

Controversy: Vedolizumab Should Not Be Used as a First Line Biologic in IBD

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Benaroya Research Institute

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Newer Does Not Mean Better

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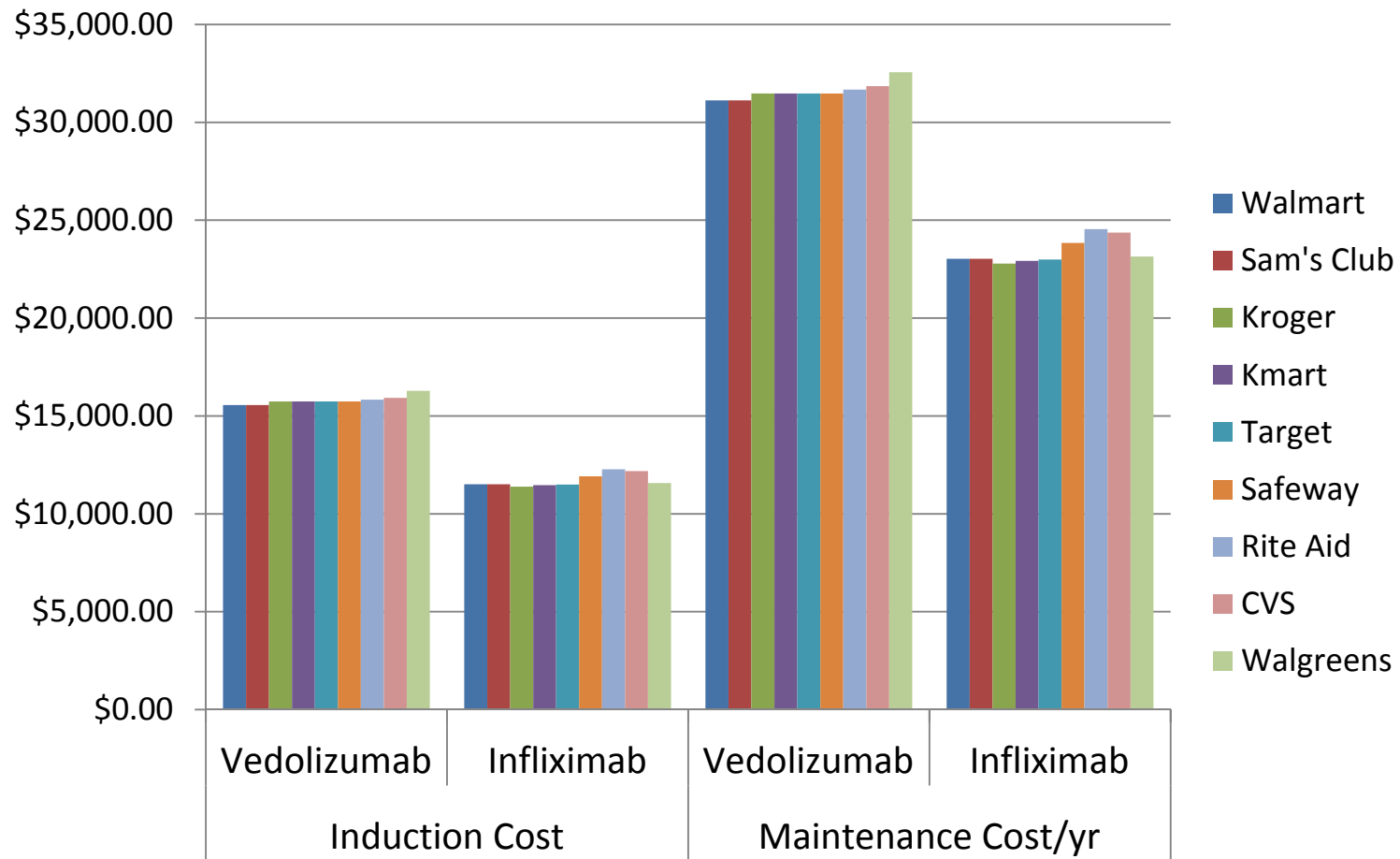
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What makes an agent “first line”?

- Cost
- Convenience
- Safety
- Efficacy

Cost: Vedolizumab is more expensive than infliximab



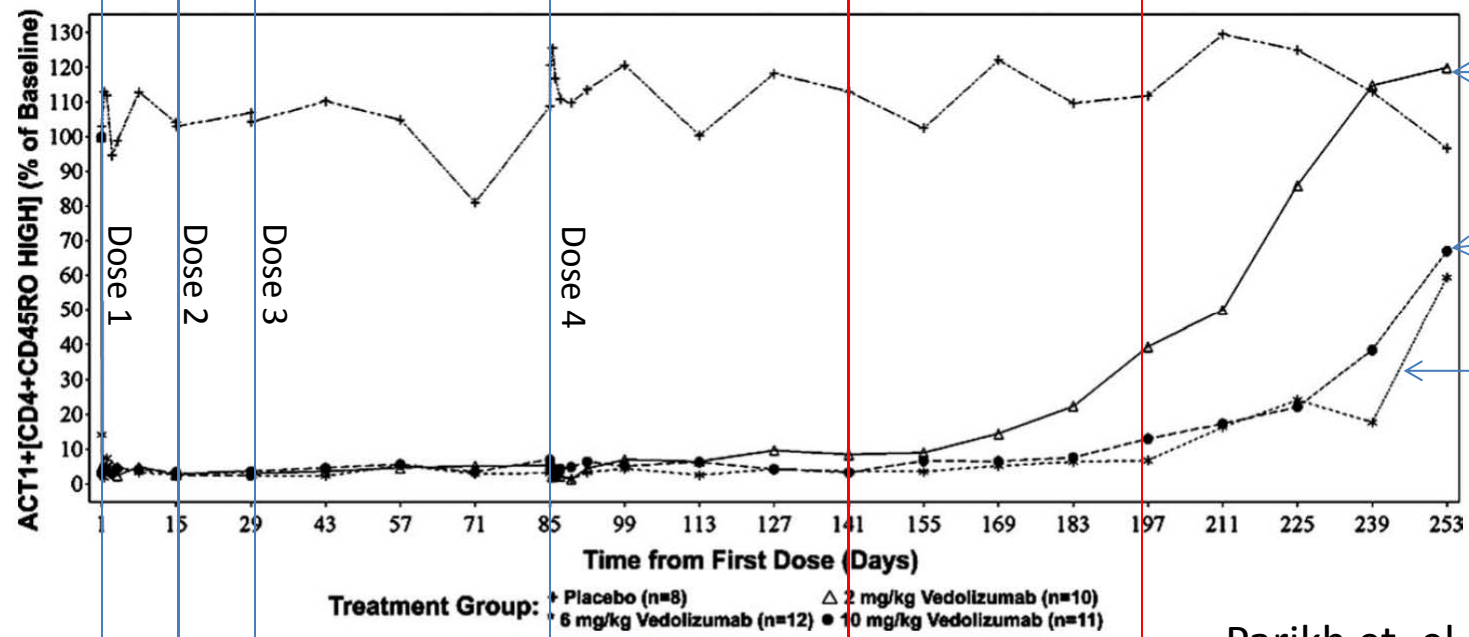
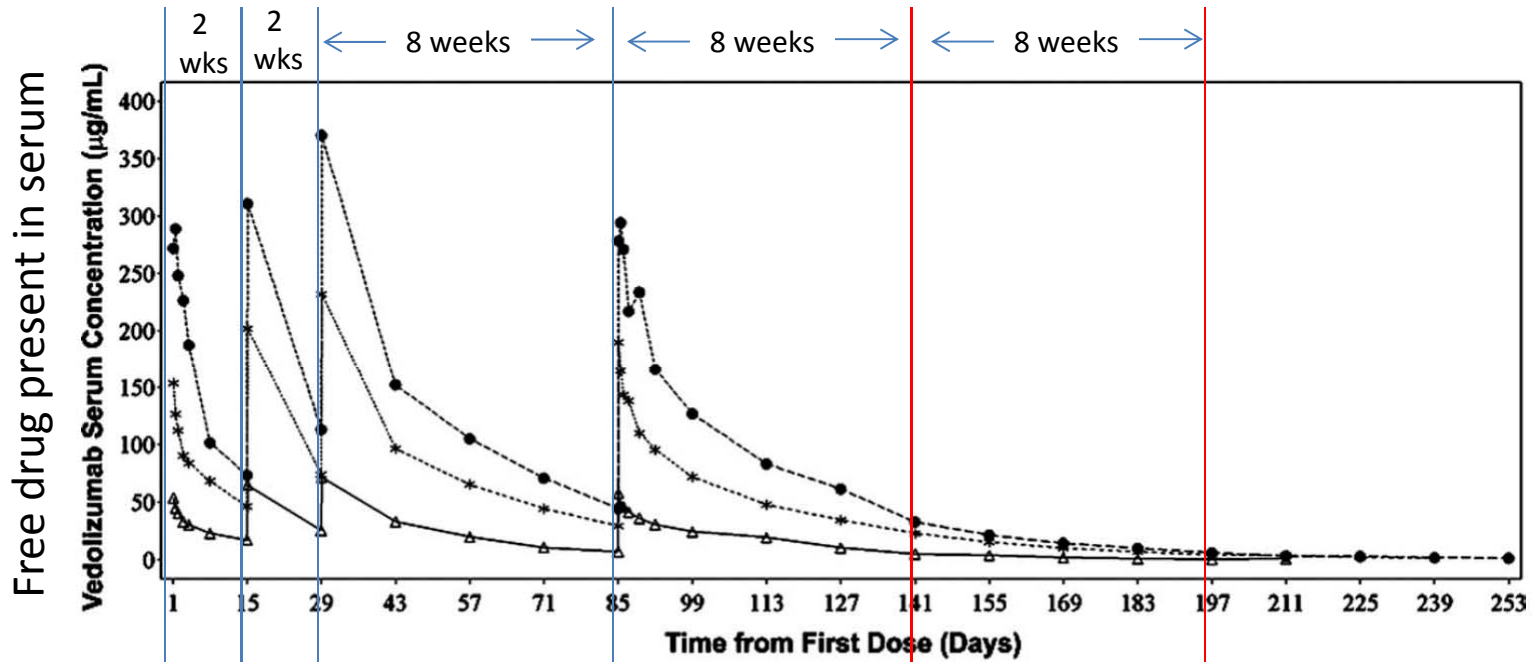
Data from GoodRx.com

Assuming standard dosing for 70 kg patient

Convenience: Vedolizumab has an infusion schedule identical to infliximab

- Induction:
 - Infliximab: 5 mg/kg IV at week 0, 2, 6
 - Vedolizumab: 300 mg IV at week 0, 2, 6
- Maintenance:
 - Infliximab: 5 mg/kg every 8 weeks IV
 - Vedolizumab: 300 mg every 8 weeks IV
- No subcutaneous form of Vedolizumab

% of cells with unbound $\alpha 4\beta 7$
(inverse of receptor saturation)



150 kg
30 kg
50 kg

FIGURE 3. MAdCAM-1-Fc+ over time by dose cohort.

