Vedolizumab Should be Used as a First Line Biologic in IBD

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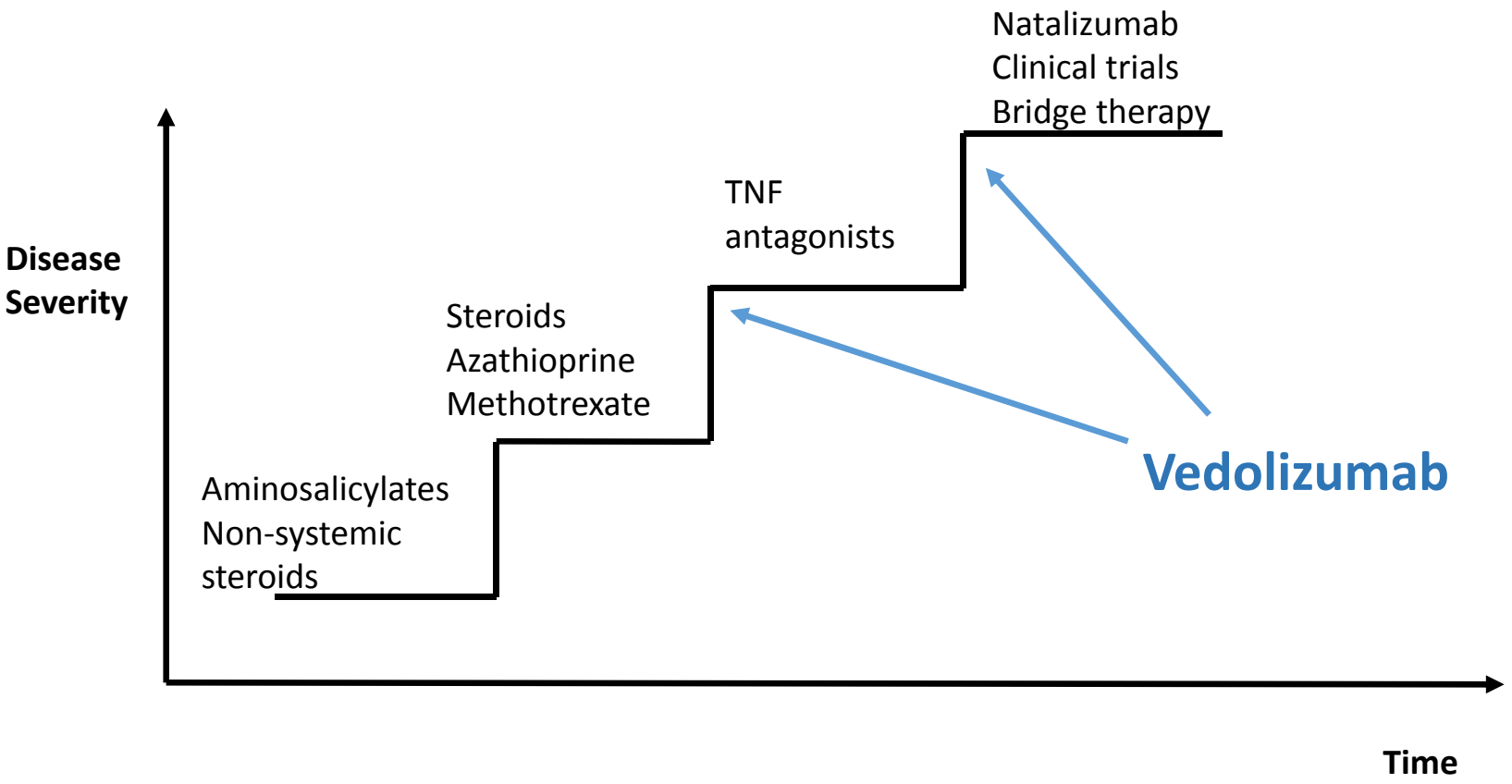
Conventional Step-up treatment algorithm for IBD

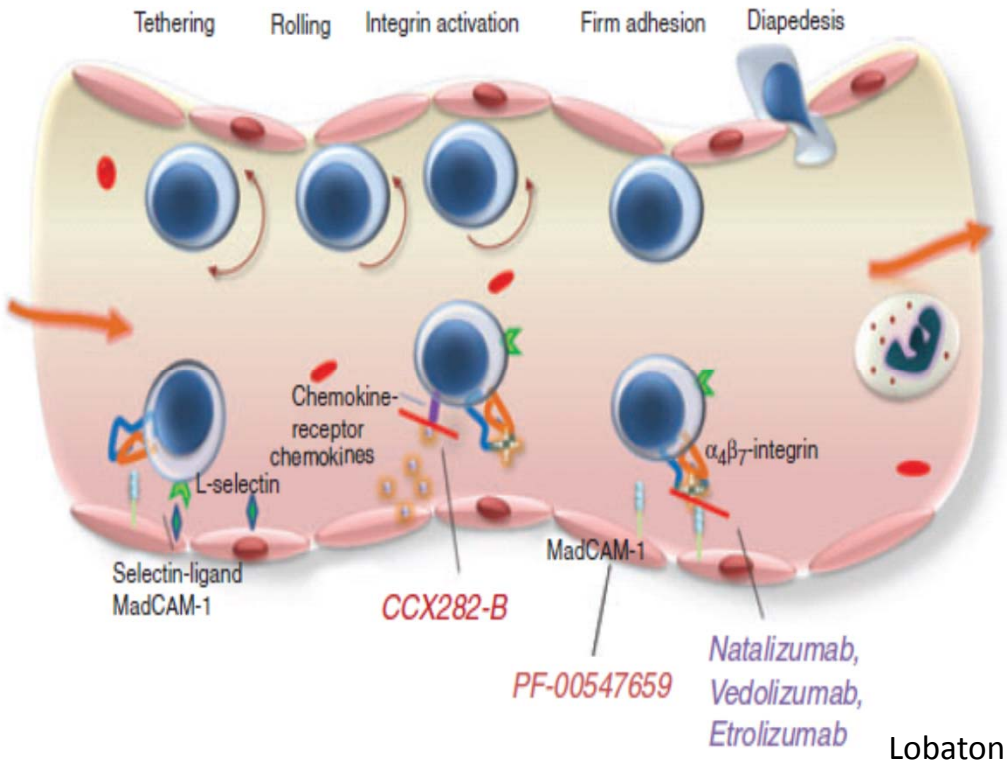


Considerations for Positioning Therapies in IBD

- Safety
  - Short term
  - Long term
- Efficacy
  - Induction in active luminal disease
  - Maintenance of remission
  - Steroid sparing
  - Mucosal healing
  - Strictures/Fistulas
  - Extra-intestinal manifestations
  - Prevention of surgeries/hospitalizations
- Cost

