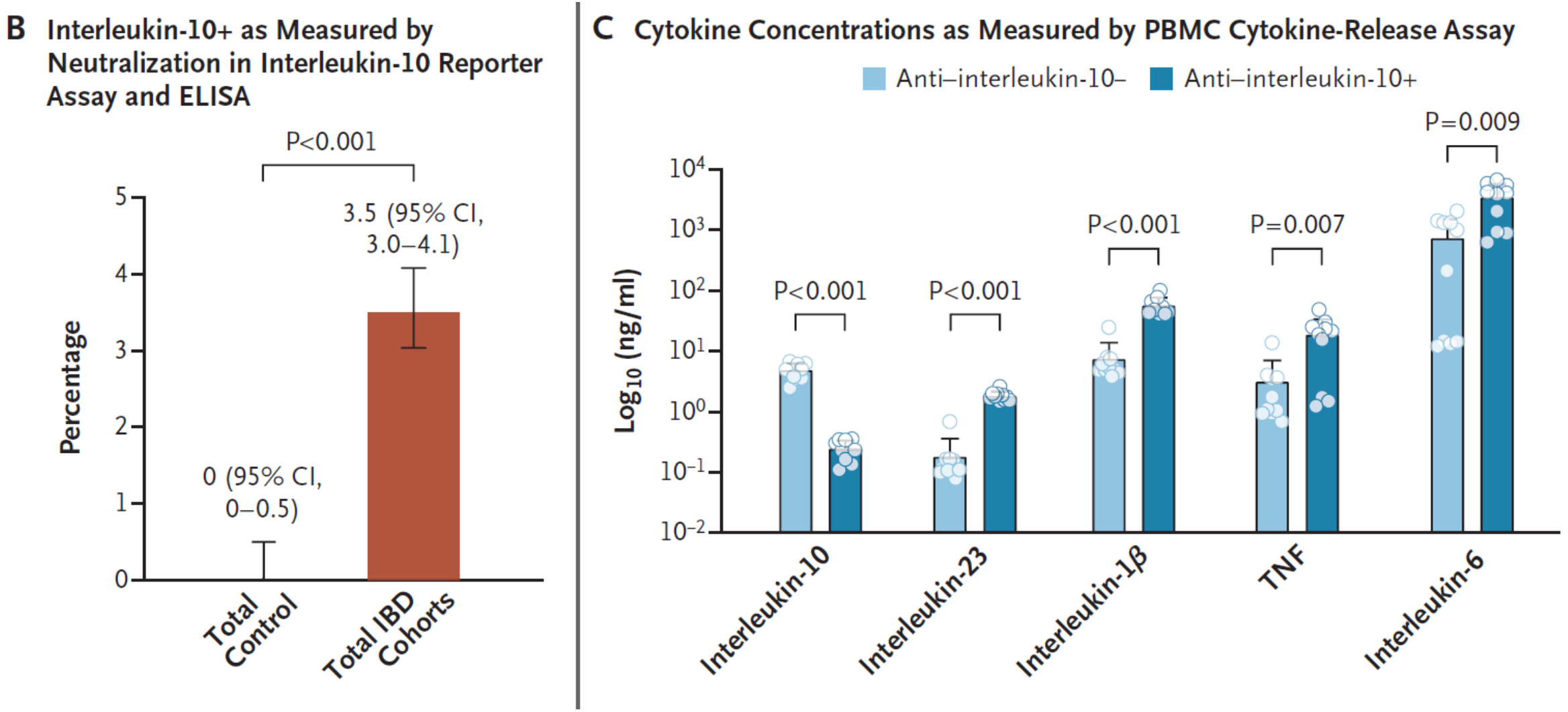
Emerging treatment options for EIMs in IBD



ADA, adalimumab; CZP, certolizumab; EN, erythema nodosum; Goli, golimumab; IFX, infliximab; IL, interleukin; JAK, Janus kinase; PG, pyoderma gangrenosum; SpA, axial spondyloarthropathy; TNF, tumour necrosis factor; Tofa, tofacitinib; VDZ, vedolizumab.