Safety: Is Vedolizumab a safer drug than an anti-TNF agent?

Crohn's Disease

- Vedolizumab:
 - GEMINI-II & III
- Anti-TNF agents:
 - Infliximab
 - Targan et. al. '97
 - ACCENT-I & II
 - Adalimumab
 - CHARM
 - CLASSIC-I & II
 - Certolizumab
 - Schreiber et. al. '05
 - PRECISE-I & II

Ulcerative Colitis

- Vedolizumab:
 - Feagan et. al., '05
 - GEMINI-I
- Anti-TNF agents:
 - Infliximab
 - ACT-I & II
 - Adalimumab
 - ULTRA-I & II
 - Golimumab
 - PURSUIT-SC & M

Safety: Vedolizumab seems like it *should* be safer than anti-TNF

Anti-TNF agents:

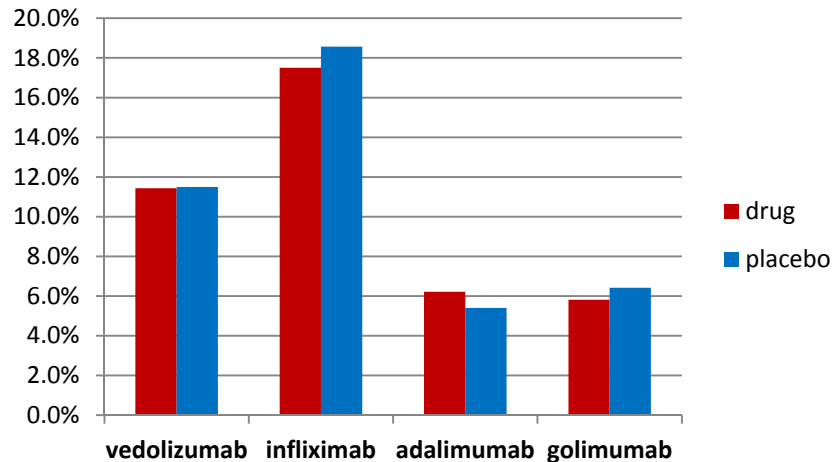
- Block a ubiquitous feature of inflammation (TNF)
- Act throughout the body
- Cause immune cell apoptosis
- Associated with anti-drug immune responses

Vedolizumab:

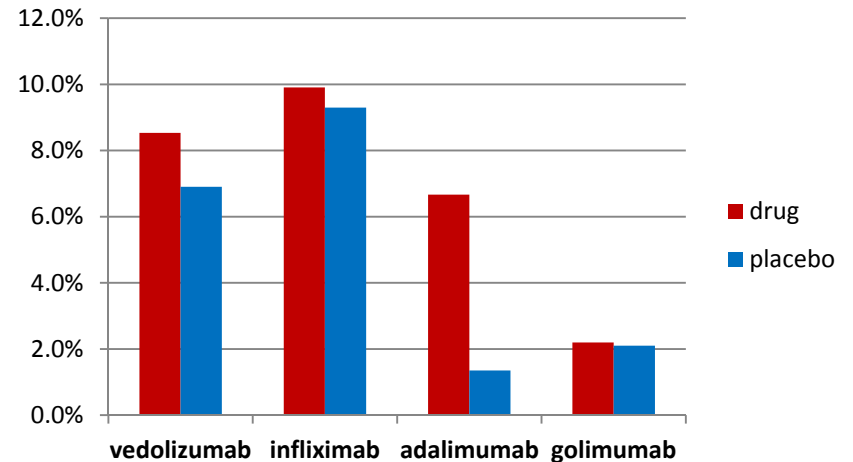
- Blocks lymphocyte migration, not function
- Specific to gut only
- Does not cause apoptosis
- Associated with minimal anti-drug immunogenicity

Vedolizumab is not clearly better tolerated than anti-TNF agents

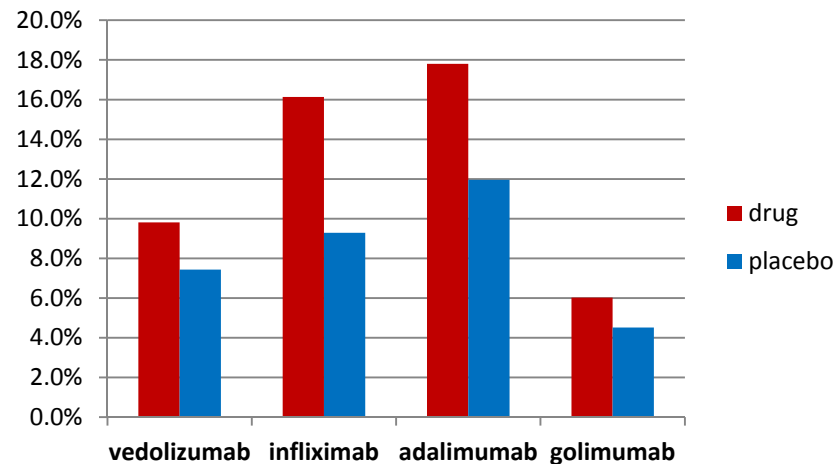
Headaches



Nausea

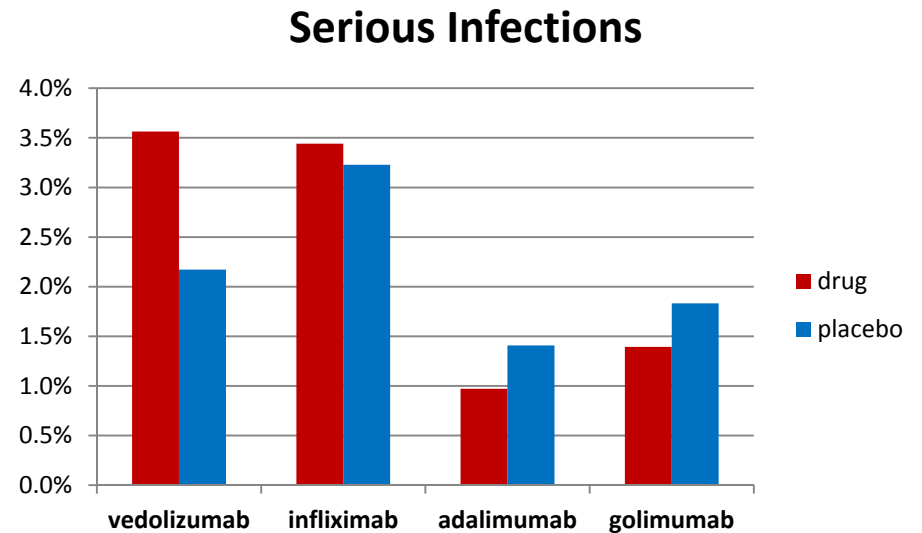
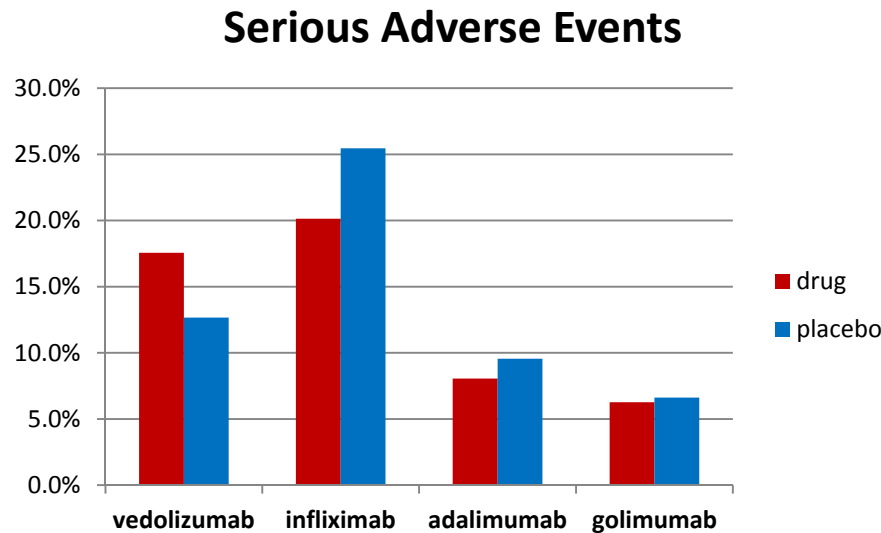