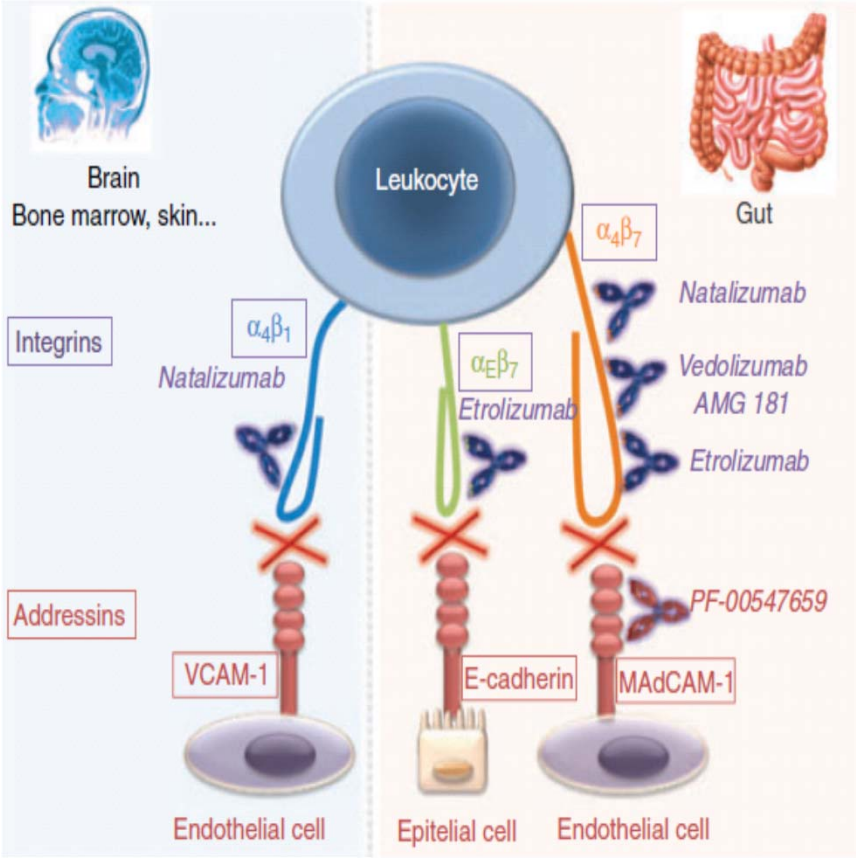
SAFETY

Integrins facilitate trafficking of circulating leukocytes to specific tissues



Lobaton T, Alimentary Pharm Ther 2014

α4β7 integrin binding to MADCAM-1 mediates leukocyte trafficking to the gut



Lobaton T, Alimentary Pharm Ther 2014

Vedolizumab, a monoclonal antibody to the gut homing α4β7 integrin, does not affect cerebrospinal fluid T-lymphocyte immunophenotype

Catherine Milch [a], Tim Wyant [a], Jing Xu [a], Asit Parikh [b,*], Whitney Kent [a], Irving Fox [a], Joseph Berger [c]

- 14 healthy subjects age 18-45 enrolled
  - LP performed before and 5 wks after a single dose of vedolizumab 450 mg IV
- Vedolizumab was not detected in any CSF sample
- No change in CD4:CD8 ratio in the CSF before vs after vedolizumab
- No change in mean or median absolute cell counts in CSF
- No changes in peripheral blood leukocytes
- **Zero Cases of PML seen with Vedolizumab**
  - **3000 patients in clinical trials**
  - **Approx 1000 with 2+ yrs of exposure**

C. Milch et al. / Journal of Neuroimmunology 264 (2013) 123–126

Adverse Effects with Vedolizumab are Uncommon

Table 1. Adverse Reactions in ≥3% of ENTYVIO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

Vedolizumab Prescribing Information

Infections with TNF antagonists

TNF therapy is an independent predictor of serious infection[1]

- TREAT registry (6273 patients followed over 5 years)
  - Predictors of serious infection:
    - Moderate to severe disease activity (HR 2.24)
    - Narcotics (HR 1.98)
    - Steroids (HR 1.57)
    - **Infliximab (HR 1.43)**

Older patients (age >65) are at particularly high risk of infection[2]

- Prospective Cohort Study (3079 patients over 10 years)
  - Patients over age 65 on TNF therapy had increased risk of **serious infection** (11%) or **death** (10%) compared to younger patients on TNF therapy

[1]Lichtenstein GR, Am J Gastro 2012
[2]Cottone M, Clin Gastro Hepatol 2011

Black Box Warning with Infliximab

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy.[1,2] Treatment for latent infection should be initiated prior to REMICADE use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

Black Box Warning with Infliximab

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE *[see Warnings and Precautions (5.2)]*.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

Black Box Warning with Vedolizumab

Other warnings and precautions

Infliximab

- Serious infections
  - mycobacterial, invasive fungal
- Malignancies
  - lymphoma, HSTCL, skin cancers, other malignancies
- Hep B reactivation
- Heart failure
- Hepatotoxicity
- Hematologic reactions
- Hypersensitivity reactions
- Neurologic reactions
- Autoimmunity
  - drug-induced lupus, psoriasis
- Live vaccines

Vedolizumab

- Hypersensitivity reactions
- Infections
- PML
- Hepatotoxicity
- Live and Oral vaccines

Long term safety of vedolizumab

- We don't have long term safety data for vedolizumab
- However…

  We do have data on natalizumab (anti-alpha 4 integrin):

  - 5 year analysis of Tysabri Observational Program (TOP)
  - 4821 total patients
  - 2496 patients with > 2 yrs of exposure
  - 2% serious infections
  - Pneumonia 0.4%, serious UTI 0.3%
  - Opportunistic infections (other than PML) 0.2%

J Neurol Neurosurg Psychiatry 2014

Safety Comparison: Vedo vs TNF antagonists

	TNF antagonist	Vedolizumab
Nasopharyngitis	=	
Serious infections		+
Infusion reactions		+
PML	=	
Demyelinating disease		+
CHF		+
Autoimmunity (DILE, psoriasis, etc)		+
Lymphoma		+

