

IBD Treatment

Ali Keshavarzian MD



- Diffuse mucosal inflammation limited to colon
- Affects rectum
- May involve all or part of rest of colon



- Patchy transmural inflammation
- May affect any part of GI tract



IBD treatment: Where are we

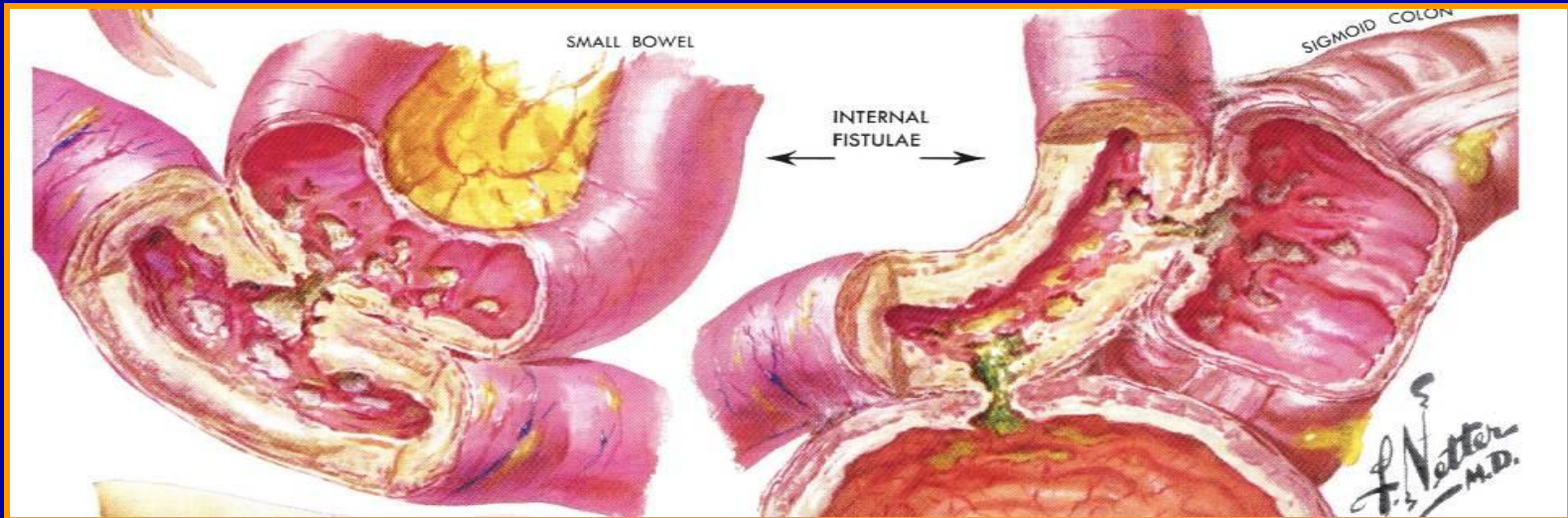
- Goals
 - Induce remission
 - Maintain remission
 - Reduce complications
 - Improve quality of life
- How this is achieved
 - Step-up approach

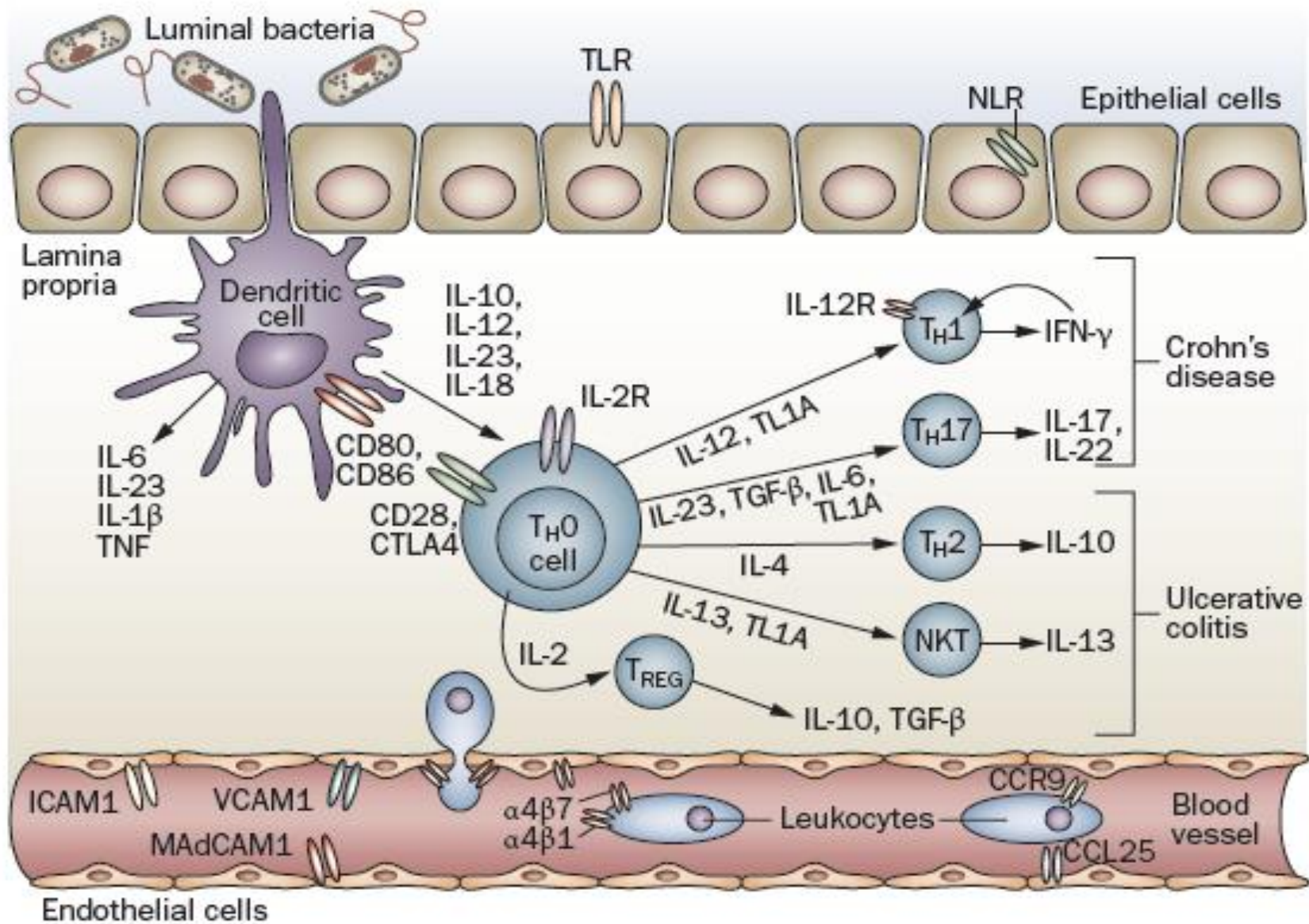
IBD treatment: Where we are headed

- Goals
 - Previous goals AND
 - Change the natural history of the disease (reduce steroid dependence, durably heal the mucosa, and reduce hospitalization/surgery).
- How this is achieved
 - Earlier use of stronger medication-”Top-down approach”

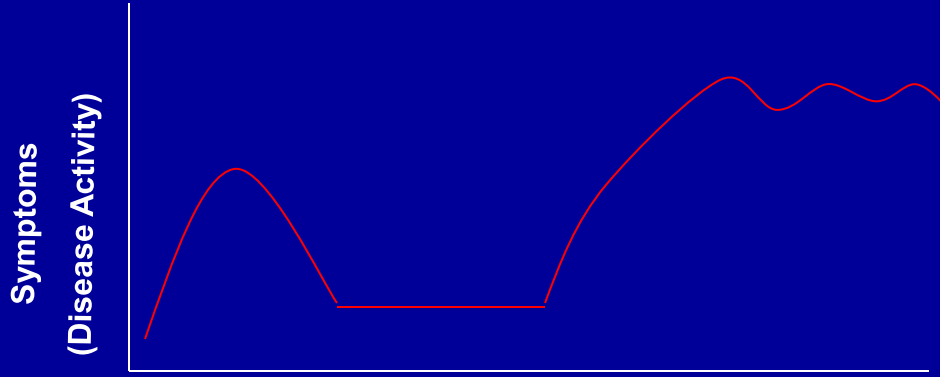
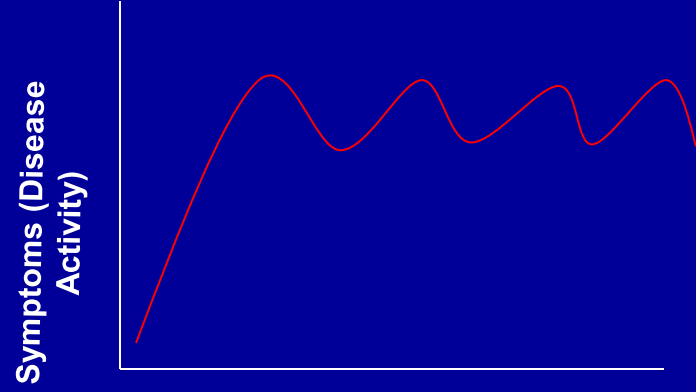
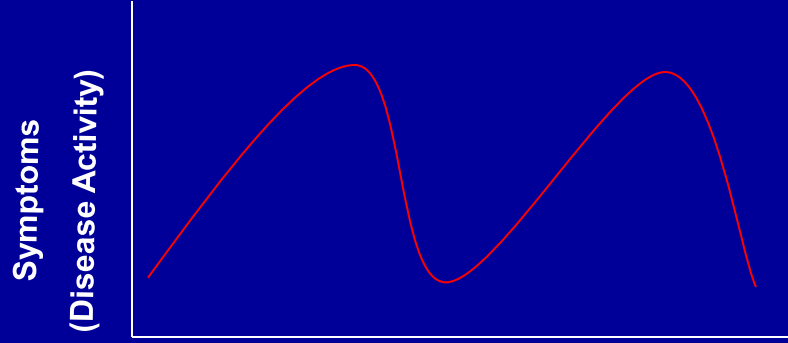
History of Crohn's

