

Biologic Drugs in Inflammatory Bowel Disease

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Outline

- Types of biologic drugs
- How do they work?
- How effective are they?
- Safety/Toxicity concerns with biologics

Biologic Drugs

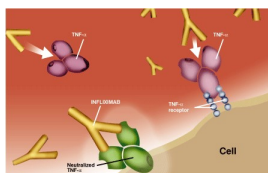
- Drugs are called “biologic” because they are produced by living cells, not manufactured.
- Immune cells in the body create proteins called antibodies that attach to specific targets (bacteria, viruses)
- Biologic drugs are antibodies designed to attach to specific proteins or hormones involved in inflammation that causes IBD

Biologic Drugs

- Anti-tumor necrosis factor (TNF) – α
 - Infliximab (Remicade®) – UC and CD
 - Adalimumab (Humira®) – UC and CD
 - Certolizumab (Cimzia®) – CD only
 - Golimumab (Simponi®) – UC only
- Anti-integrin
 - Vedolizumab (Entyvio®) – UC and CD
- Anti-interleukin (IL) -12/23
 - Ustekinumab (Stelara®) – CD only

Biologic Drugs

- Tumor necrosis factor (TNF) – α
 - Inflammatory hormone involved in IBD
 - Activates white blood cells that cause ulcers and inflammation in IBD
 - Crohn’s > Ulcerative colitis



Biologic Drugs – Anti-TNF

- Infliximab (Remicade®)
- FDA Approval
 - Adult and pediatric moderate to severe Crohn’s
 - Induction and maintenance
 - Adult and pediatric moderate to severe UC
 - Induction and maintenance
 - Treatment of bowel to skin fistulas and rectovaginal fistulas

Biologic Drugs – Anti-TNF

- Infliximab (Remicade®)
- Dosing
 - Intravenous infusion over ~2 hours
 - Based on weight
 - Induction: week 0, 2, and 6
 - Maintenance: every 8 weeks

Biologic Drugs – Anti-TNF

- Infliximab (Remicade®)
- Advantages
 - Levels of the drug in the blood can be measured
 - Don't need to inject self
- Disadvantages
 - Need to come to clinic/hospital for infusions

Biologic Drugs – Anti-TNF

- Adalimumab (Humira®)
- FDA Approval
 - Moderate to Severe Crohn's in adults and pediatrics
 - Induction and maintenance
 - Moderate to Severe ulcerative colitis in adults
 - Induction and maintenance
- Dosing
 - Self administered injection under the skin
 - Induction: 160mg (4 syringes) on week 0, 80mg (2 syringes) on week 2, 40mg on week 4
 - Maintenance: 40mg (one syringe) every 2 weeks

Biologic Drugs – Anti-TNF

- Advantages
 - Medication given at home
 - Levels of the drug can be measured
- Disadvantages
 - You (or friend/family) must administer the shot

Biologic Drugs – Anti-TNF

- Certolizumab (Cimzia®)
- FDA Approval
 - Moderate to severe Crohn's disease in adults
 - Induction and maintenance
- Dosing
 - Self administered injection under the skin
 - Induction: 400mg (two syringes) on week 0, 2, and 4
 - Maintenance: 400mg (two syringes) every 4 weeks

Biologic Drugs – Anti - TNF

- Certolizumab (Cimzia®)
- Advantages
 - Inject medication at home
- Disadvantages
 - Cannot measure drug level in the blood
- ? Advantage
 - Large molecule that does not cross placenta
 - Safety for baby in pregnancy? (more later)

Biologic Drugs – Anti - TNF

- Golimumab (Simponi®)
- FDA Approval
 - Moderate to severe ulcerative colitis in adults
 - Induction and maintenance
- Dosing
 - Self administered injection under the skin
 - Induction: 200mg (two syringes) on week 0, 100mg (one syringe) week 2.
 - Maintenance: 100mg every 4 weeks

Biologic Drugs – Anti - TNF

- Golimumab (Simponi®)
- Advantages
 - Inject medication at home
 - Low total number of injections
- Disadvantages
 - Cannot measure drug level in the blood

Definitions

- Response
 - Improvements in abdominal pain, diarrhea and rectal bleeding, but not necessarily completely normal bowel function.
- Remission
 - Improvements in abdominal pain and diarrhea to essentially normal bowel function.