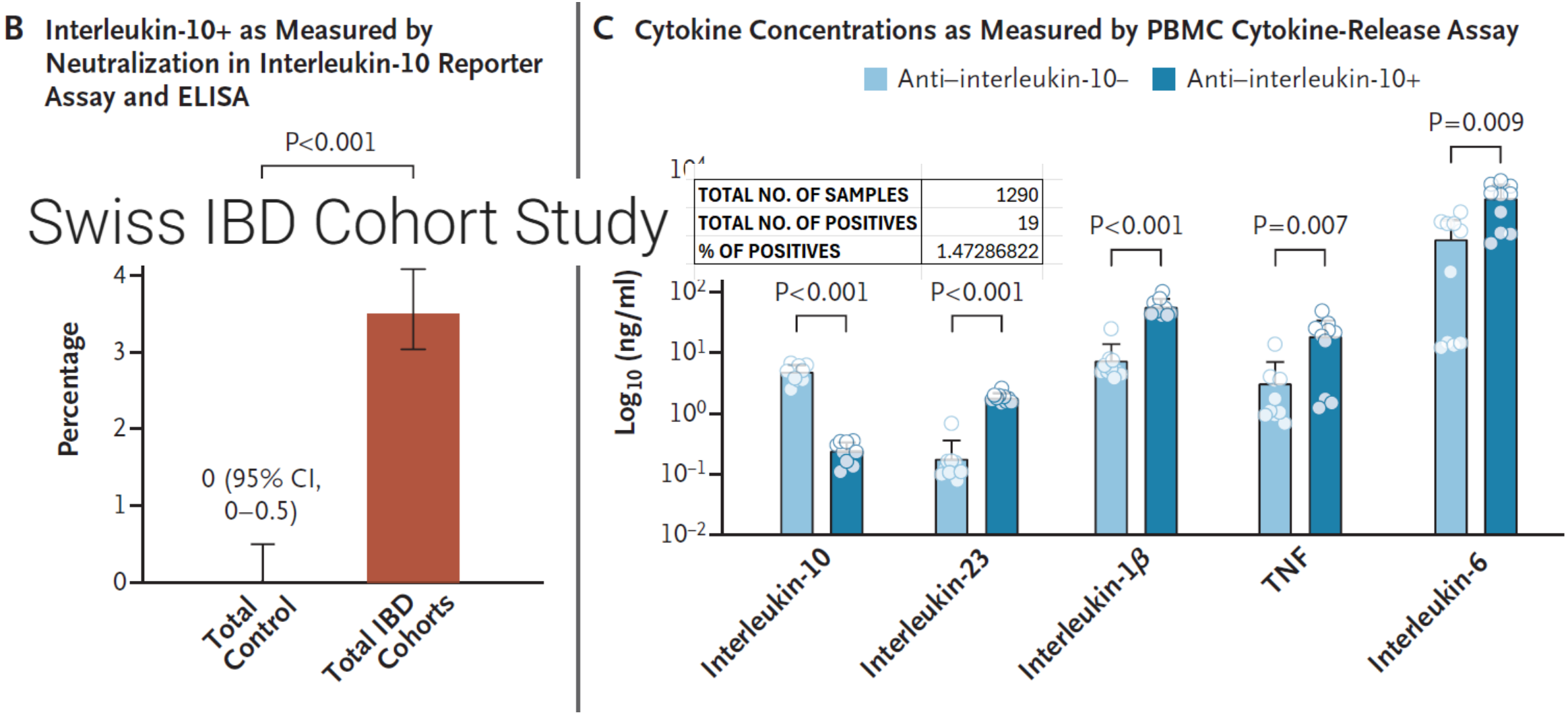
Greuter T, Rieder F, Kucharzik T, Peyrin-Biroulet L, Schoepfer AM, Rubin DT, Vavricka SR. Emerging treatment options for extraintestinal manifestations in IBD. Gut. 2021 Apr;70(4):796-802