- First described in 1932 by Dr. Burrill B. Crohn
- Original treatments were either sulfasalazine and/or prednisone





IBD CLINICAL COURSE



IBD - Environmental Triggers

Altered flora

Antibiotics



Diet



IBD
Onset and
Reactivation

Altered barrier functions

Acute infections



NSAIDs



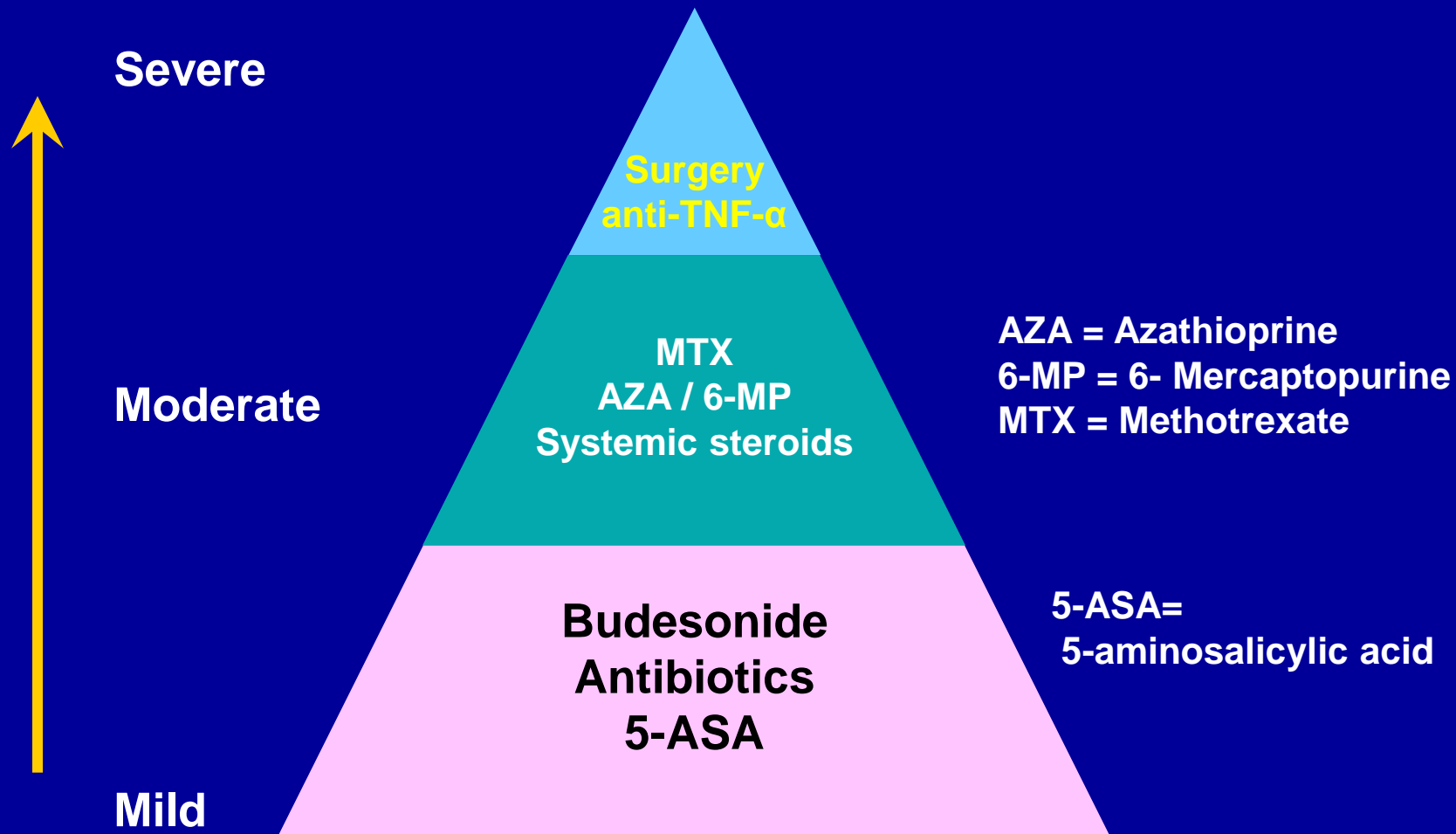
Smoking



Stress



Current “Therapeutic Pyramid” for Crohn's disease



Adapted from: Hanauer et al, Am J Gastroenterol 2001; 96: 635

Aminosalicylates



Sulfasalazine

Oral preparations

Mesalamine

- Acrylate coated
- Ethylcellulose encapsulated



Rectal preparations



Mesalamine

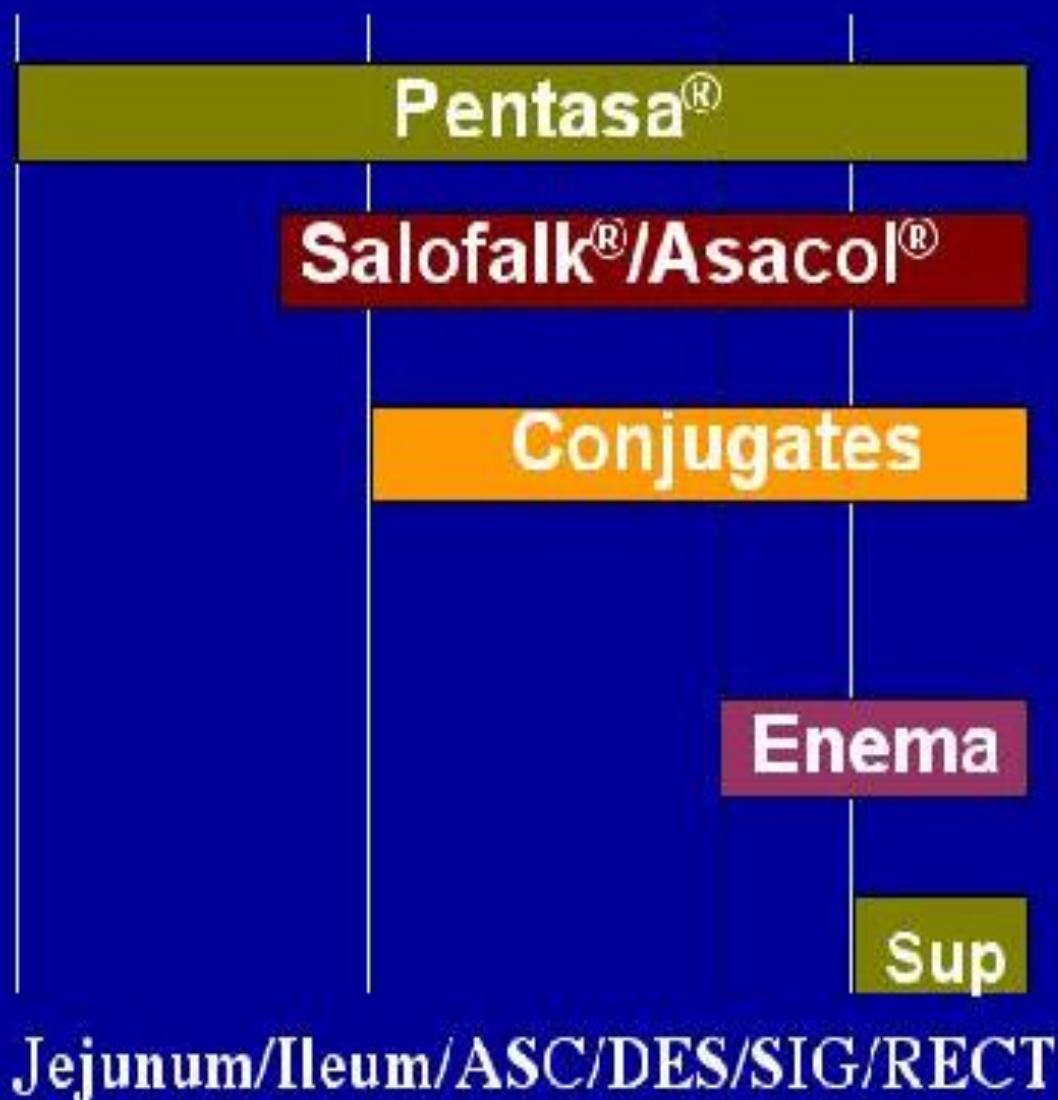