Nasopharyngitis



Data from all GEMINI, ACT, ULTRA, PURSUIT, CHARM, CLASSIC and ACCENT trials

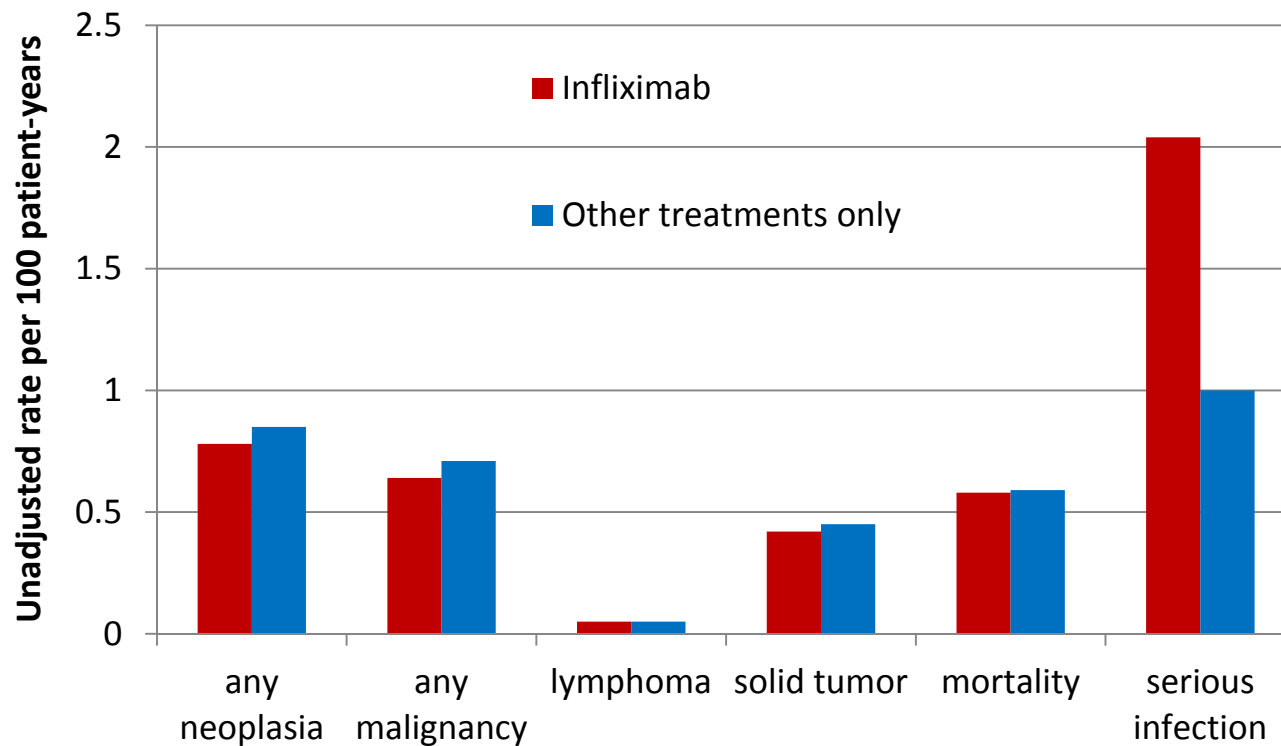
Vedolizumab is not clearly safer than anti-TNF agents



Note: No PML reported with vedolizumab to date

Long-term safety data on anti-TNF agents, but not vedolizumab

TREAT Registry: 6,273 Crohn's patients with an average of 5.2 years follow-up



Lichtenstein et. al., *Am J Gastroenterol* 2012; 107:1409–1422.

Lichtenstein et. al., *Am J Gastroenterol* 2014;109:212-23.

Efficacy: Is Vedolizumab a better drug than an anti-TNF agent?

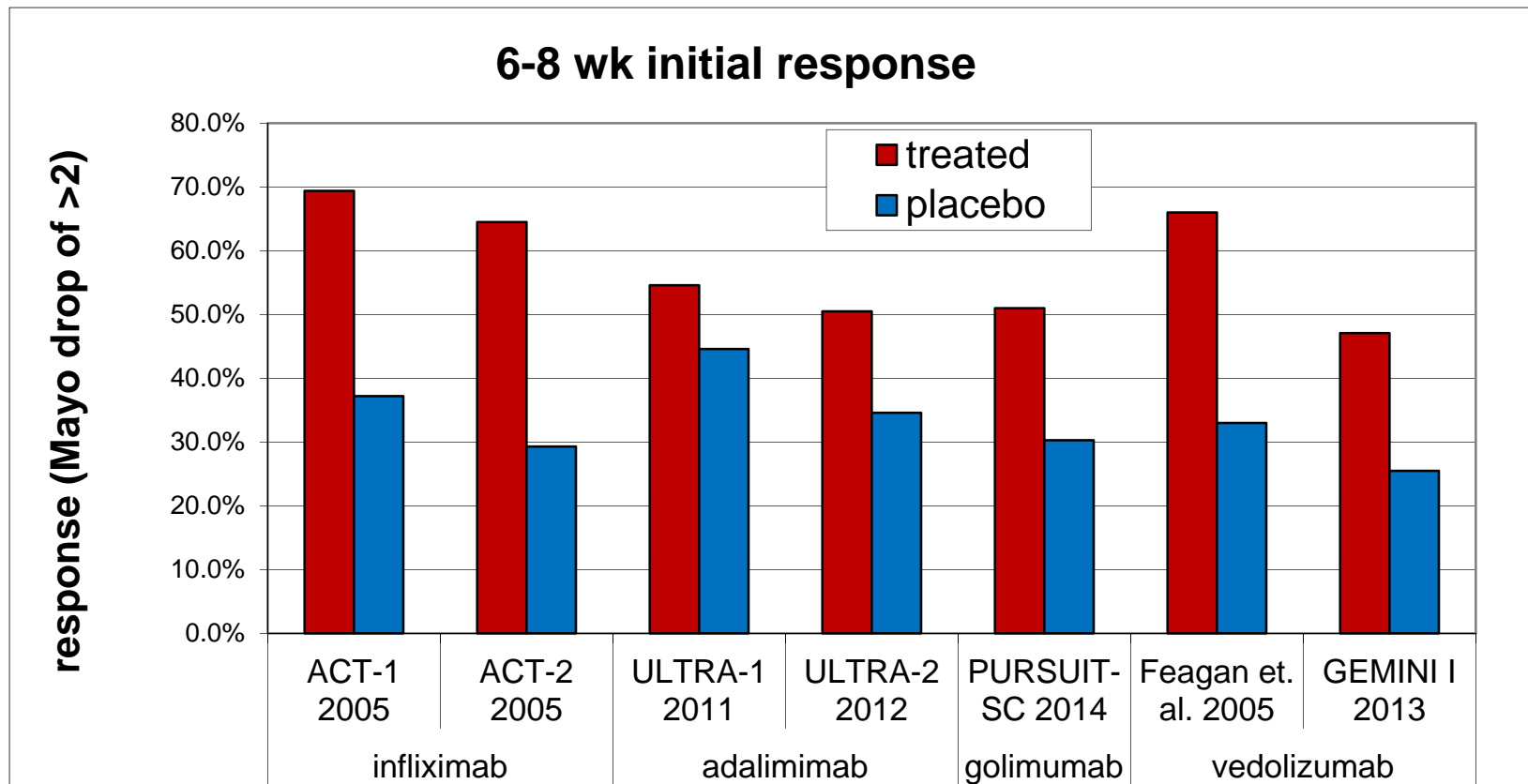
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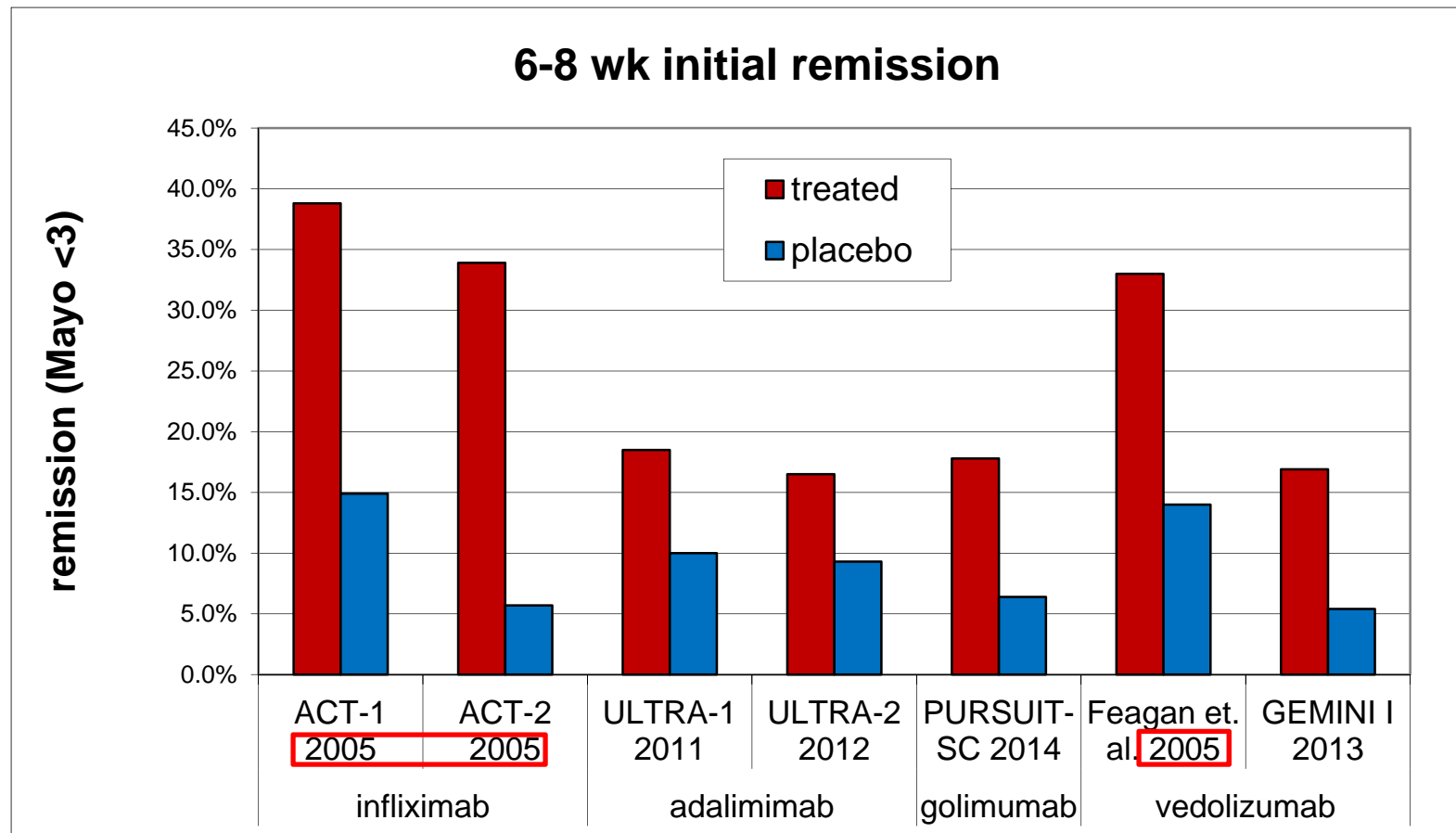
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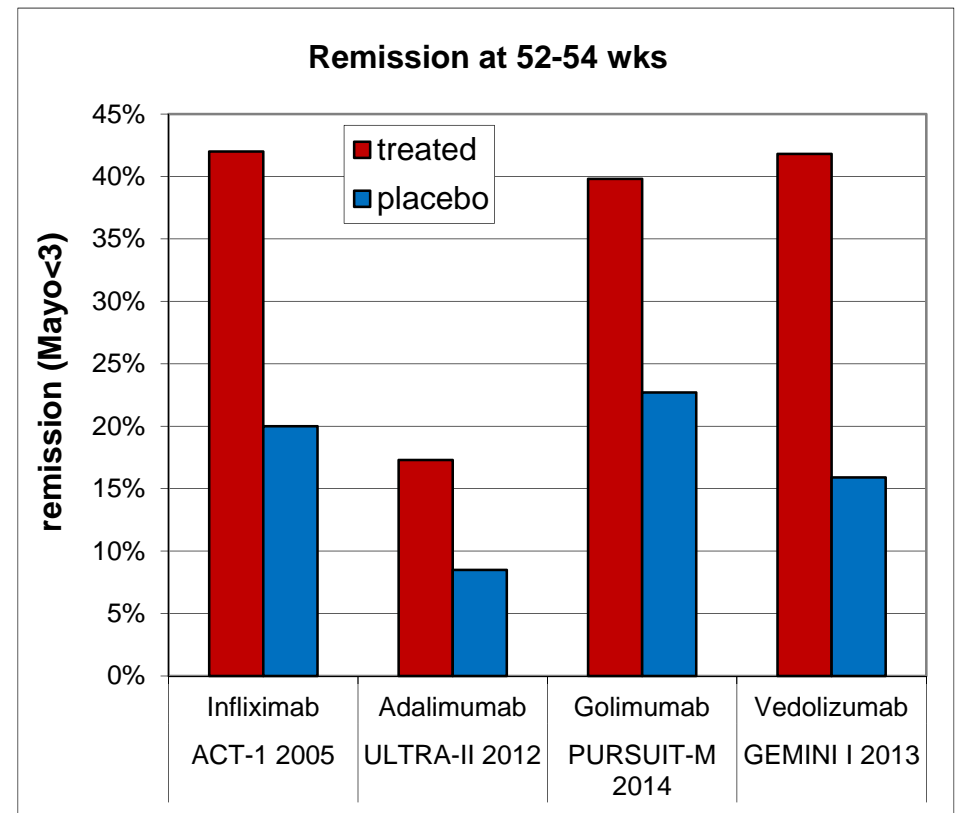
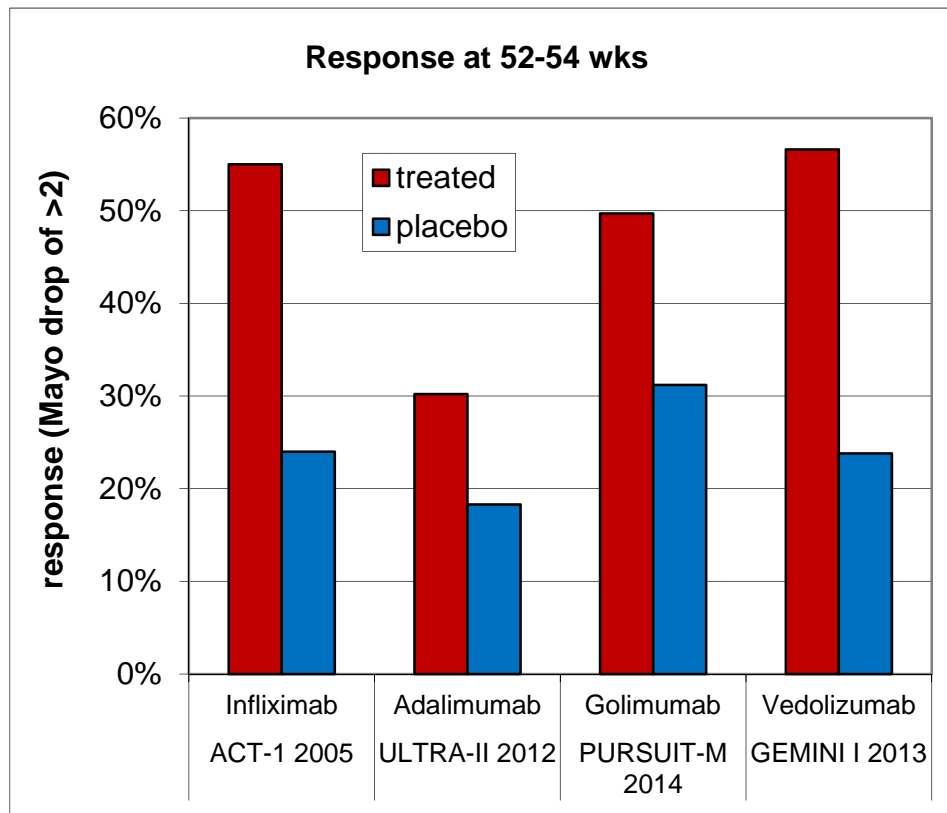
Vedolizumab is not clearly better than anti-TNF for UC induction