Definition of Patient Subgroups



Gharahdaghi N, Yeh PJ, Ceron-Gutierrez L, ….. Uhlig HH. Interleukin-10 Autoantibodies and HLA-DRB1*01:03 in Inflammatory Bowel Disease. N Engl J Med. 2026 Jun 11;394(22):2212-2222

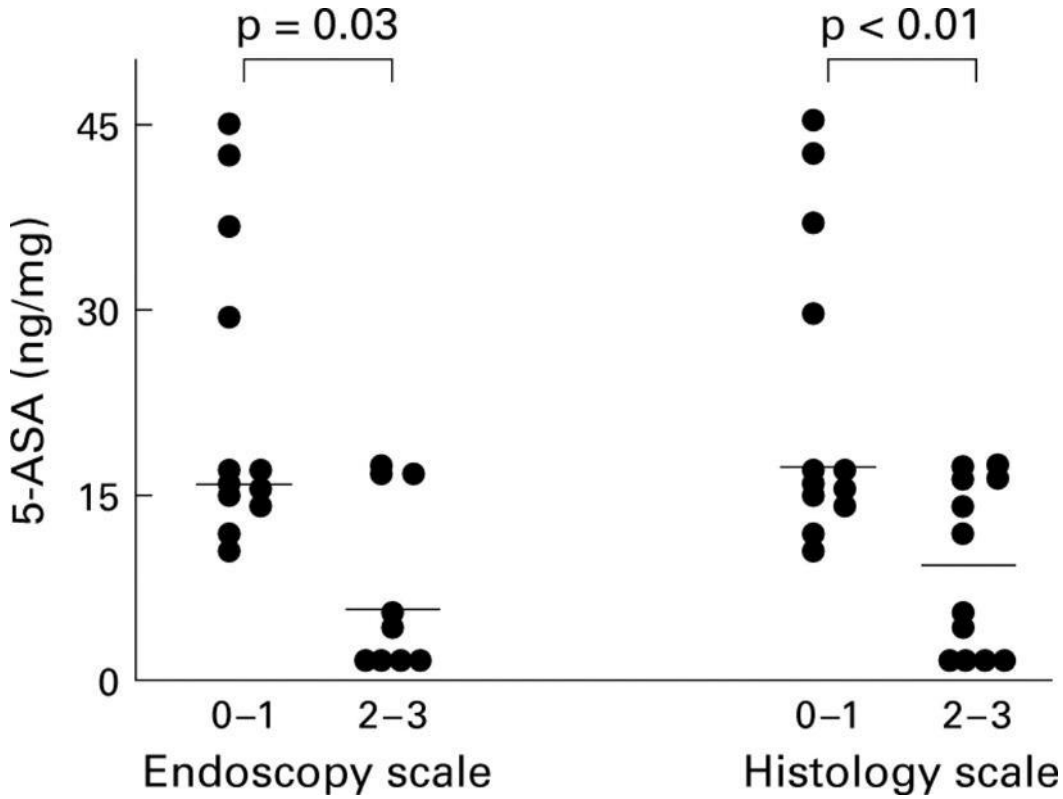
Definition of Patient Subgroups



Gharahdaghi N, Yeh PJ, Ceron-Gutierrez L, ….. Uhlig HH. Interleukin-10 Autoantibodies and HLA-DRB1*01:03 in Inflammatory Bowel Disease. N Engl J Med. 2026 Jun 11;394(22):2212-2222