Balsalazide — Inert vehicle



Olsalazine — 5-ASA dimer

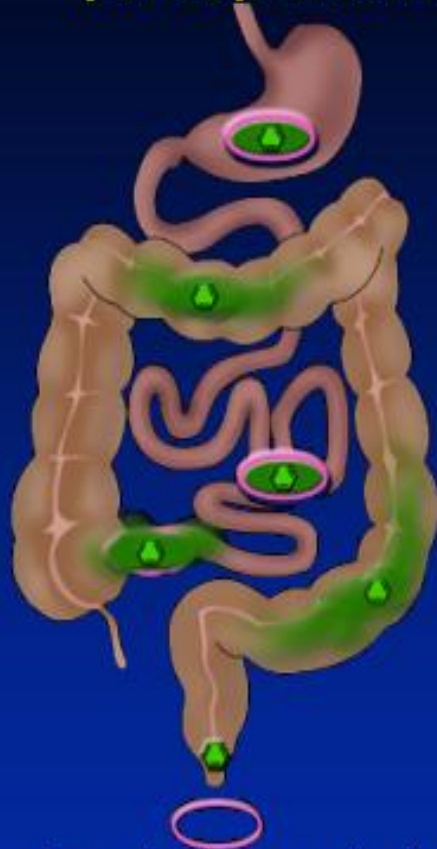


5-ASA Delivery Systems: Sites of Action



IBD - Oral Aminosalicylate Delivery

pH-dependent



**Acrylate-coated
mesalamine**

**Asacol[®], Claversal[®],
Salofalk[®], Roffersal[®]**

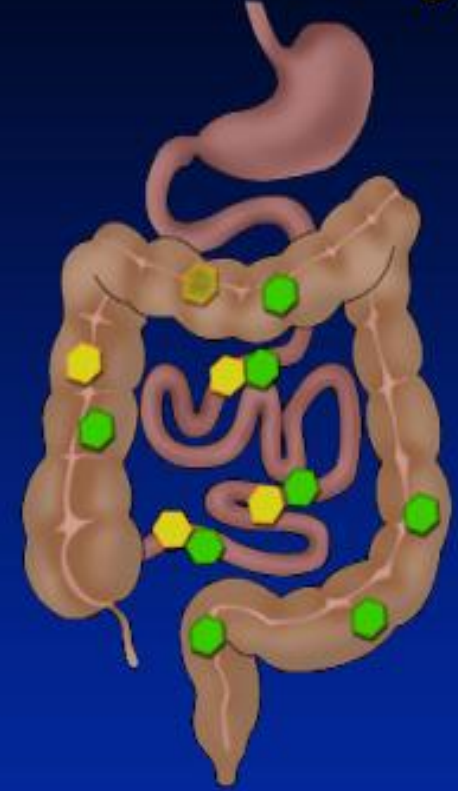
Time release



**Ethylcellulose-
encapsulated
mesalamine**

Pentasa[®]

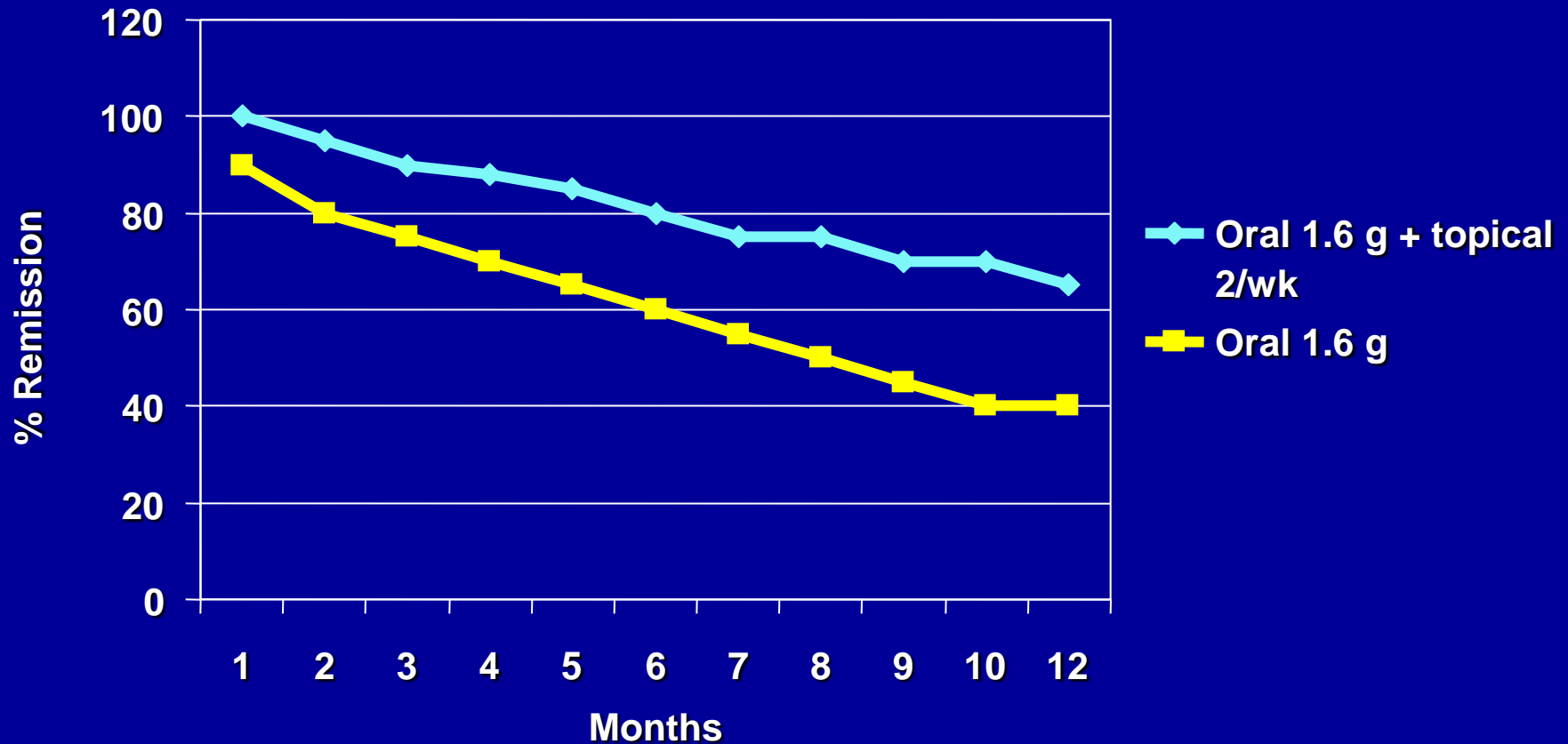
Bacterial cleavage



**Azobond - linked
5-ASA**

**Sulfasalazine - Azulfidine[®]
Olsalazine - Dipentum[®]
Balsalazide - Colazal[®]**

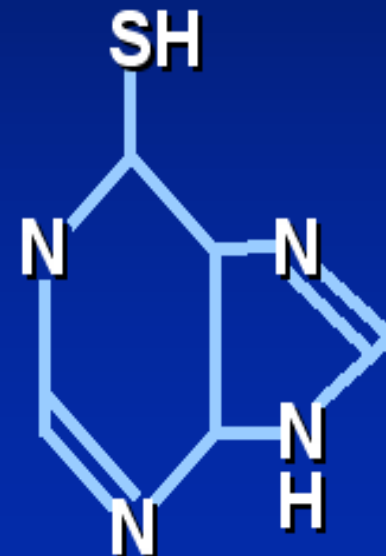
Combined Oral + Topical Mesalamine for Maintenance of Distal UC