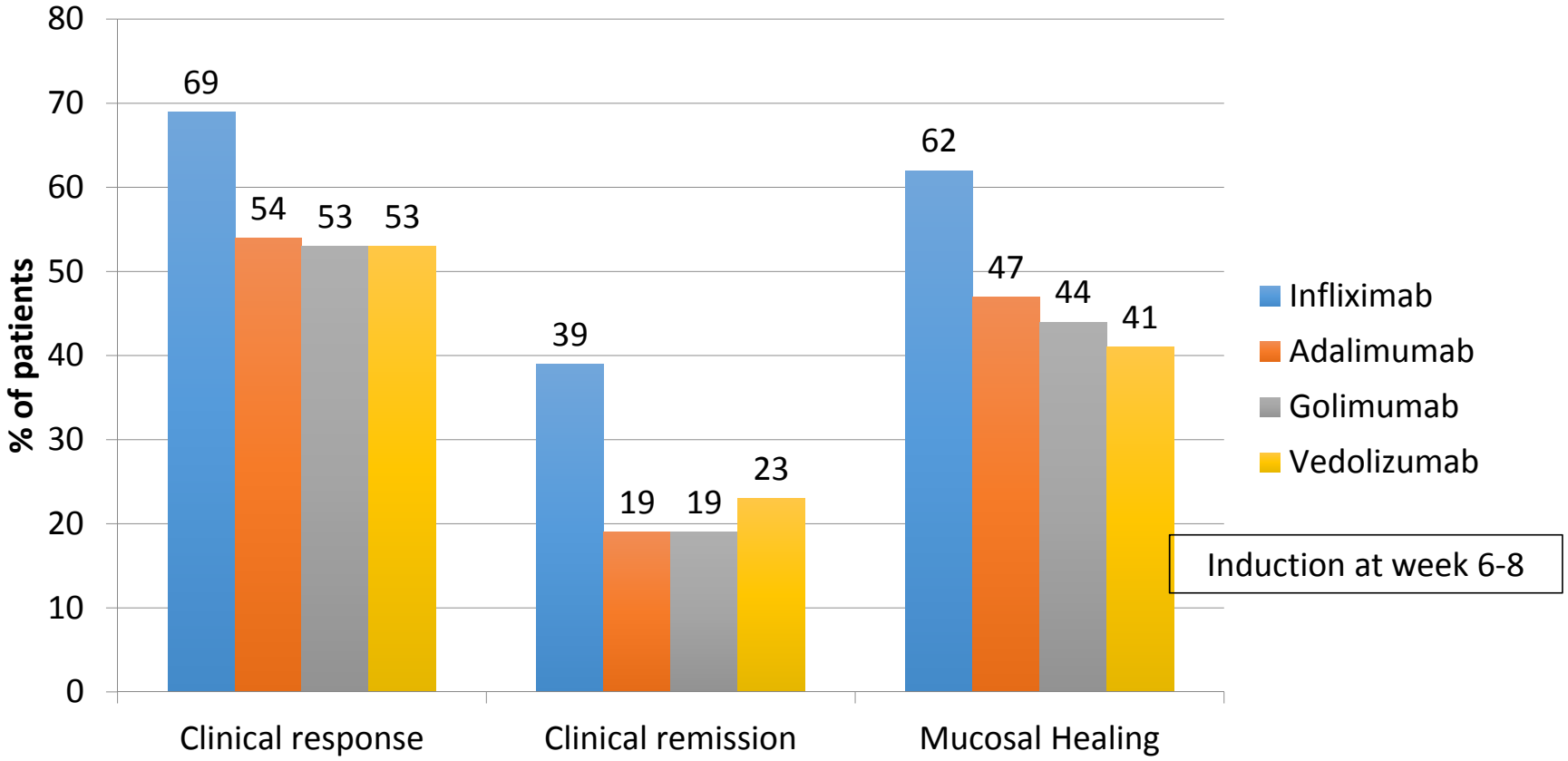
Overall, vedolizumab has a cleaner safety profile than TNF antagonists

Uncertainty about long term safety:

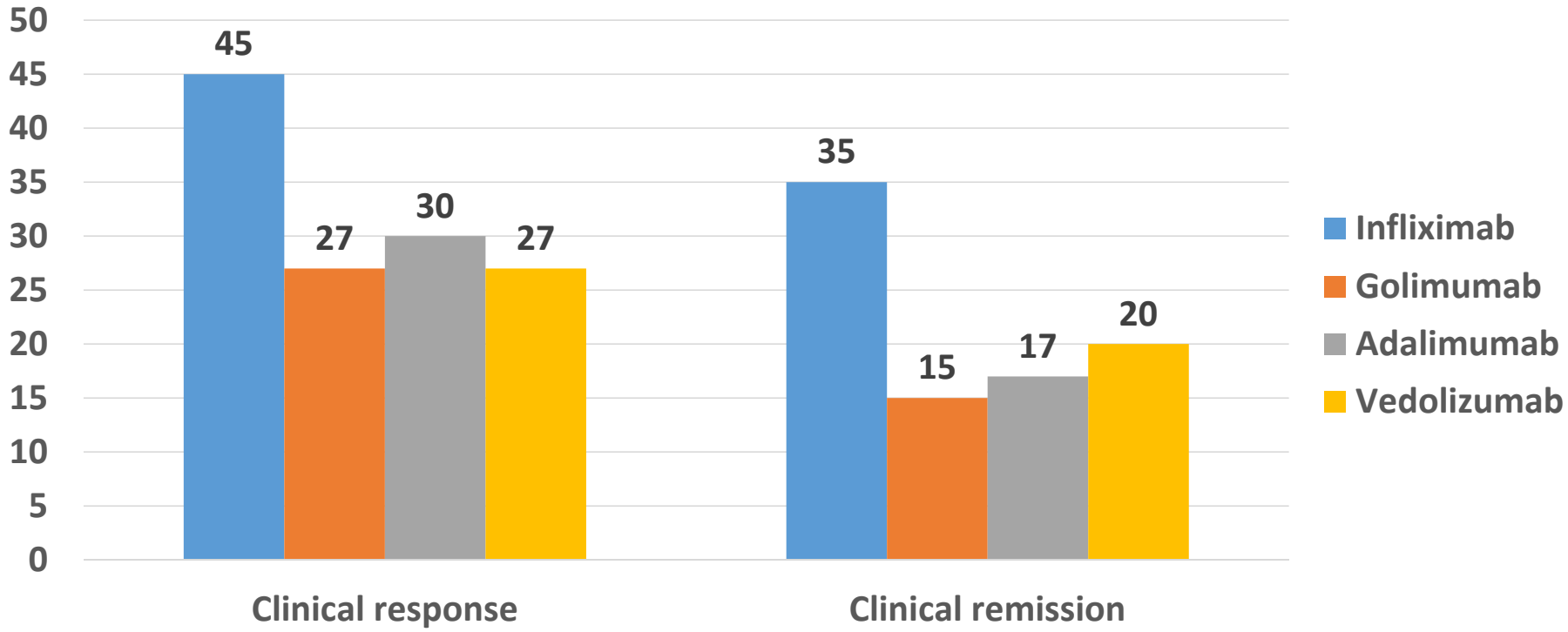
- Aside from PML, natalizumab is safe and well-tolerated
- Vedolizumab is the most well-studied IBD drug prior to release

COMPARATIVE EFFECTIVENESS

Induction of Remission in Ulcerative Colitis



Maintenance of Remission in UC at 1 year



Network Meta-Analysis of Biologics in UC: Vedolizumab more effective than TNF antagonists