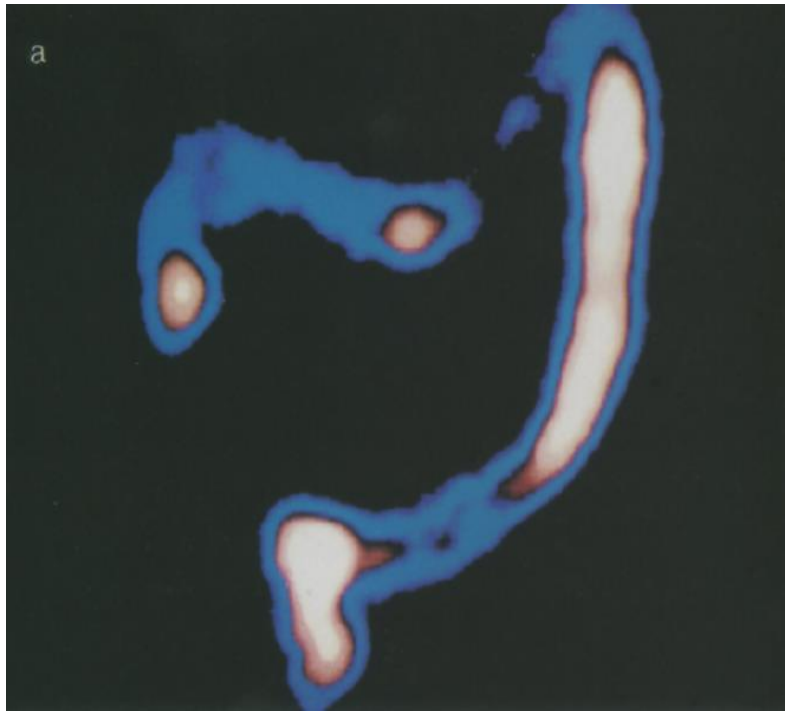
The impact of administration route: Mucosal concentrations are crucial

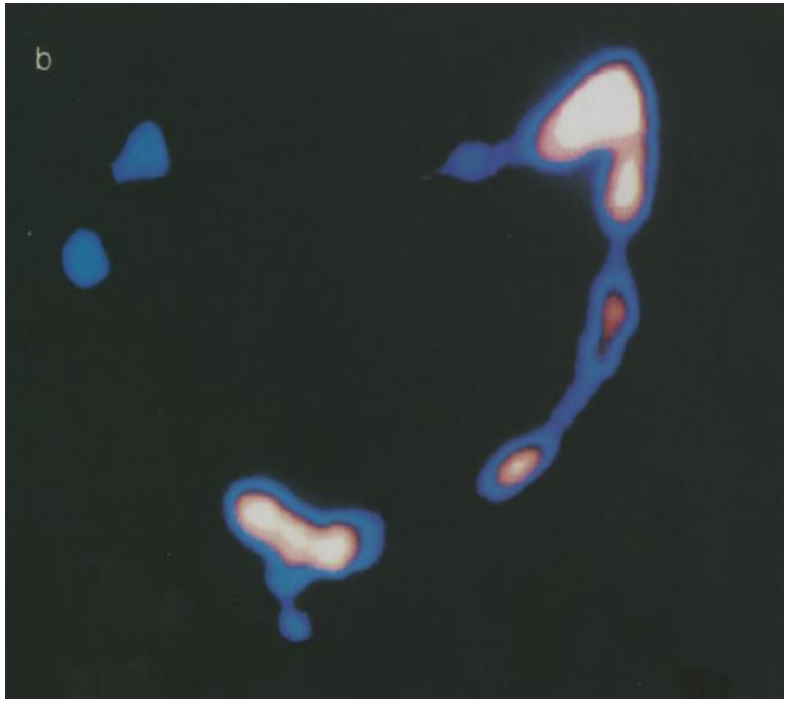
Distribution of 5-aminosalicylic acid (5-ASA) mucosal concentrations according to endoscopic and histological grading of colitis.