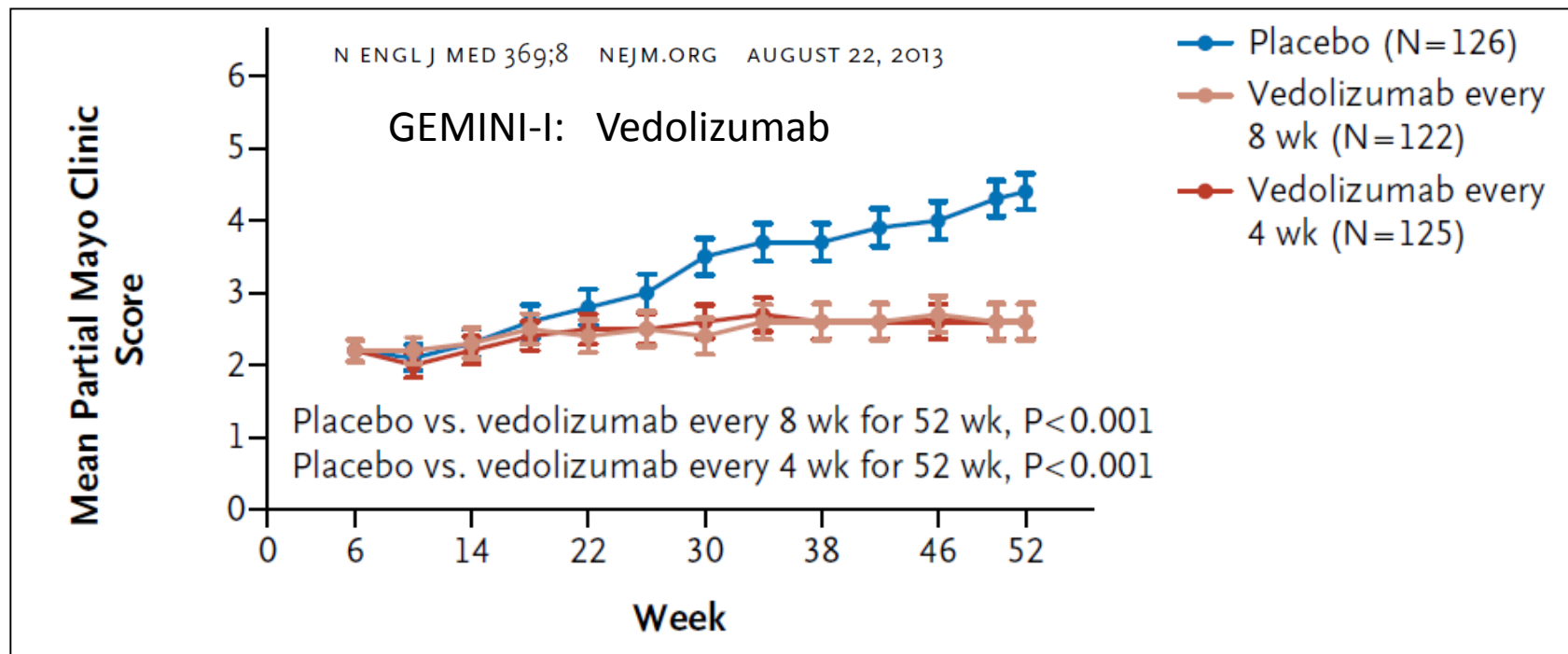
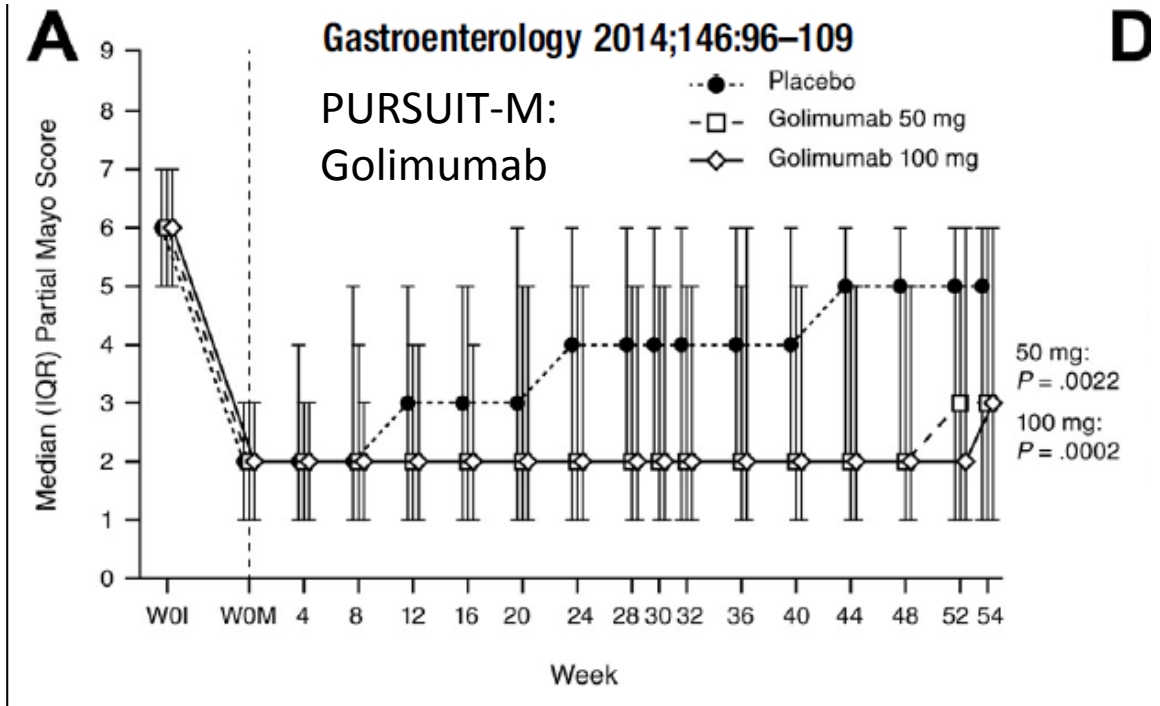
Vedolizumab is not clearly better than anti-TNF for UC induction