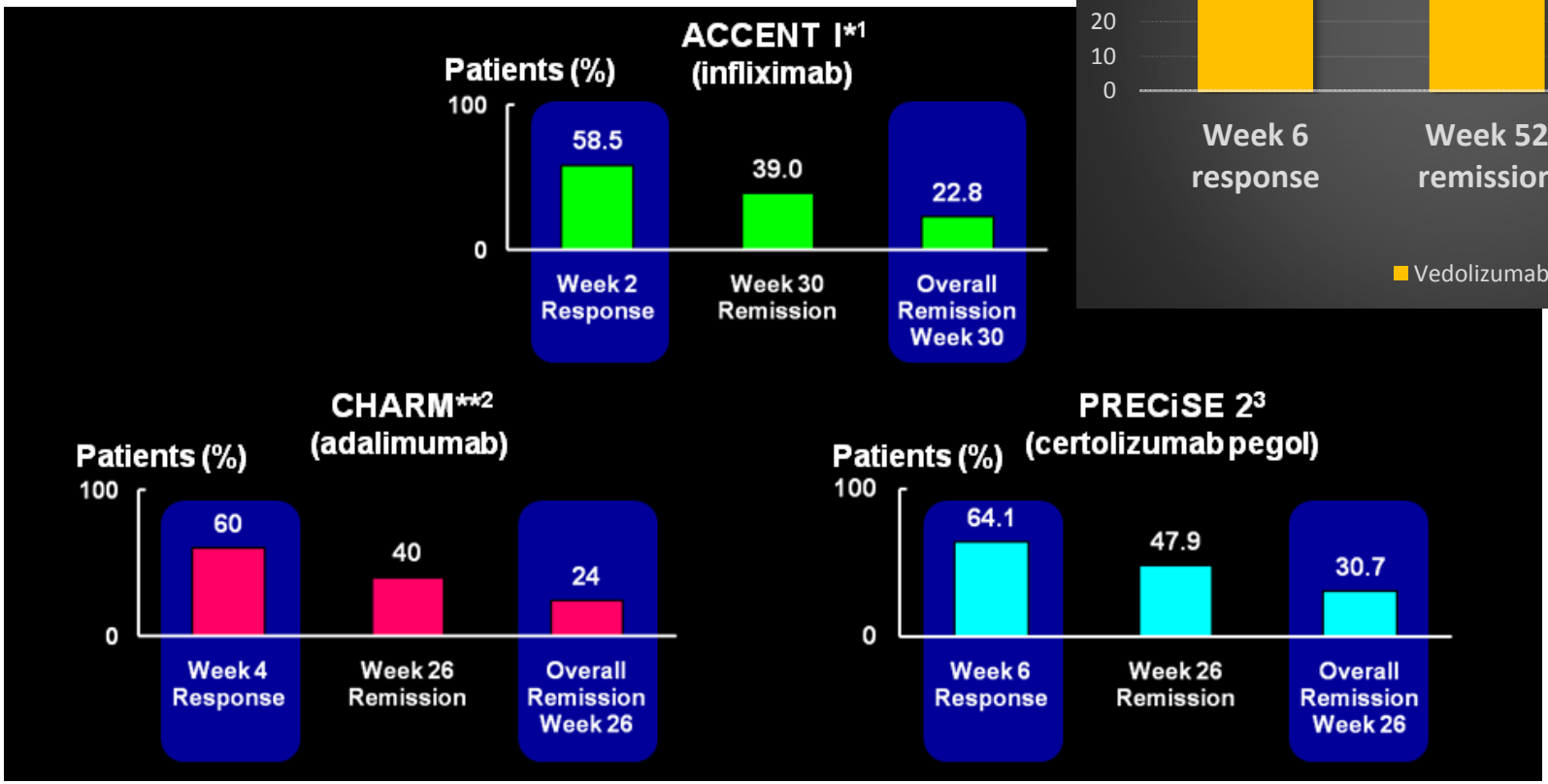
	Odds Ratio (95% CI) for vedolizumab Q8W vs. listed comparator			
Subpopulation (endpoint at week 52)	**Placebo**	**Adalimumab 40mg eow**	**Golimumab 100mg**	**Infliximab 5mg/kg**
Anti-TNF naive				
Durable clinical response	5.27* (2.68-11)	3.96* (1.67-9.84)	2.33* (1.04-5.41)	3.18* (1.14-9.2)
Clinical remission	3.63* (1.75-7.72)	1.81 (0.74-4.9)	2.03 (0.84-5.05)	2.93* (1.03-8.28)
Discontinuation due to AEs	0.31 (0.06-1.13)	0.14* (0.02-0.67)	0.21* (0.03-0.99)	0.34 (0.05-1.69)
Mucosal healing	4.79* (2.33-9.93)	3.21* (1.33-7.35)	NA	2.43 (0.87-6.66)
CSF remission	2.57 (0.92-7.57)	12 (0.23-5.97)	NA	1.66 (0.39-6.99)
Anti-TNF experienced/failure				
Durable clinical response	4.89* (1.74-16.0)	2.04 (0.44-9.01)	NA	NA
Clinical remission	12.0* (3.14-78.0)	3.4 (0.4-33.0)	NA	NA
Discontinuation due to AEs	NA	NA	NA	NA
Mucosal healing	9.09* (2.74-40.0)	6.72* (1.36-41.0)	NA	NA
CSF remission	NA	NA	NA	NA

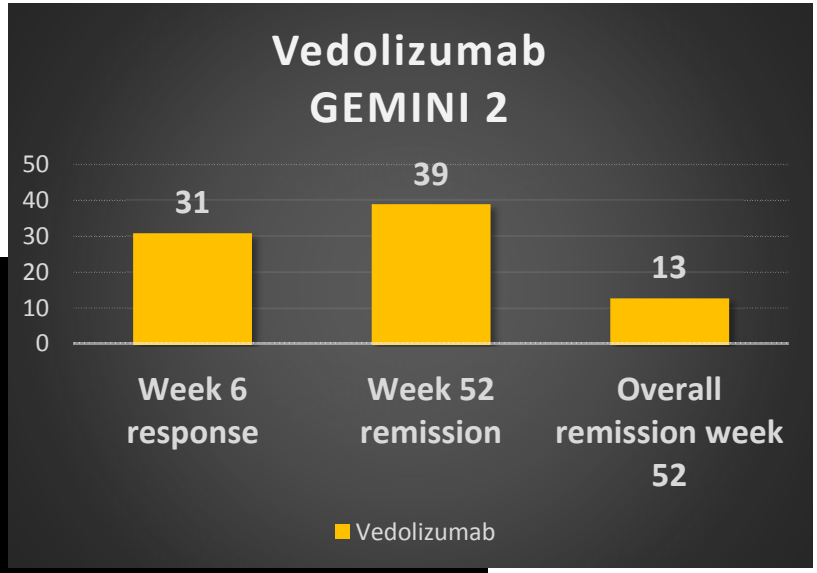
AE = adverse event; CI = confidence interval; CSF = corticosteroid free; eow = every other week; NA = not applicable; Q8W = every 8 weeks.