Azathioprine



6-Mercaptopurine



RBC



CD - Maintenance Therapy

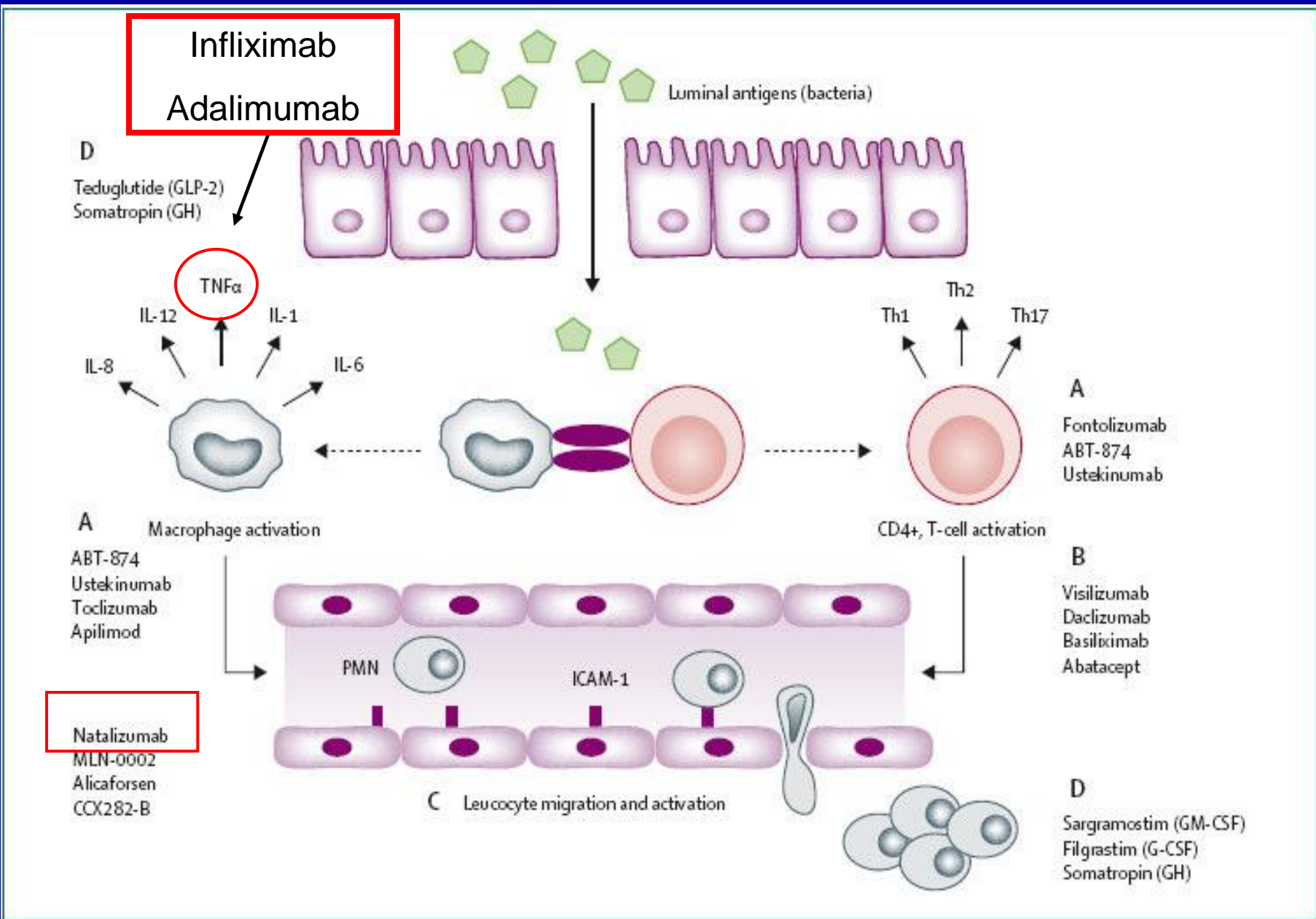


II. New biologic agents for IBD

Anti-TNF-alpha agents

Anti-IL-12/anti-IL23

Natalizumab



Infliximab
Adalimumab

D
Teduglutide (GLP-2)
Somatropin (GH)

TNF α

IL-12, IL-1, IL-8, IL-6

Luminal antigens (bacteria)

Th1, Th2, Th17

A
Fontolizumab
ABT-874
Ustekinumab

A
Macrophage activation
ABT-874
Ustekinumab
Tocilizumab
Apilimod

CD4+, T-cell activation

B
Vilizumab
Daclizumab
Basiliximab
Abatacept

Natalizumab
MLN-0002
Alicaforsen
CCX282-B

PMN

ICAM-1

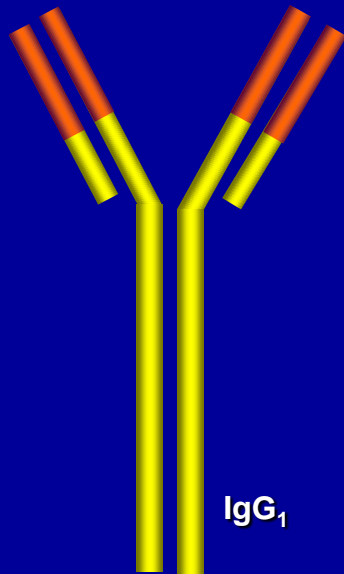
C Leucocyte migration and activation

D
Sargramostim (GM-CSF)
Filgrastim (G-CSF)
Somatropin (GH)

Figure 1: Overview of therapeutic targets in Crohn's disease: cytokine therapies (A), T-cell blocking agents (B), antiadhesion molecules (C), and growth factors (D)

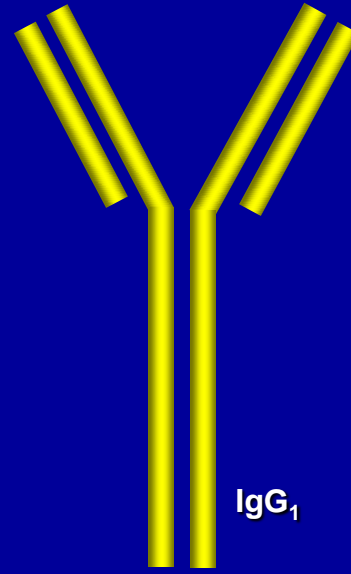
Construct of Anti-TNF- α Biologic Agents

Infliximab



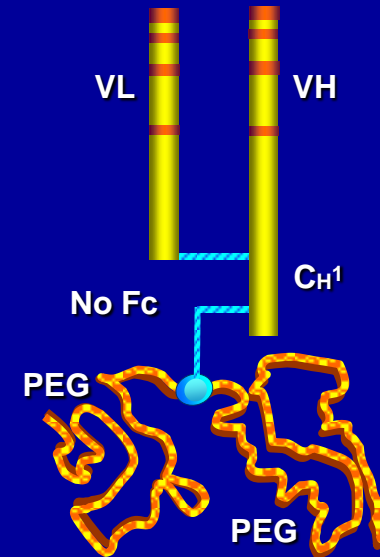
Chimeric monoclonal antibody (75% human IgG₁ isotype)

Adalimumab



Human recombinant antibody (100% human IgG₁ isotype)

Certolizumab Pegol



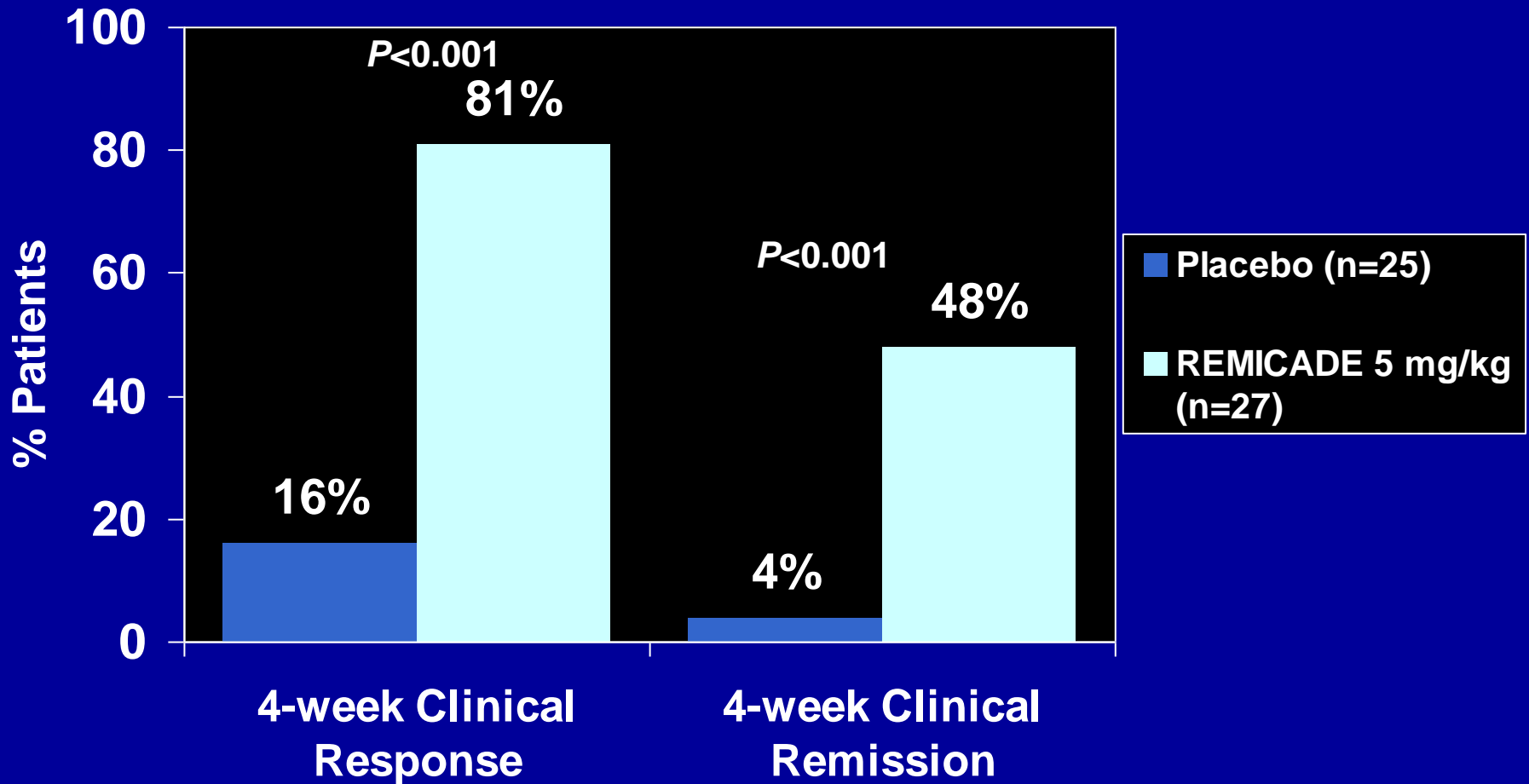
Humanized Fab' fragment (95% human IgG₁ isotype)