Vedolizumab is not clearly better than anti-TNF's for UC maintenance at 1 year



Vedolizumab efficacy for UC maintenance is comparable to anti-TNF



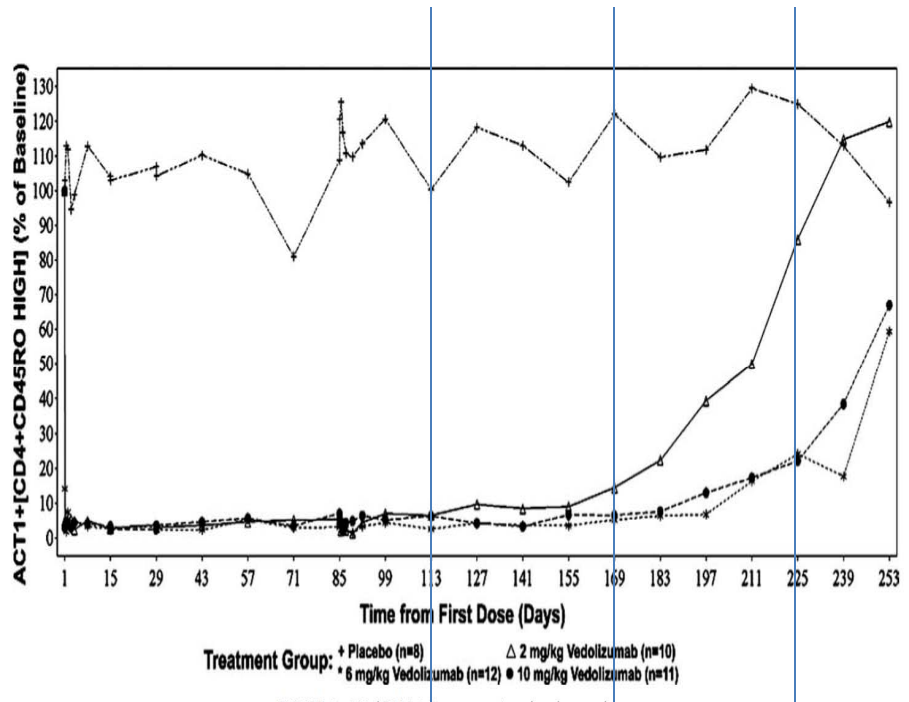
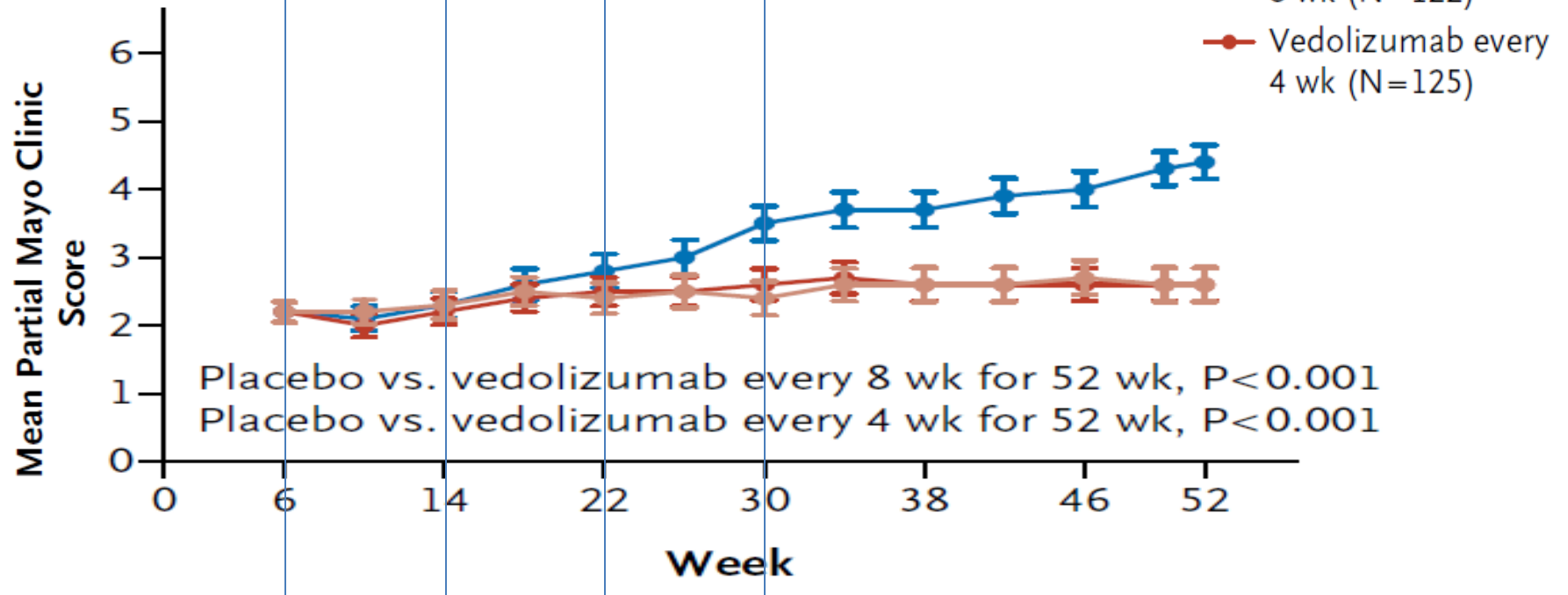
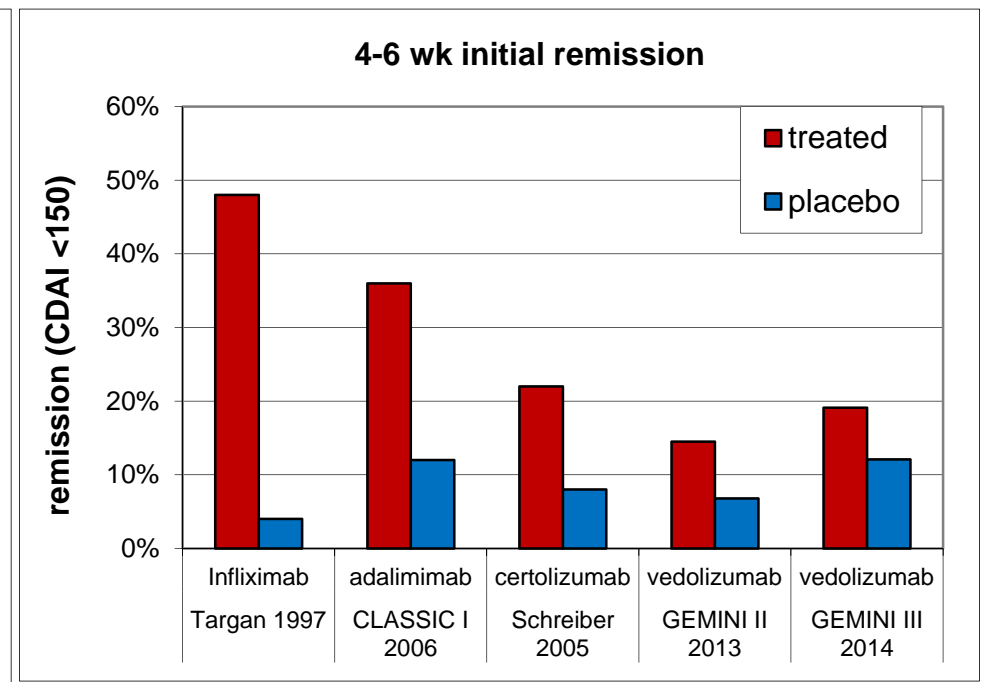
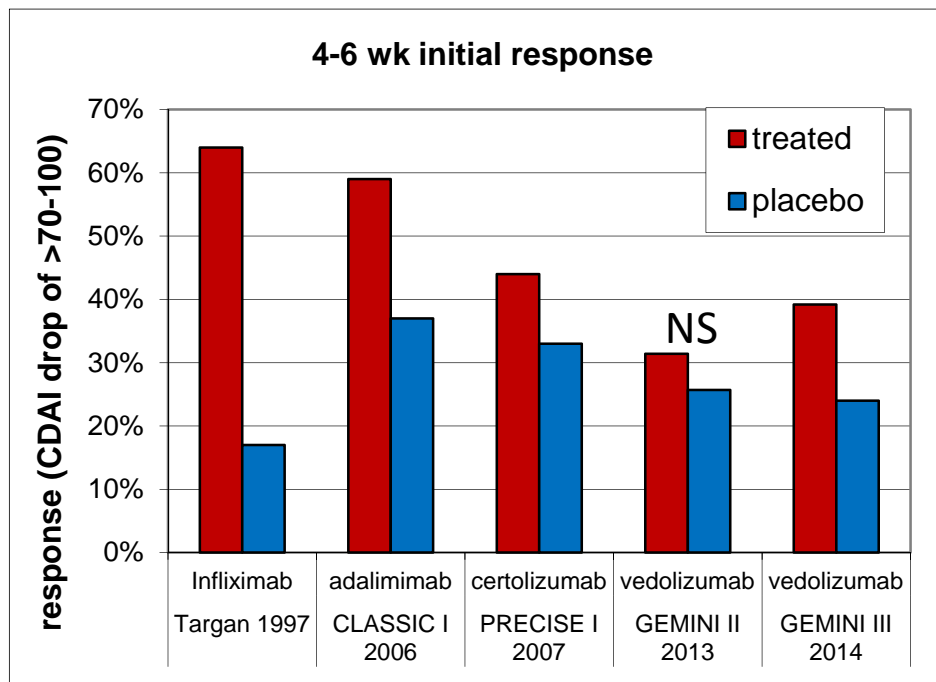


FIGURE 3. MAdCAM-1-Fc+ over time by dose cohort.