*Significant vs. comparator ($P < 0.05$).

Vickers AD, et al. P554, ECCO 2015

Biologics for Crohn's Disease

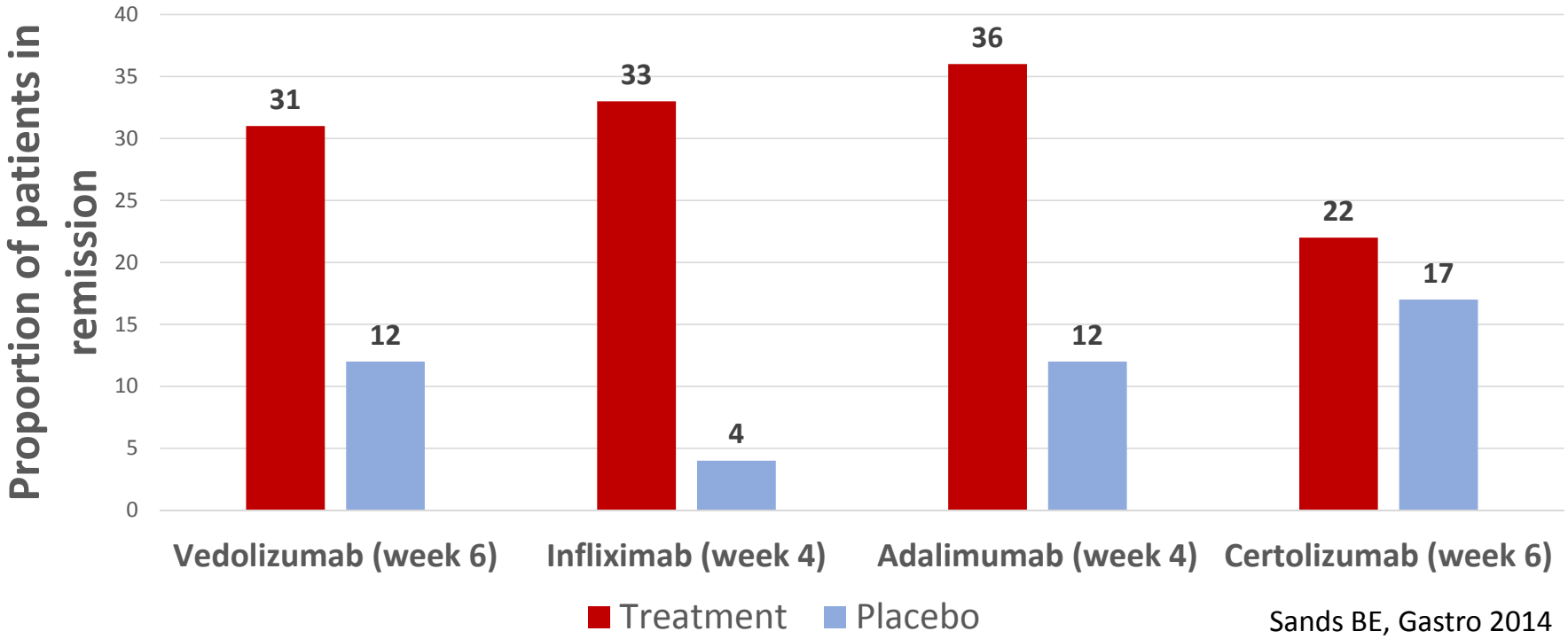




GEMINI 2 vs ACCENT/CHARM/PRECiSE 2 is not a fair comparison

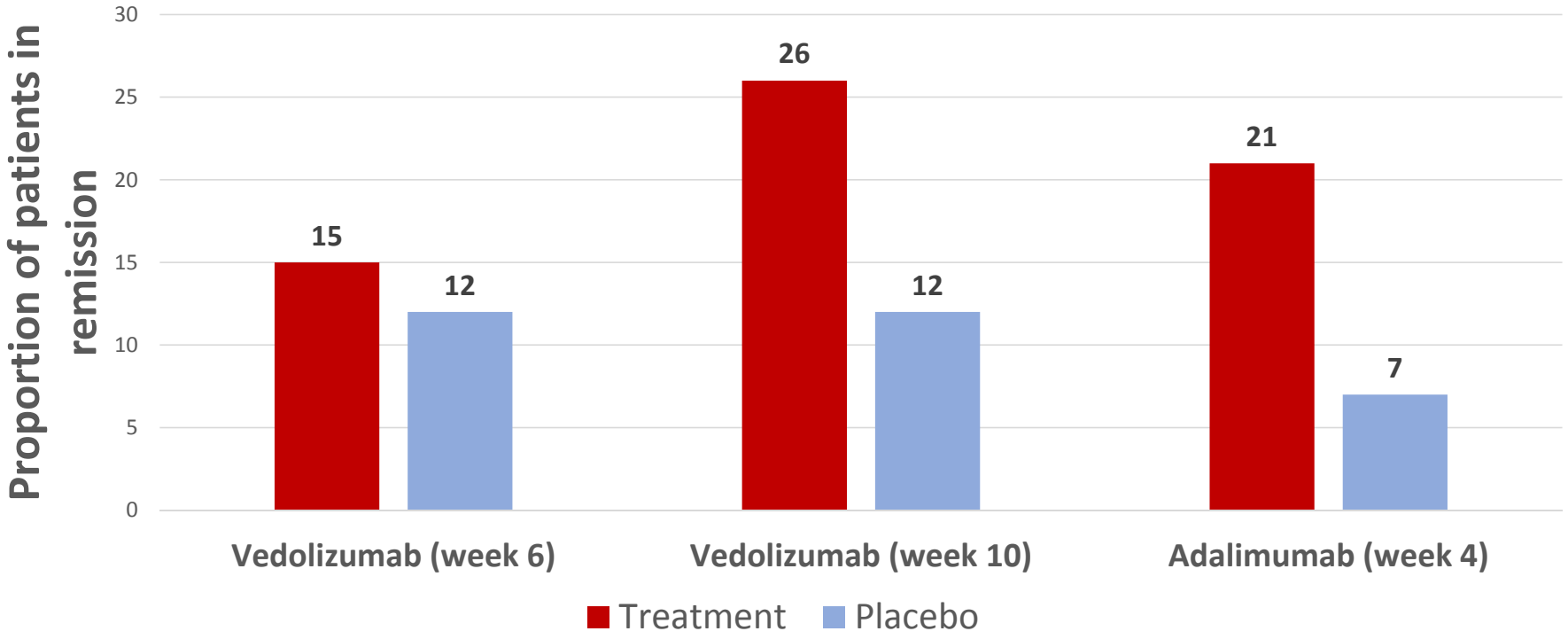
- GEMINI 2 patients were a more difficult treatment population based on:
  - More TNF failures (many failed 2 TNFs)
  - Longer disease duration
  - Higher baseline CDAI scores
  - Immunomodulators not allowed at US sites
- A 6 week endpoint is too soon to assess response for vedo in TNF-experienced patients
- Infliximab/Adalimumab trials used a 70-point CDAI response vs 100-point response for vedo/certolizumab
- Maintenance of remission assessed at week 26 in TNF studies vs week 52 for vedo