Mouse

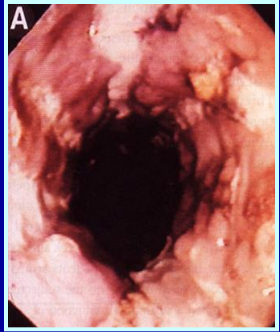
Human

PEG, polyethylene glycol.

Clinical Response and Remission with Infliximab



Biologic era in IBD management: Healing of refractory ulceration/fistula with Infliximab



Pretreatment



4 Weeks
posttreatment

Pretreatment



2 Weeks



10 Weeks



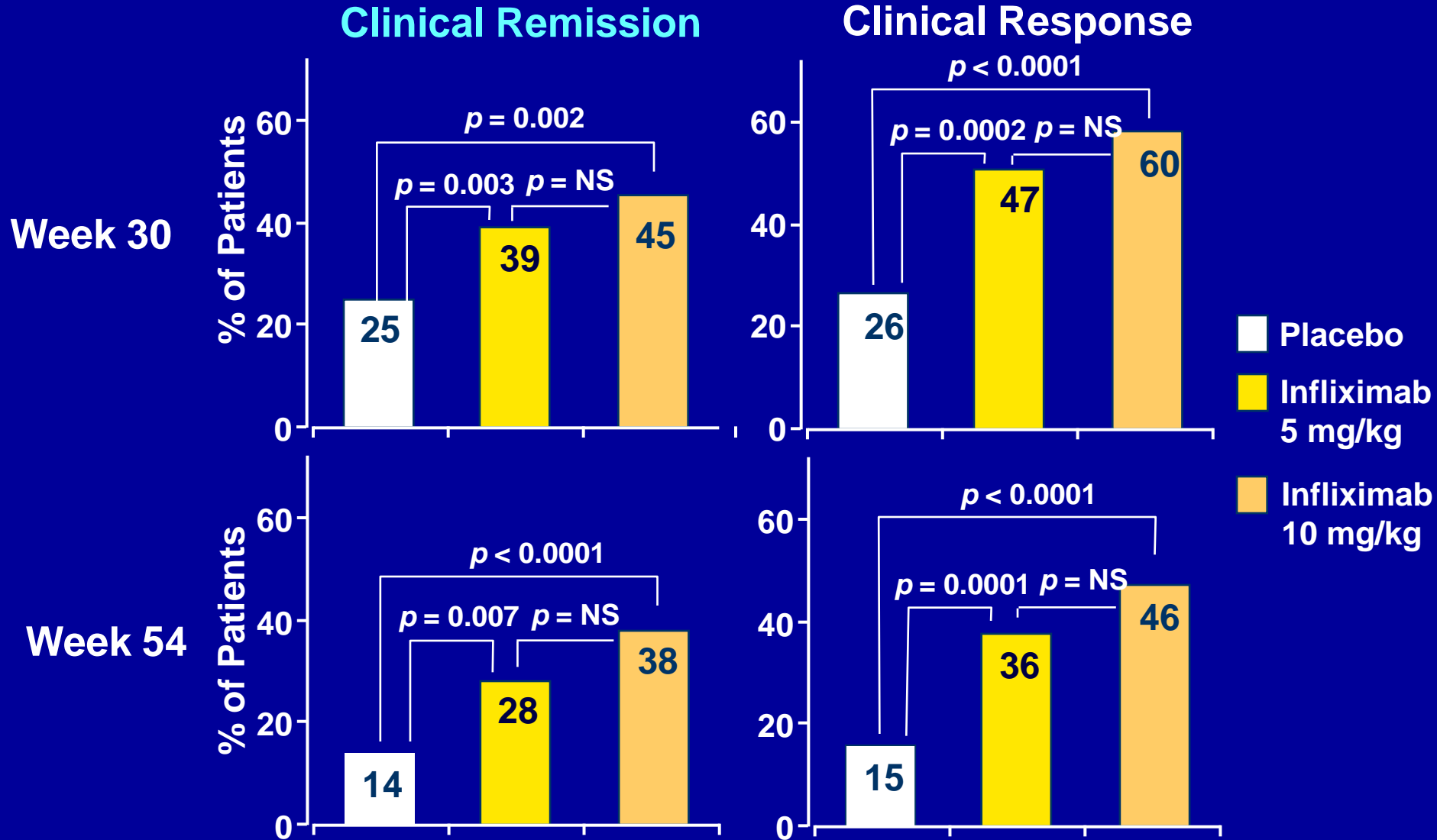
18 weeks



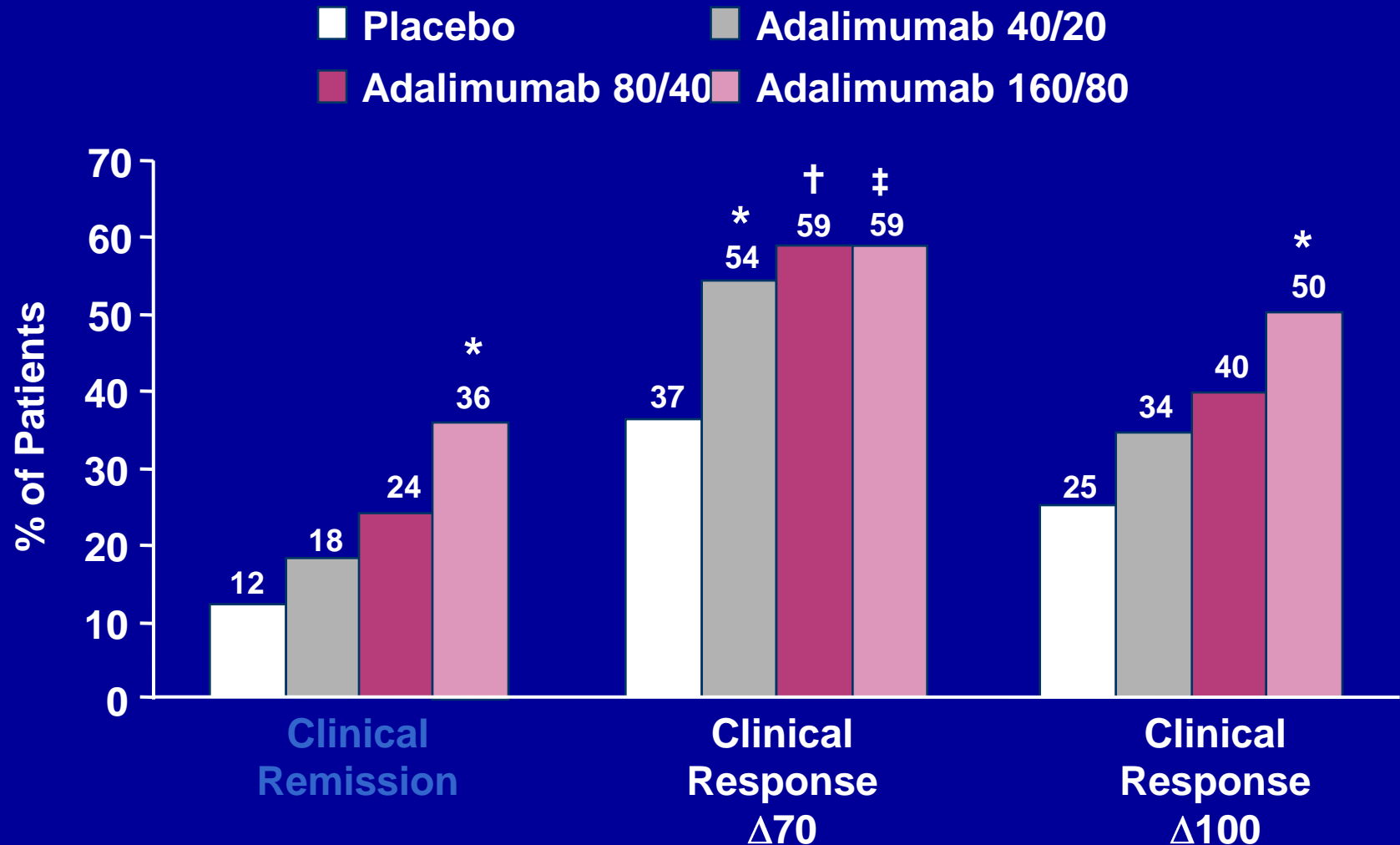
van Dullemen HM et al. *Gastroenterology*. 1995;109:129.