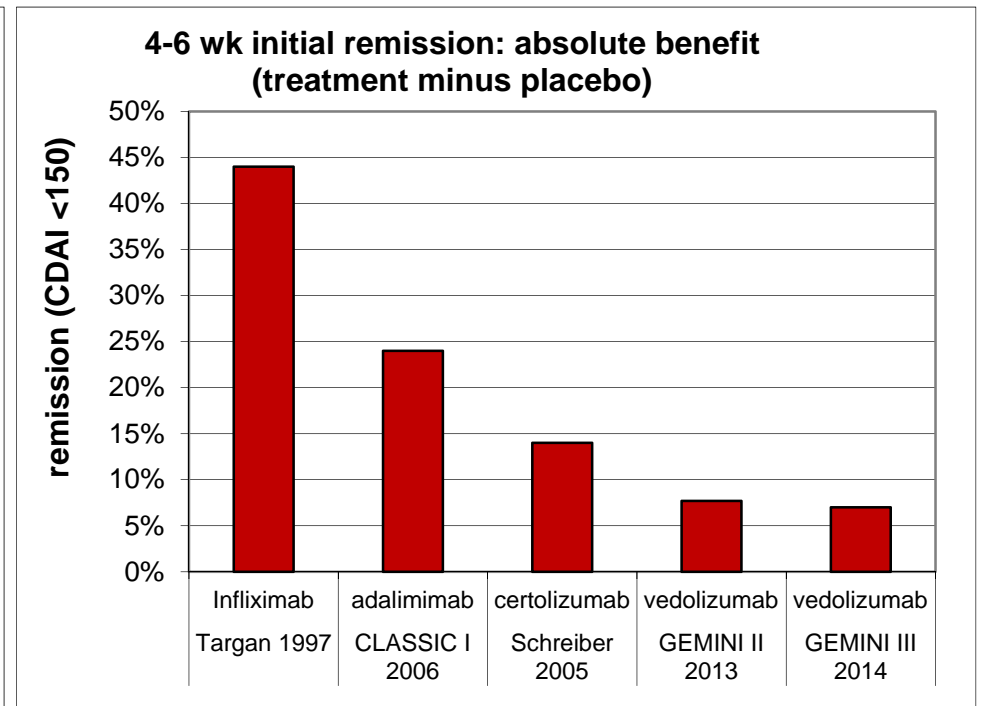
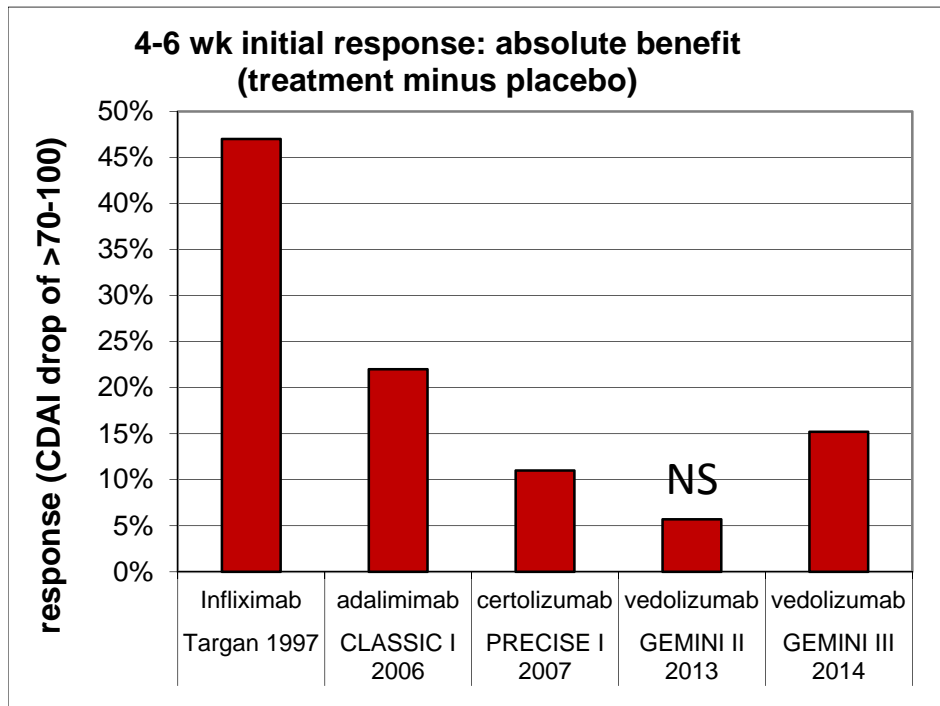
Clinical relapse
lags well behind
pharmacokinetics



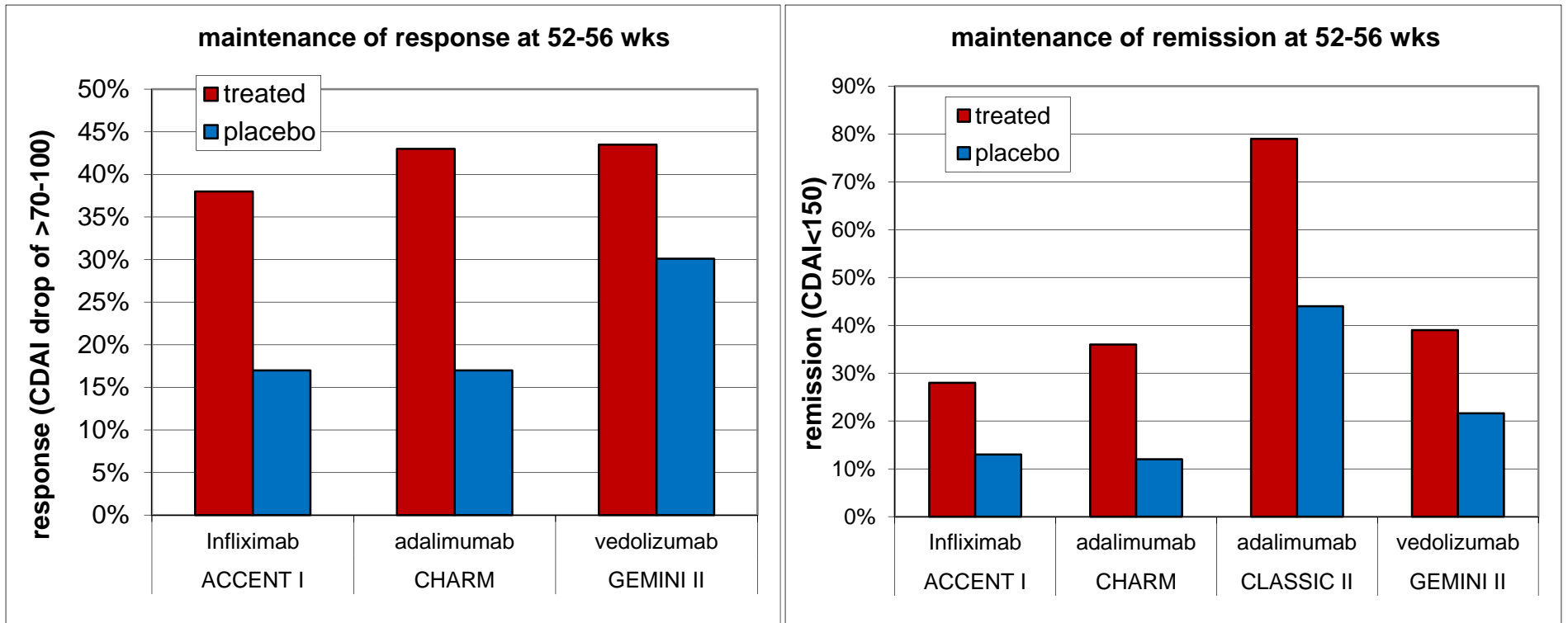
Vedolizumab is less effective than anti-TNF's for Crohn's induction at 4-6 weeks