Induction of Remission in TNF-naïve Crohn's Disease



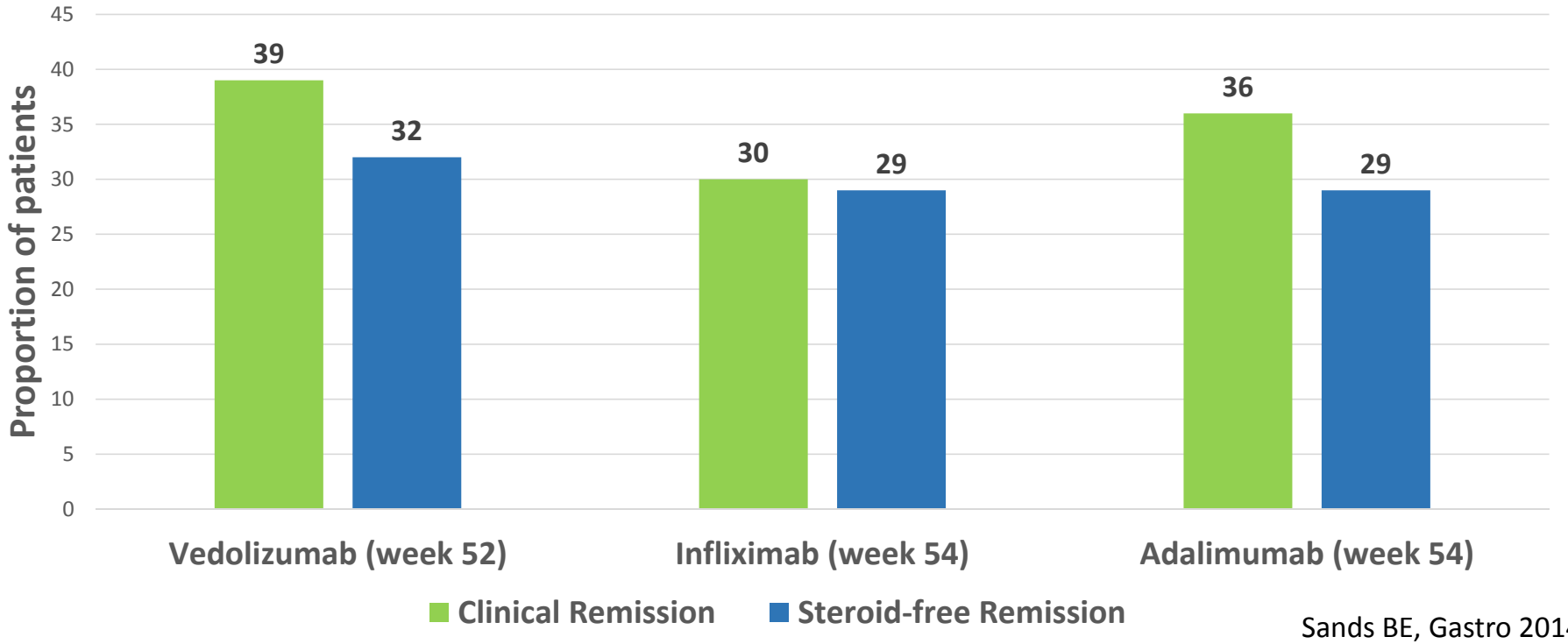
Sands BE, Gastro 2014
Targan SR, NEJM 1997
Hanauer SB, Gastro 2006
Sandborn WJ, NEJM 2007

Induction of Remission in TNF-experienced Crohn's Disease



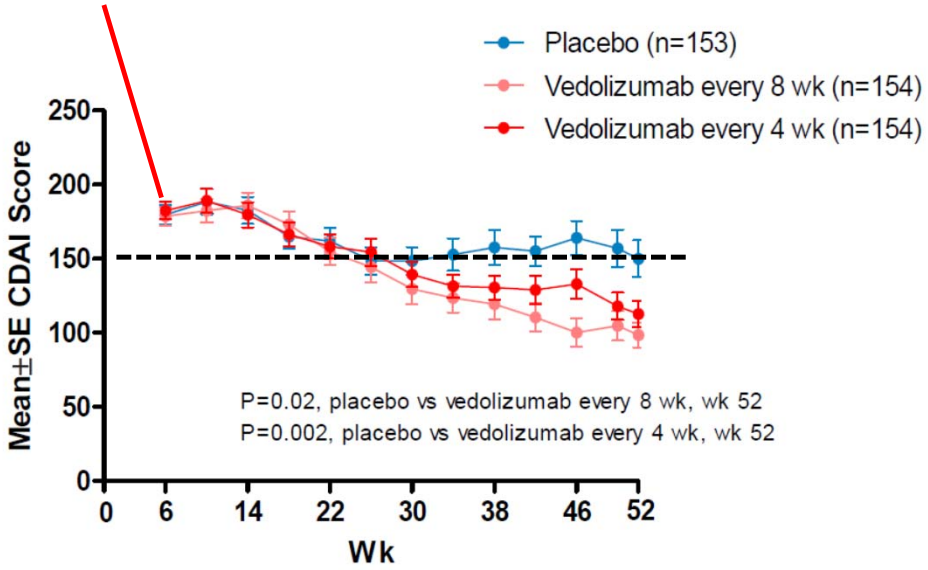
Sands BE, Gastro 2014
Sandborn WJ, Ann Intern Med 2007

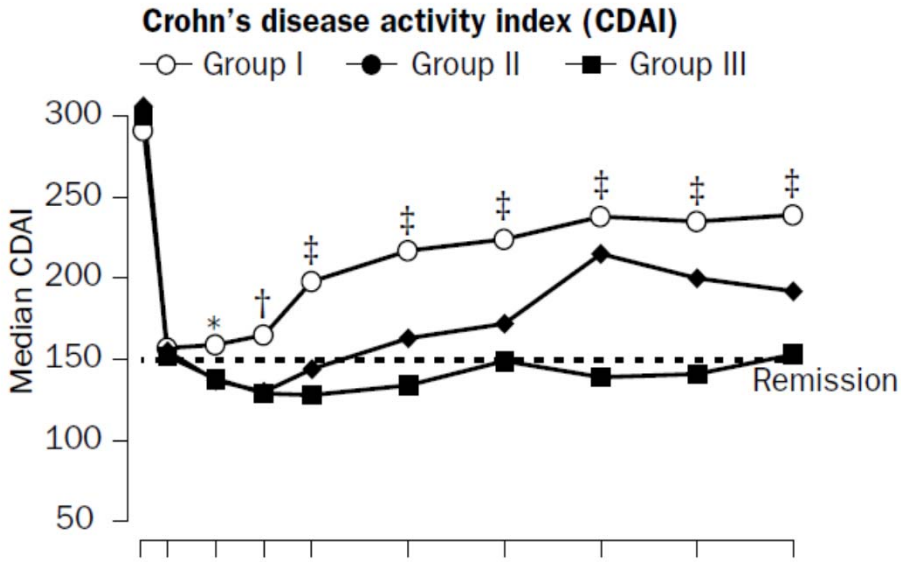
Maintenance of Remission at 1 year in Crohn's Disease among responders to induction therapy