Present DH, et al. *N Engl J Med*. 1999;340:1398–1405.

ACCENT I: Maintenance Infliximab for CD in Randomized Responders (N = 335)



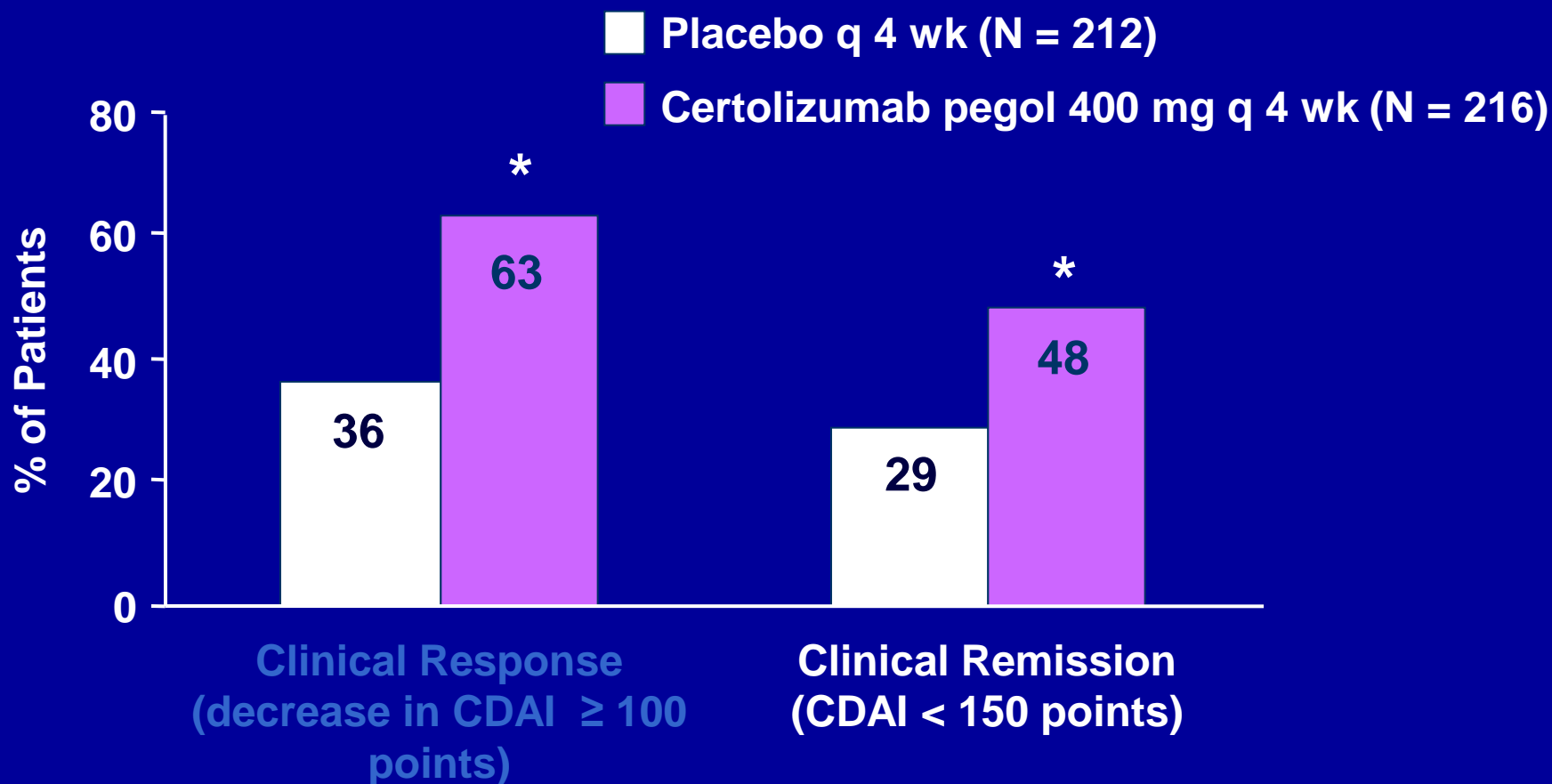
CLASSIC I: Results at Week 4



* $p < 0.05$ vs placebo; [†] $p = 0.001$ vs placebo; [‡] $p = 0.007$ vs placebo.

Clinical remission = CDAI < 150; Clinical response = $\Delta 70$ or $\Delta 100$ is a ≥ 70 or ≥ 100 point decrease in CDAI from baseline.

PRECiSE 2: Clinical Response and Remission at Week 26 in Patients With CD Randomized Responders (N = 428)



* $p < 0.001$ vs placebo.

Schreiber S, et al. *Gut*. 2005;54(Suppl VII):A82.