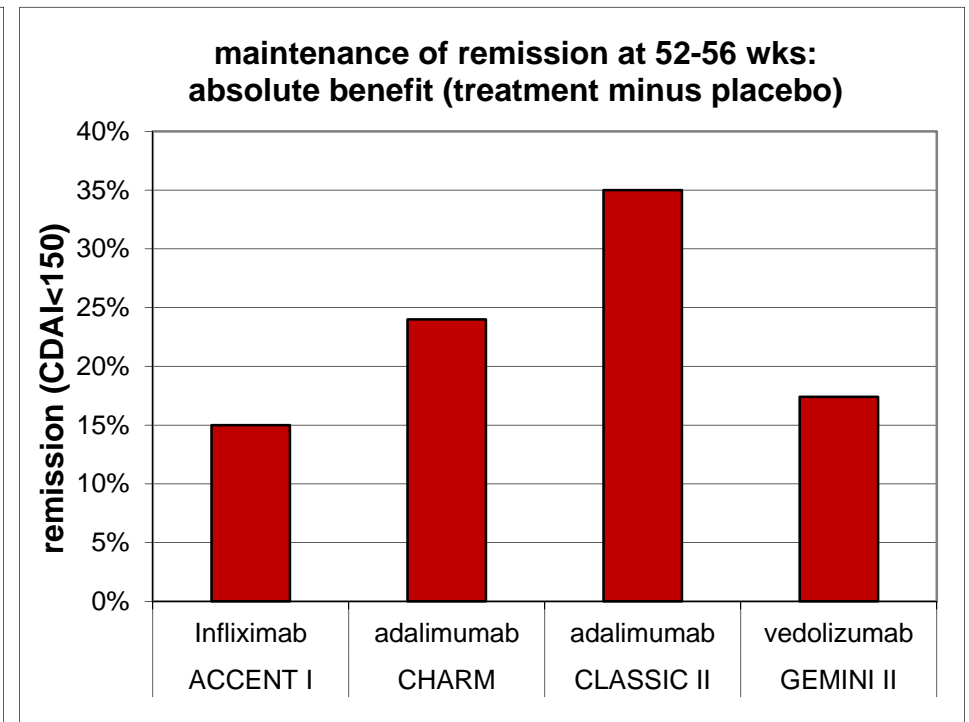
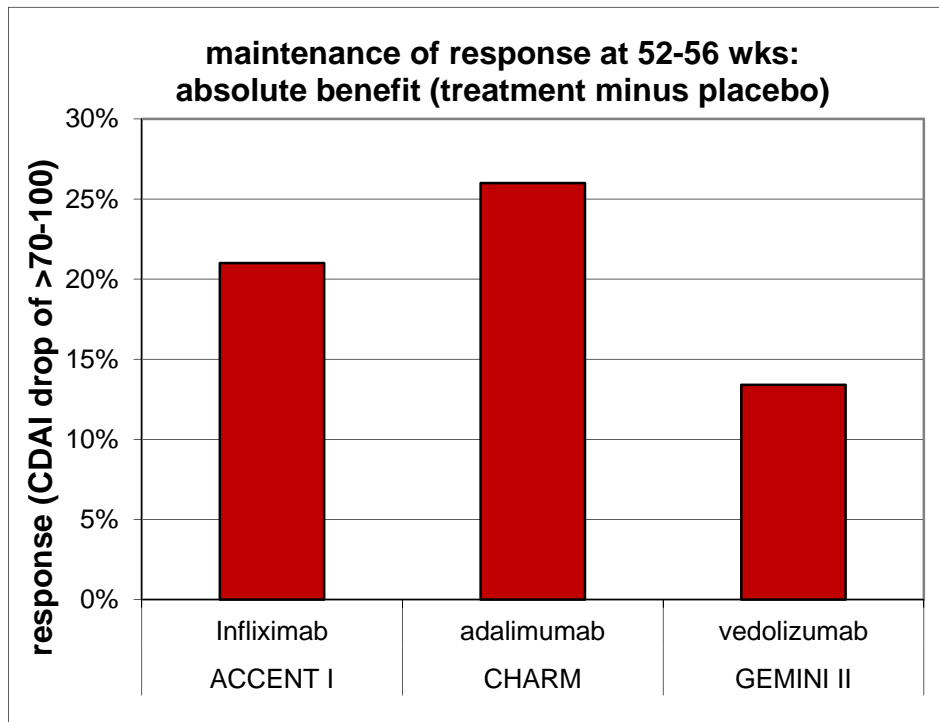
Vedolizumab is less effective than anti-TNF's for Crohn's induction at 4-6 weeks



Vedolizumab is not clearly better than anti-TNF's for Crohn's maintenance at 1 year



Vedolizumab is not clearly better than anti-TNF's for Crohn's maintenance at 1 year

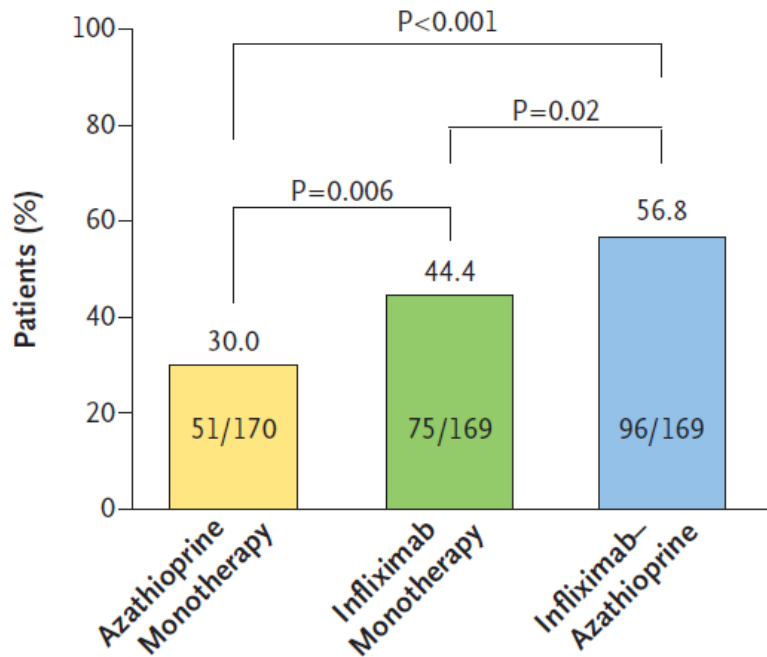


Anti-TNF agents work better in combination with immunomodulators

Crohn's: SONIC

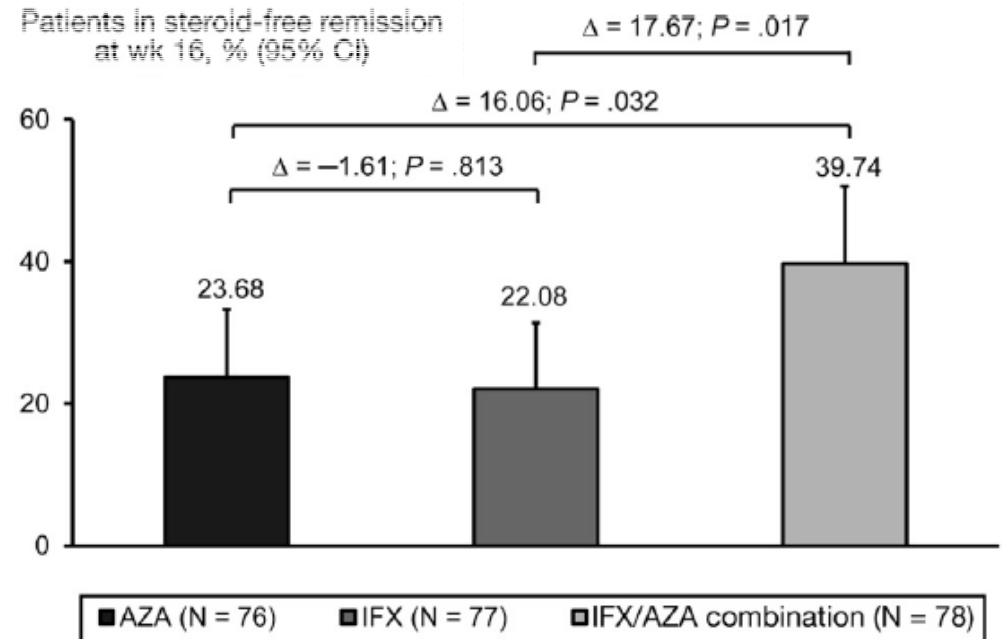
Colombel et. al., *N Engl J Med* 2010;362:1383-95

A Corticosteroid-free Clinical Remission at Wk 26



UC: SUCCESS

Panaccione et. al., *Gastroenterology* 2014;146:392-400



No data on combination therapy with vedolizumab

So, for efficacy:

- if vedolizumab = anti-TNF alone

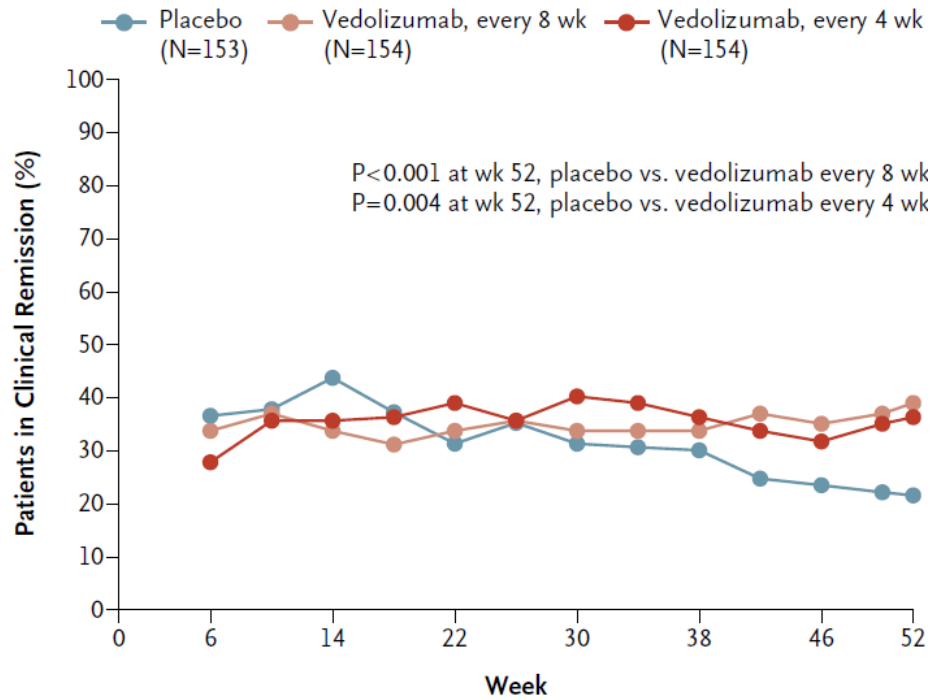
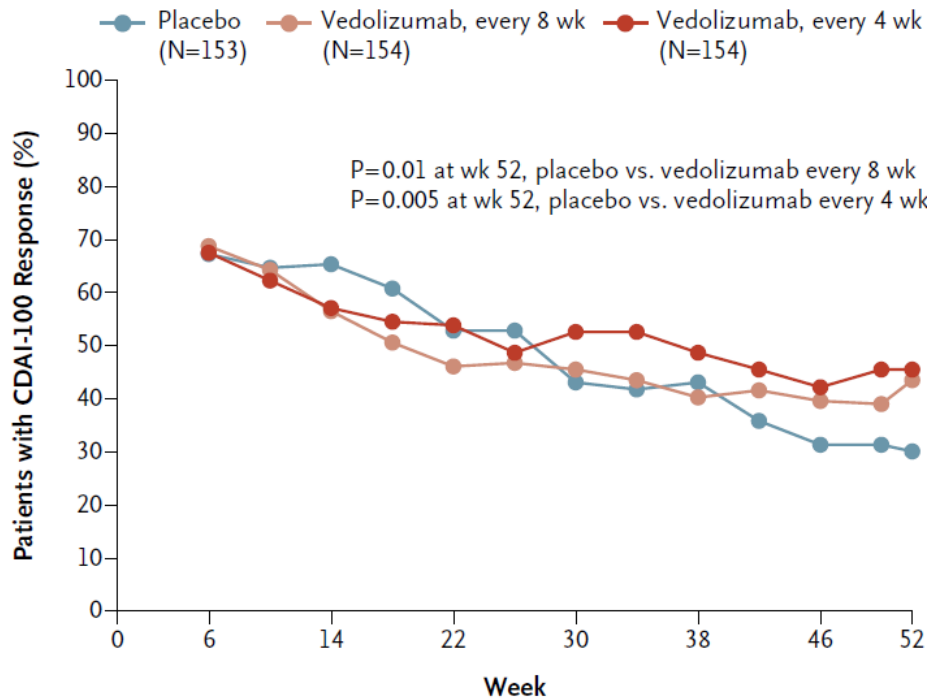
And