Frieri G et al. Gut 2000;47:410-414

Distribution of Foams and Enemas





Foam **Enema**

60 min after application

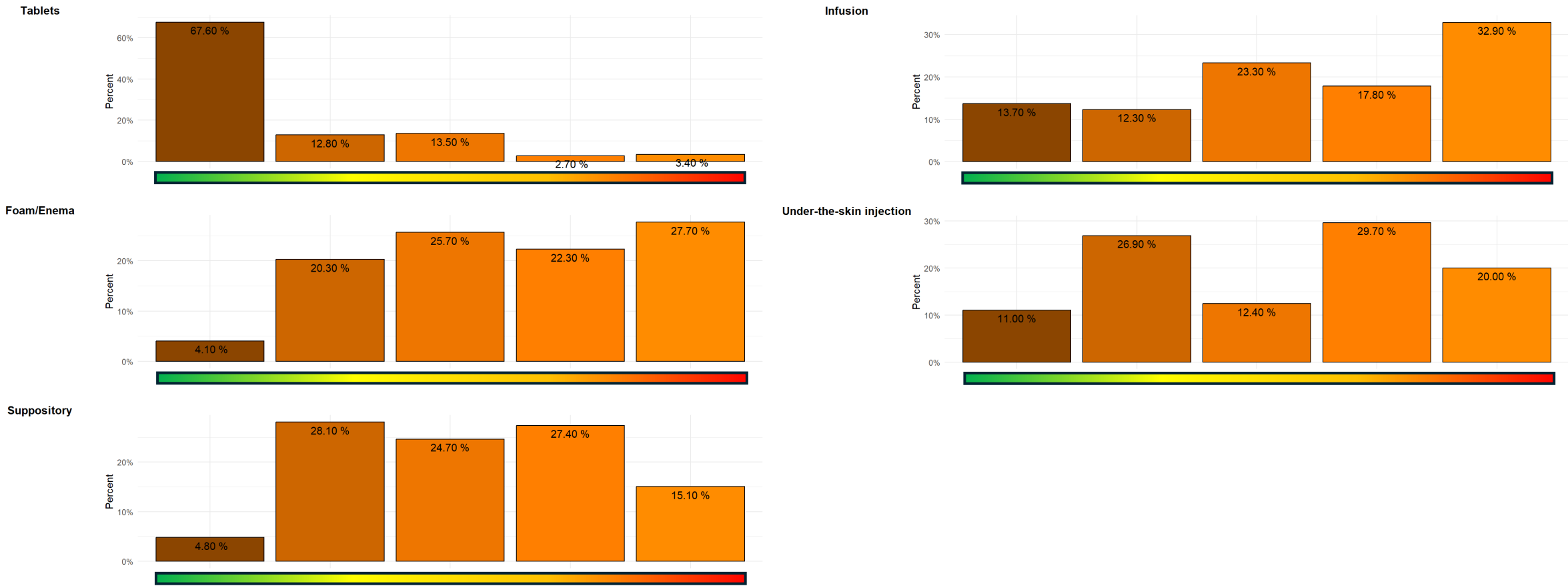
Campieri et al, Dig Dis Sci, 1992, pp. 1890-189

Patient survey: Convenience of topical therapy

- 35% of patients discontinued topical treatment prematurely
- Reasons for discontinuation:
  - Unpleasant application (51.3%)
  - Preference for tablets (51.3%)
  - Ineffectiveness (41.1%)

Kreienbühl A, Rogler R, Biedermann L, Maillard M, Pittet V on behalf of the Swiss IBDnet (SIBDCS) investigators. Gastroenterologists' and patients' perspective on the use of rectal 5-ASA formulations in ulcerative colitis patients. Unpublished data

Patient preferences



Kreienbühl A, Rogler R, Biedermann L, Maillard M, Pittet V on behalf of the Swiss IBDnet (SIBDCS) investigators. Gastroenterologists' and patients' perspective on the use of rectal 5-ASA formulations in ulcerative colitis patients. Unpublished data

- messages: Current Therapeutic Challenges in IBD Therapy

- The therapeutic management of IBD remains challenging despite major advances with biologics and small molecules.
- The “therapeutic ceiling” makes it difficult for many patients to find an effective drug
- Long-term disease control is still challenging
- Personalized medicine (finding the right drug for the right patient) is difficult as no predictive markers exist
- EIMs may have significant influence of the Quality of life
- First patient subgroups have recently been identified (IL-10 AB +) ➔ specific therapies
- Fibrosis and fistula formation cannot be targeted
- Topical (rectal) therapy would be preferable (higher drug concentrations, less systemic effects) but is less tolerated by the patients

Thank you for your attention