Sands BE, Gastro 2014
Hanauer SB, Lancet 2002
Colombel JF, Gastro 2007

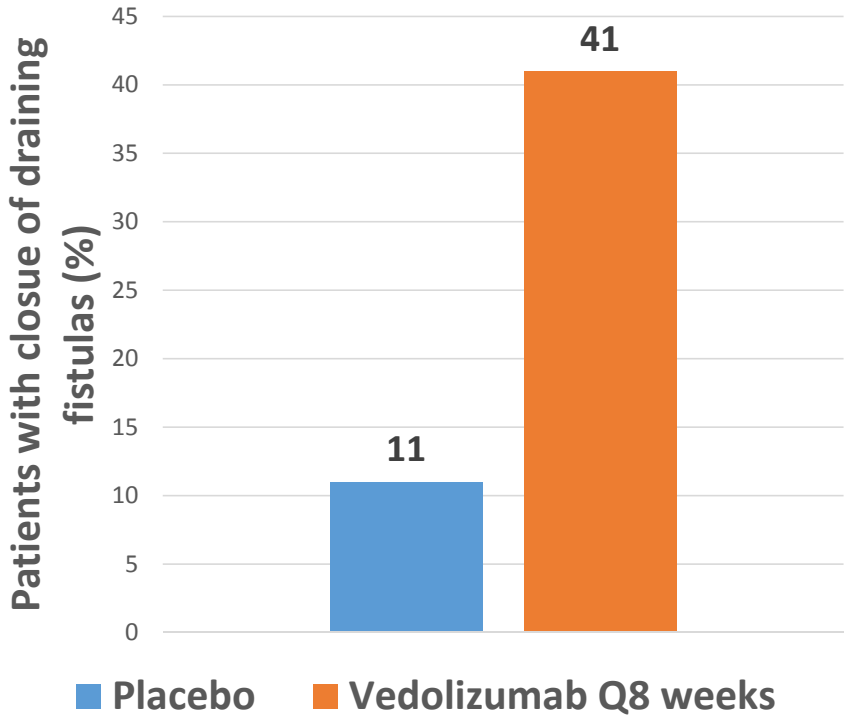
Patients continue to improve over time with vedolizumab

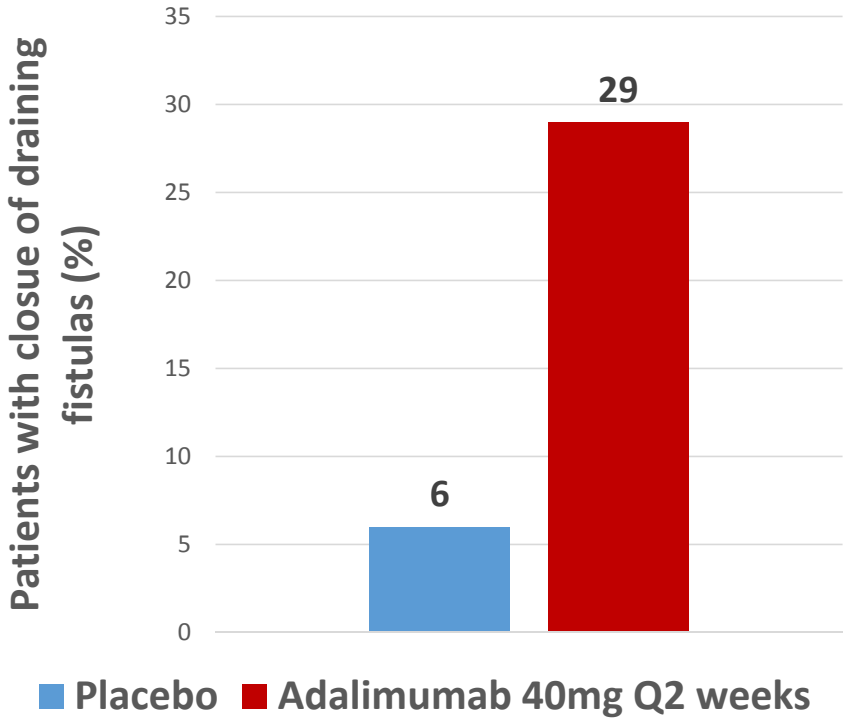




Sands BE, Gastro 2014
Hanauer SB, Lancet 2002

Fistula Healing with Vedolizumab vs Adalimumab





Sandborn WJ, NEJM 2013
Colombel JF, Gastro 2007

COST

Cost of vedolizumab is comparable to TNF antagonists

	Infliximab*		Adalimumab	Vedolizumab*
WAC price per unit	$884.88		$1251.31	$4819.00
Dose (80kg patient)	400mg	800mg	40mg	300mg
Price per dose	$3539.32	$7079.04	$1251.31	$4819
Induction drug cost	$10,618.56		$7507.86	$14, 457.00
First year drug cost	$21,237.12	$42,474.24	$32,534.06	$28.914.00

*Drug cost only. Does not include IV administration costs

P322 Cost per clinical outcomes with biologics for the treatment of moderately to severely active ulcerative colitis

	Estimate	95% confidence interval	Estimate	95% confidence interval	Estimate	95% confidence interval	Estimate	95% confidence interval
	Probability of induction response		**Probability of sustained response at 52 weeks**		**NNT for sustained response at 52 weeks**		**Cost per sustained responder at 52 weeks in GBP**	
Placebo	0.34	(0.31; 0.37)	0.12	(0.09; 0.15)	Reference		Reference	
INF 5mg/kg[1]	0.69	(0.62; 0.76)	0.34	(0.23; 0.47)	4.5	(2.9; 8.9)	58,685	(37,664; 116,829)
ADA 160/80/40 mg[2]	0.49	(0.42; 0.56)	0.22	(0.14; 0.31)	10.2	(5.0; 45.4)	67,529	(32,931; 300,539)
GOL 200/100/100 mg[3]	0.57	(0.49; 0.65)	0.31	(0.22; 0.41)	5.2	(3.4; 9.5)	77,851	(51,421; 142,299)
VDZ 300mg[4]	0.63	(0.51; 0.75)	0.40	(0.26; 0.59)	3.6	(2.2; 7.5)	53,130	(33,210; 111,482)
	Probability of induction remission		**Probability of sustained remission at 52 weeks**		**NNT for sustained remission at 52 weeks**		**Cost per patient in sustained remission at 52 weeks in GBP**	
Placebo	0.09	(0.07; 0.11)	0.04	(0.03; 0.05)	Reference		Reference	
INF 5mg/kg[1]	0.34	(0.27; 0.41)	0.16	(0.09; 0.24)	8.5	(4.8; 18.9)	111,435	(63,789; 249,642)
ADA 160/80/40 mg[2]	0.17	(0.13; 0.22)	0.08	(0.04; 0.14)	22.4	(9.7; 108.8)	148,087	(63,884; 719,599)
GOL 200/100/100 mg[3]	0.23	(0.17; 0.29)	0.13	(0.08; 0.21)	10.2	(6.0; 20.7)	153,213	(90,593; 309,873)
VDZ 300mg[4]	0.28	(0.18; 0.40)	0.19	(0.11; 0.32)	6.5	(3.5; 15.4)	95,833	(51,855; 228,719)