- anti-TNF + azathioprine > anti-TNF alone

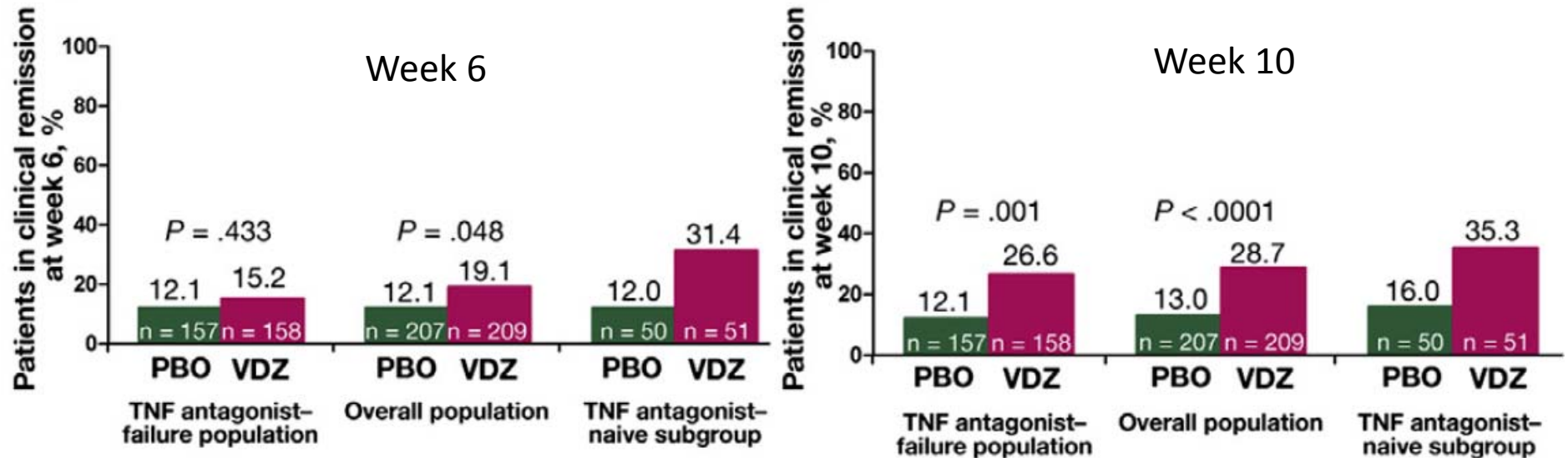
Then

- anti-TNF + azathioprine > vedolizumab

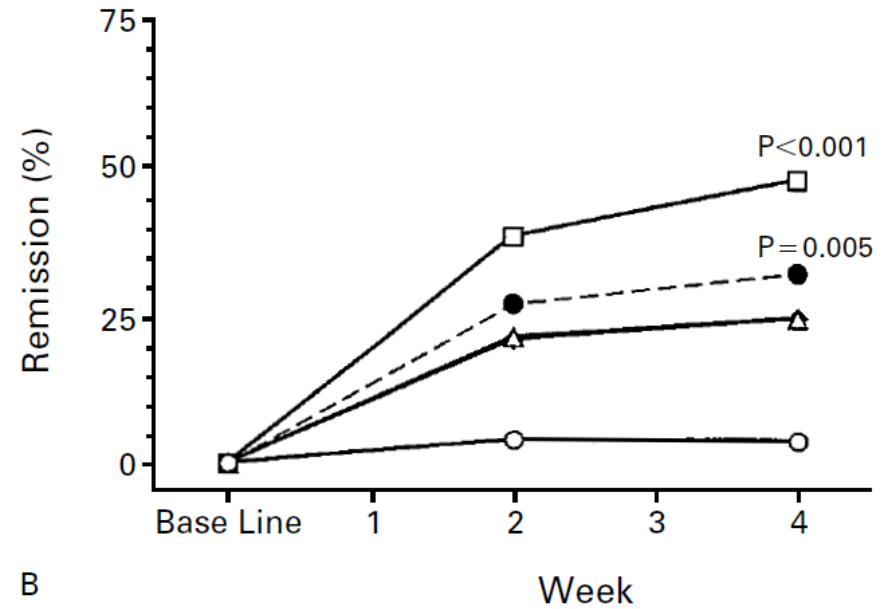
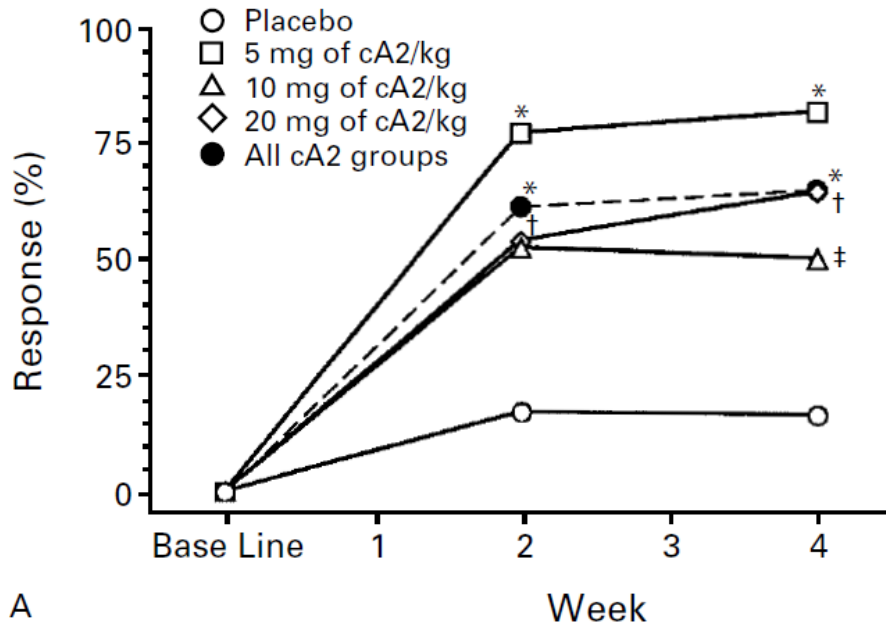
Vedolizumab is slow to show maintenance efficacy in Crohn's



Vedolizumab shows more efficacy at week 10 than week 6 for Crohn's induction of remission (GEMINI-III)



Infliximab (cA2) works quickly



A SHORT-TERM STUDY OF CHIMERIC MONOCLONAL ANTIBODY cA2 TO TUMOR NECROSIS FACTOR α FOR CROHN'S DISEASE

STEPHAN R. TARGAN, M.D., STEPHEN B. HANAUER, M.D., SANDER J.H. VAN DEVENTER, M.D., PH.D., LLOYD MAYER, M.D., DANIEL H. PRESENT, M.D., TANJA BRAAKMAN, M.D., KIMBERLY L. DEWOODY, M.S., THOMAS F. SCHAIBLE, PH.D., AND PAUL J. RUTGEERTS, M.D., PH.D., FOR THE CROHN'S DISEASE cA2 STUDY GROUP

Is Vedolizumab a slower biologic?

- Fast drugs—good for induction
 - Glucocorticoids
 - Calcineurin inhibitors
 - Anti-TNF biologicals
- Slow drugs—good for maintenance
 - Thiopurines
 - Methotrexate
 - Vedolizumab



Mechanism of action may differentiate speed of biopharmaceuticals

- Anti-TNF agents
 - Block soluble hormone with a short half life
 - TNF is rapidly synthesized
 - TNF effects are immediate
- Anti-integrins (Vedolizumab)
 - Block circulating cells with a long half life
 - Mucosal lymphocyte recirculation is slow

How would one use a slow drug as “first line” therapy?

- Too slow to be practical for inpatient use
- Too slow to be induction therapy for urgent patients
- Use alongside a faster induction agent?
 - Steroids or calcineurin inhibitor?
 - Increased toxicity
 - A faster biologic agent?
 - Increased cost, immunogenicity

What if it doesn't work?:

Cannot dose-optimize vedolizumab

- Only one dosing regimen
 - Not weight-based
 - Fixed schedule
- No assays to monitor levels
 - Serum levels of free drug
 - Receptor saturation on circulating lymphocytes

Should Vedolizumab be “first line”?

- Cost
 - More than infliximab, unless:
 - Patient >100 kg
 - Infliximab dose > 5 mg/kg or interval < q8 wks
 - Vedolizumab dose interval > q8 wks
 - Cannot compare to SQ medications due to IV fees
- Convenience
 - Similar to infliximab (unless able to lengthen dose interval)
 - Worse than SQ medication
- Safety
 - Similar to anti-TNF’s for common or early events
 - Unknown for rare or late events (minimal post-marketing data)
- Efficacy
 - Similar to anti-TNF for UC induction and maintenance
 - Worse than anti-TNF for Crohn’s induction
 - Possibly comparable to anti-TNF for Crohn’s maintenance

Conclusion

- First line therapy for UC or Crohn's should be combination therapy with anti-TNF + thiopurine, if possible
- If thiopurine-intolerant or obese, vedolizumab and anti-TNF therapy are comparable for UC
- Vedolizumab is inferior to anti-TNF monotherapy for Crohn's