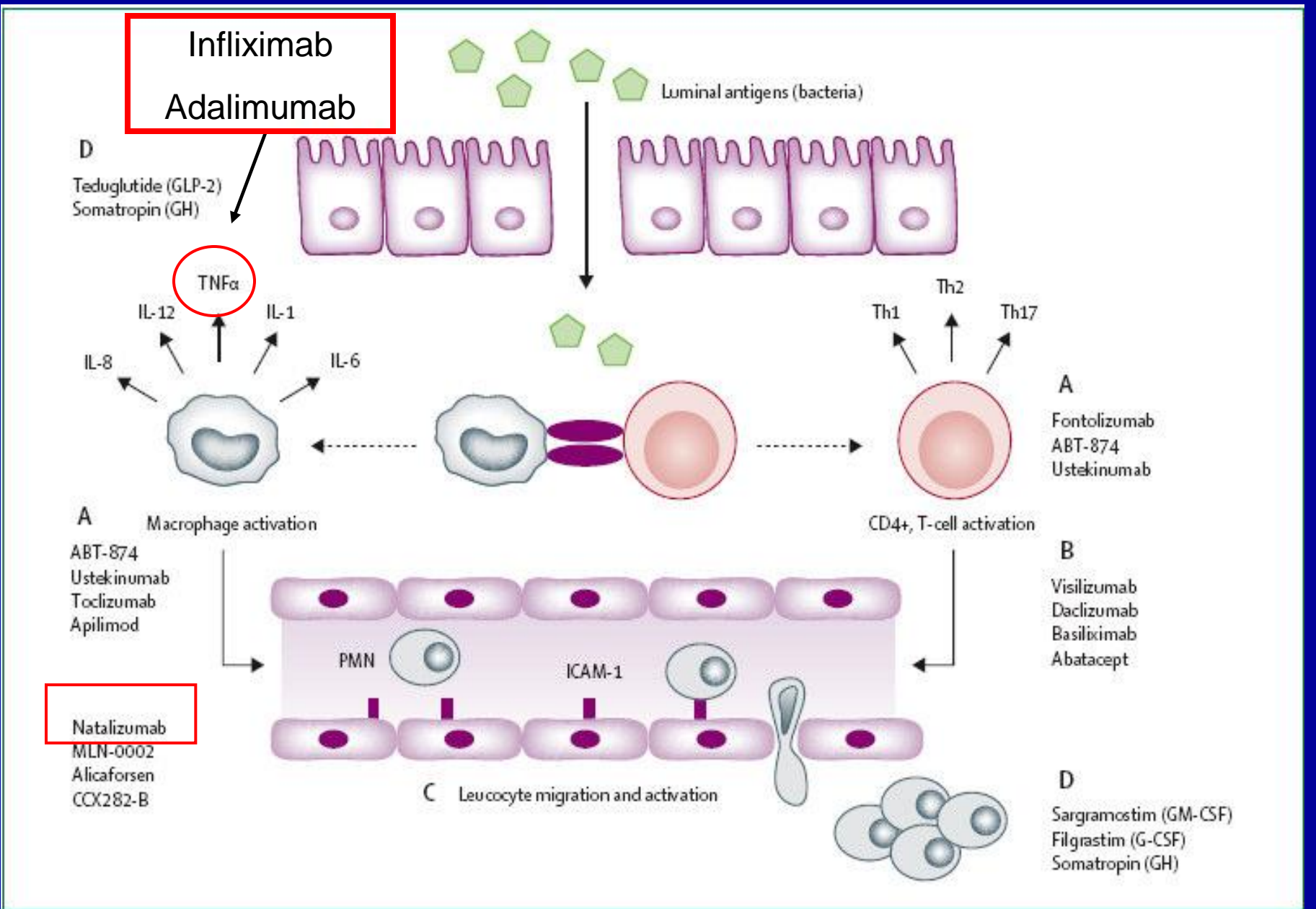
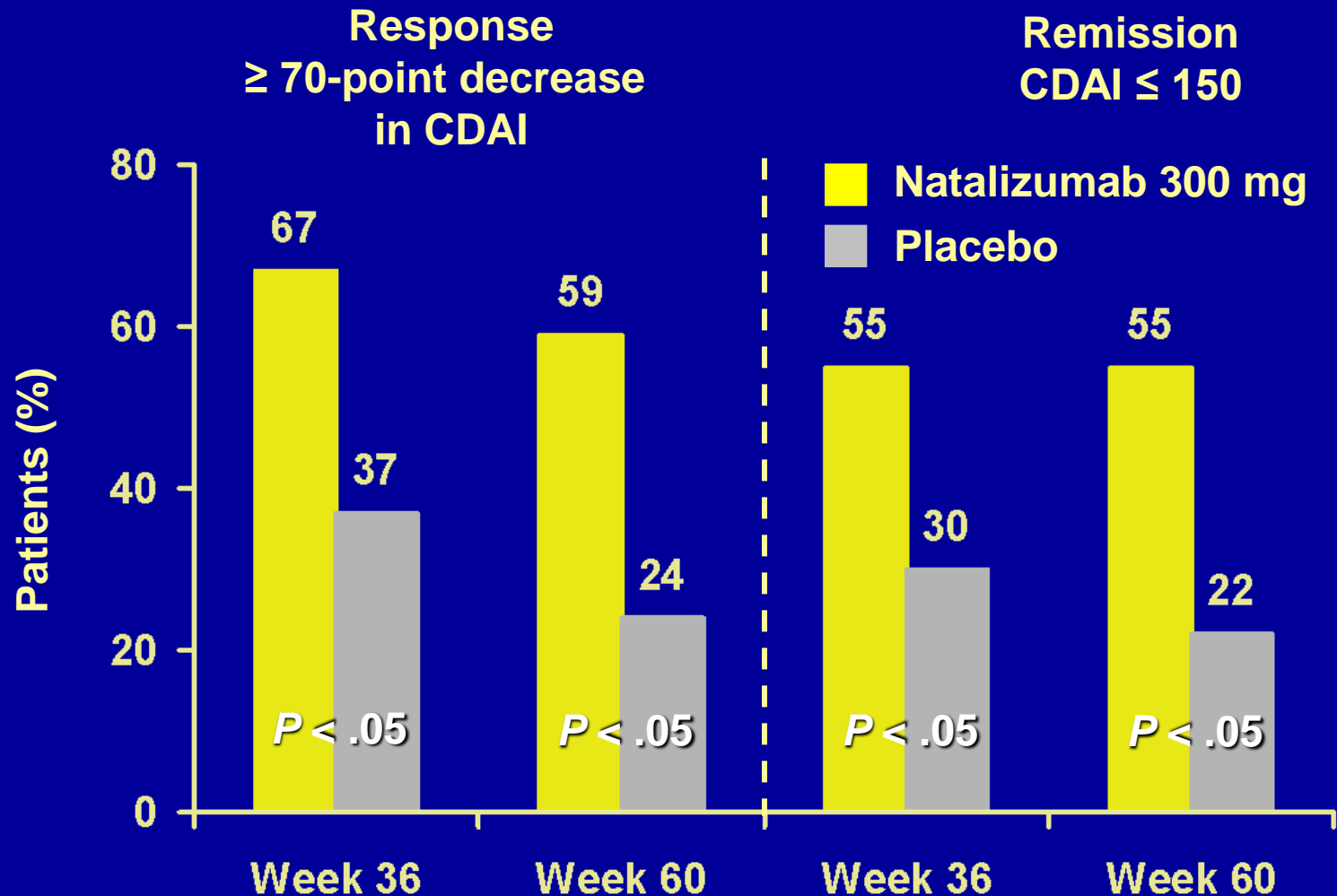


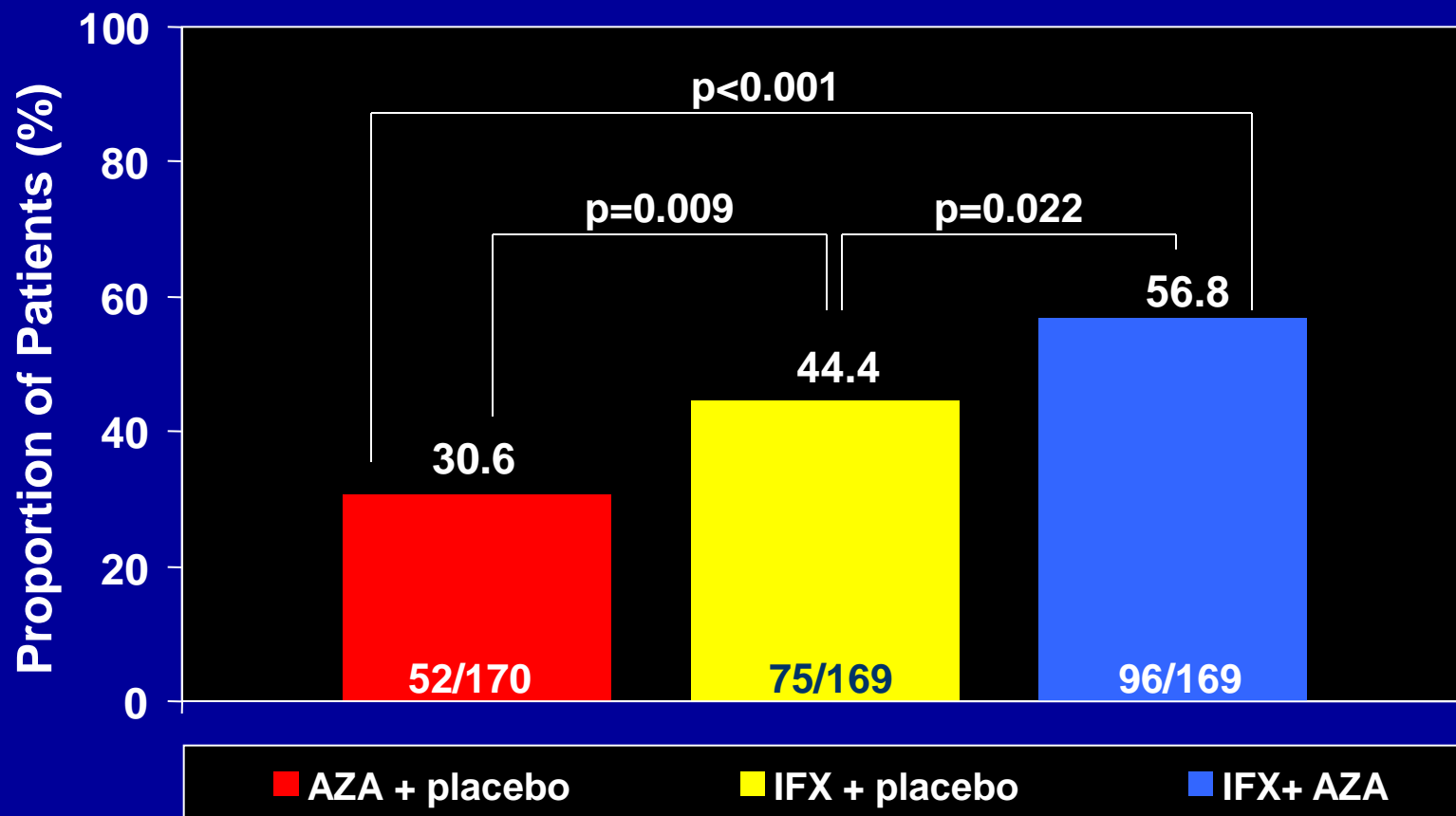
Figure 1: Overview of therapeutic targets in Crohn's disease: cytokine therapies (A), T-cell blocking agents (B), antiadhesion molecules (C), and growth factors (D)