Abbreviations: ADA, adalimumab; CI, confidence interval; GOL, golimumab; IFX, infliximab; NNT, number needed to treat; VDZ, vedolizumab.

[1]infliximab 5mg/kg induction treatment (week 0, 2, and 6) followed by every 8 weeks as maintenance treatment;

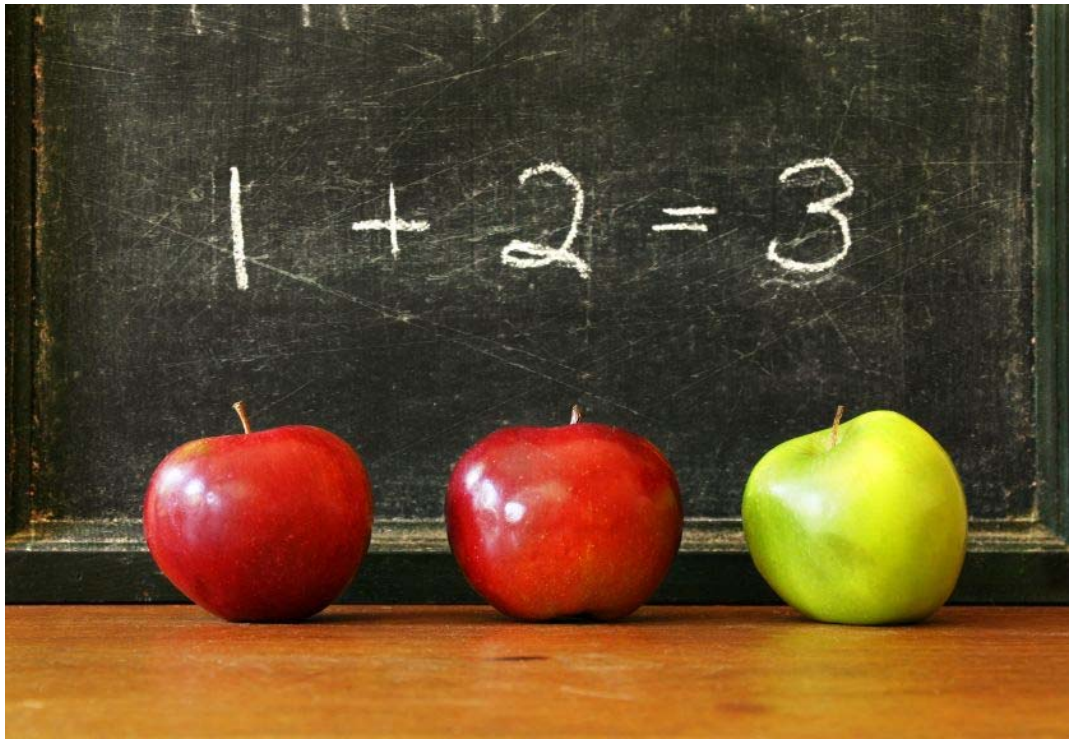
[2]adalimumab 160 mg at week 0, 80 mg at week 2 for induction treatment followed by 40mg every other week as maintenance treatment;

[3]golimumab 200mg at week 0, 100 mg at week 2 for induction treatment followed by 100mg every 4 weeks maintenance treatment;

[4]vedolizumab 300mg induction treatment (week 0,2, and 6) followed by every 8 weeks maintenance treatment.

Jansen J, ECCO 2015

PUTTING IT ALL TOGETHER



Common Critiques of Vedolizumab

Critique	Response
Vedo is too new. TNF antagonists are tried and true	If we followed this logic we'd still be using steroids and sulfasalazine
Risk of PML with vedo	No cases seen so far CSF studies show no effect on CNS lymphocytes
Uncertainty about long term safety	Vedo is the most well-studied IBD therapy prior to its release Aside from PML risk, natalizumab is safe and well tolerated
Vedo efficacy is modest compared to TNF antagonists for Crohn's	Not true. Efficacy very similar when comparing apples to apples
Vedo onset is too slow	Not in UC patients or TNF-naïve Crohn's patients Be patient and bridge with steroids if needed
Vedo does not treat fistulas	Not true.
Vedo does not treat extra-intestinal manifestations	No data. But fortunately EIMs that don't respond to tx of the bowel are uncommon (uveitis, pyoderma, spondyloarthritis)

Scorecard: VDZ vs TNF in ulcerative colitis

	Vedolizumab		TNF antagonists
Short term safety	Good	=	Good
Long term safety	Better (so far)	+	Good
Induction of active disease	Good	=	Good
Maintenance of remission	Good	=	Good
Severe hospitalized UC	No data		+ Good (IFX)
Reduction in surgeries/hospitaliz	No data		+ Good
Extra-intestinal manifestations	No data		+ Good
Cost	Expensive	=	Expensive

Scorecard: Vedolizumab vs TNF in Crohn's disease

	Vedolizumab		TNF antagonists
Short term safety	Good	=	Good
Long term safety	Better (so far)	+	Good
Induction of active disease	Good	=	Good
Maintenance of remission	Good	=	Good
Fistulas	Fair	=/+	Good
Reduction in surgeries/hospitaliz	No data	+	Good
Extra-intestinal manifestations	No data	+	Good
Cost	Expensive	=	Expensive

Considerations in positioning vedolizumab for IBD

- Superior safety profile (so far)
  - Elderly patients
  - Relative contraindications to TNF: heart failure, lymphoma, demyelinating disease, history of malignancy
- Similar efficacy in TNF naïve patients
- Similar durability of maintenance effect
- No harm to trying vedolizumab first
- Recommendation: vedolizumab before TNF for most IBD patients
- Special scenarios:
  - Severe hospitalized UC→ favor infliximab
  - Severe outpatient IBD (on the verge of hospitalization)
  - Extraintestinal manifestations (spondyloarthritis, pyoderma, uveitis, etc)