Natalizumab as Maintenance Therapy for Crohn's Disease: *ENACT-2 Trial*

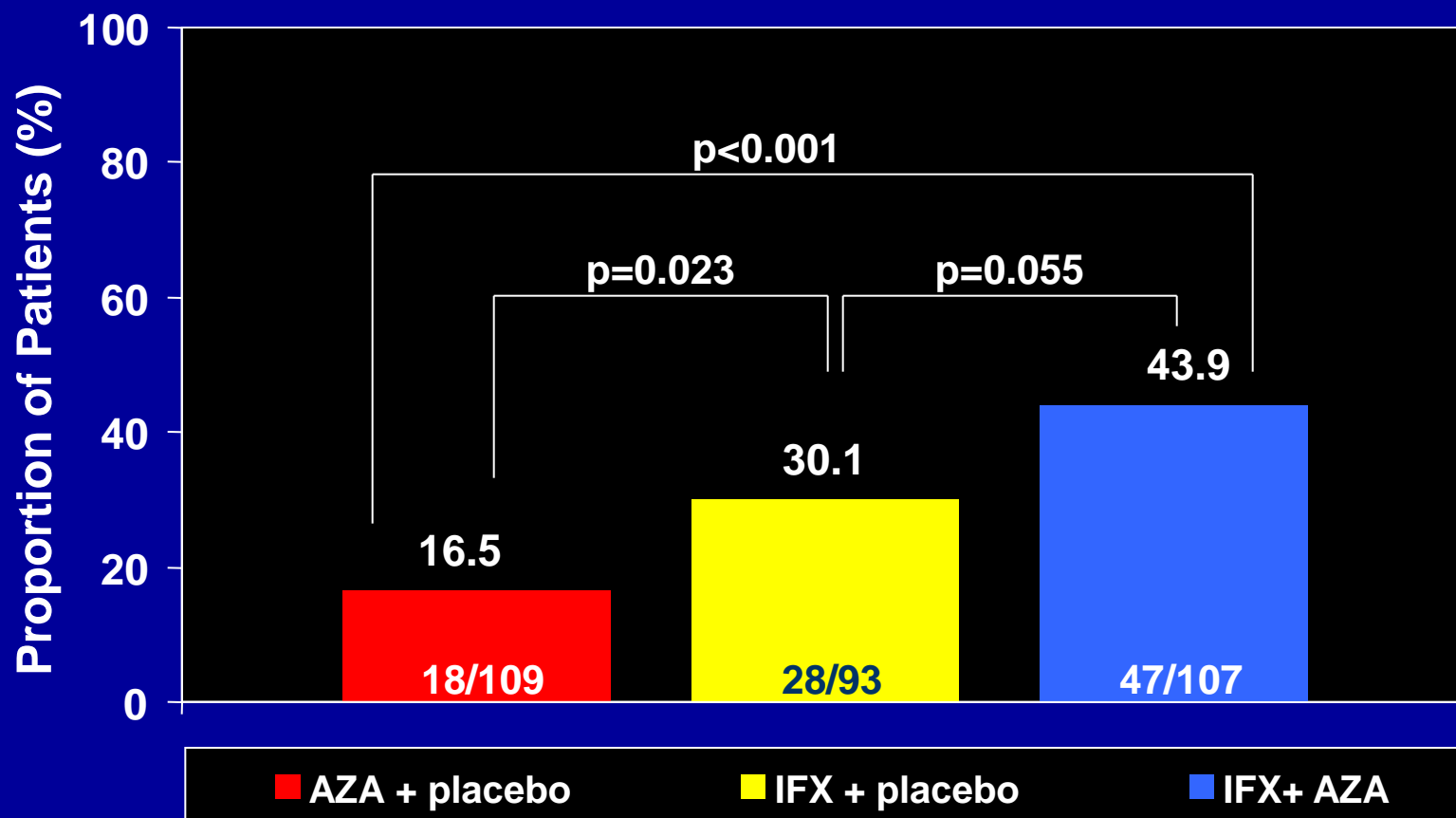


Corticosteroid-Free Clinical Remission at Week 26

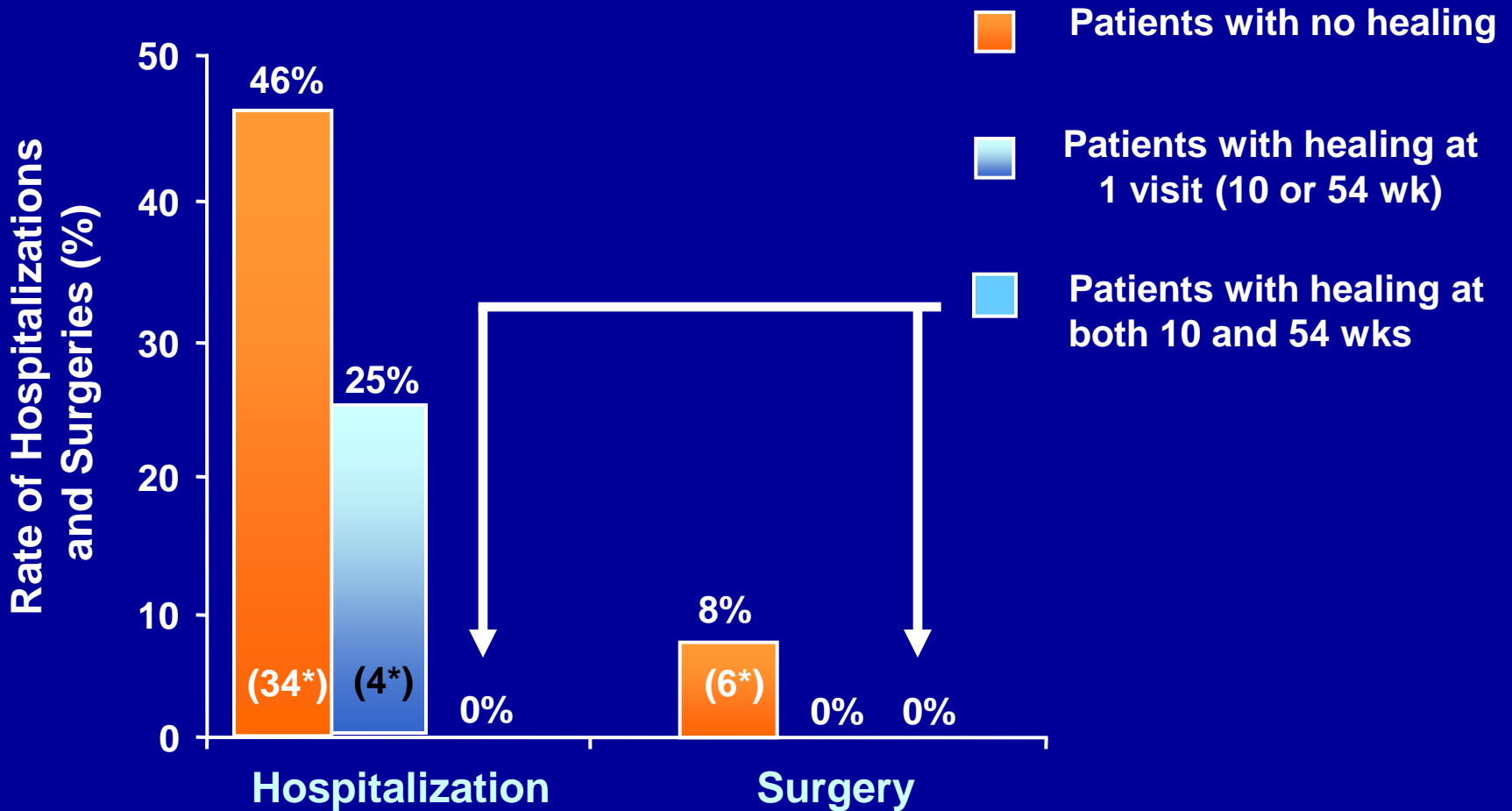
Primary Endpoint



Mucosal Healing at Week 26



Endoscopic Healing and Reduced Hospitalizations and Surgeries: Infliximab maintenance for Crohn's disease



*Number per 100 patients

Rutgeerts P et al. *Gastrointestinal Endoscopy*. 2006.

Mucosal Healing in Crohn's

Therapy	Mucosal Healing	Decreased Need for Surgery	Decreased Recurrence after Surgery
Corticosteroids	No	No	No
Imuran or 6-MP	Yes	No	Yes
Methotrexate	Yes	No	Unknown
Anti-TNF	Yes	Yes	Yes
Enteral Nutrition	Yes	No	Unknown

Risk vs. Benefits

Benefits

- Reduced Risk of disease flares
- Early promotion of mucosal healing
- Decreased surgeries and hospitalizations
- Improved QOL

Disadvantages

- Side effects
- Cost
- Majority of patients may not require potent treatment

5-ASA in IBD

Side Effects

- Headache
- Hair loss
- GI upset
- Diarrhea
- Skin rash
- Fever
- pancreatitis
- Alveolitis
- Bone marrow suppression
- Hepatitis
- Interstitial nephritis/salt-losing nephritis

Infliximab Safety

- Serious adverse event (43/500) 8.6%
- Serious adverse event attributed to Infliximab 6%
- Malignant disorders 1.8%
- Malignancy related to Infliximab 0.6%
- Serious Infection (TB) 4%
- Deaths 2%
- Deaths related to Infliximab 1%

Principles of Medical Management of IBD

- Second key question

Are the symptoms due to flare ups?

- Abdominal pain
 - Bowel obstruction; gall stones; kidney stones; pancreatitis; IBS, drug reaction
- Diarrhea
 - Bile acid-induced diarrhea; bacterial overgrowth, drug; IBS
- Poor health/fatigue
 - Anemia, IBS, depression, drug
- Fever
 - Infection, drug