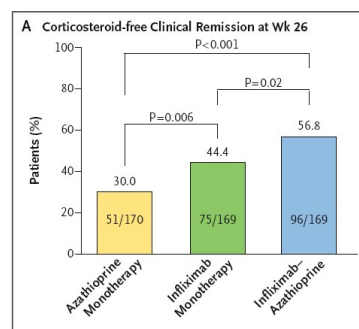
Anti-TNF - Effectiveness

- No direct comparison between the anti-TNF drugs
- Crohn's disease
 - Studied in patients that have already not responded to mesalamine, azathioprine/mercaptopurine
 - Approximately 60-70% respond to anti-TNF drugs within 6 weeks
 - Approximately 40% of responders will be in remission (symptom free) after one year
 - Approximately 65% of responders will maintain response after one year (symptom improvement, but not symptom free)

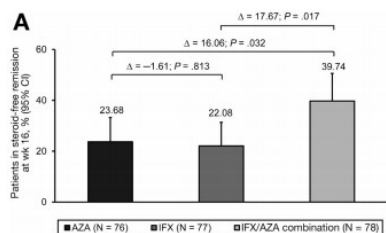
Biologic Drugs - Effectiveness

- Ulcerative Colitis
 - Studied in patients that have already failed mesalamine, azathioprine/mercaptopurine
 - Approximately 50-65% will have a response after 8 weeks
 - Approximately 30-35% will have remission after 8 weeks
 - Approximately 30-50% will have continued response after one year, 20-30% remission after one year.

Combination Therapy – Crohn's



Combination Therapy – UC



Safety/Toxicity of Anti-TNF

- Infections
 - Tuberculosis
 - Need to be tested before starting
 - Hepatitis B
 - Need to be tested before starting
 - Get vaccine if not already done

Safety/Toxicity of Anti-TNF

- Serious Infections in Crohn's disease
 - Anti-TNF increases risk 43%
 - Prednisone increases risk 57%
 - Opioid use doubles the risk
 - Moderate to severe Crohn's more than doubles the risk

Safety/Toxicity of Anti-TNF

- Infusion reaction (infliximab – Remicade)
 - Rash, trouble breathing, wheezing
 - Moderate reaction 1.2%, severe reaction 1%
 - Pre-treatment with Tylenol and Benadryl prevented reaction in all prior moderate reactors and 66% of severe reactors
 - Treatment with azathioprine reduces risk

Safety/Toxicity of Anti-TNF

- Lowered white blood cell count
 - Severe in less than 1%
 - Reversible
 - Should be monitored from time to time
- Liver Injury/Autoimmune hepatitis
 - Rare
 - Reversible
 - Should be monitored from time to time

Safety/Toxicity of Anti-TNF

- Psoriasis
 - Perhaps up to 10% with long term use
 - Reversible
 - Often can continue the biologic
- Drug-induced lupus
 - Very rare
 - Reversible
- Heart Failure
 - Very rare, potentially 1 in 2000
 - May be reversible
- Neurologic damage
 - Very rare, potentially 1 in 4000
 - Potentially permanent

Safety/Toxicity of Anti-TNF

- Skin Cancer
 - Increased risk of non-melanoma skin cancers (close to 2x increase)
 - Increased risk of melanoma skin cancer (88% increase)
 - Use sunscreen and other protection

Safety/Toxicity of Anti-TNF

- Lymphoma
 - The evidence is very conflicting
 - Azathioprine increases risk of lymphoma approx 4x (1 in 2500)
 - Combination AZA and anti-TNF increases risk of lymphoma about 6x (1 in 1667)
 - Best studies for anti-TNF alone suggests at worst less than doubling of risk (less than 1 in 5000)

Safety/Toxicity of Anti-TNF

- Hepatosplenic T Cell Lymphoma
 - Rare lymphoma (36 known cases in IBD)
 - Severe and usually fatal
 - Occurs mainly in men (94%), younger than age 35 (90%)
 - 16 treated with azathioprine, 20 treated with combination AZA/biologic
 - Risk estimates
 - Azathioprine (1 in 45,000)
 - Combination Therapy (1 in 22,000)

Anti-TNF Drugs in Pregnancy

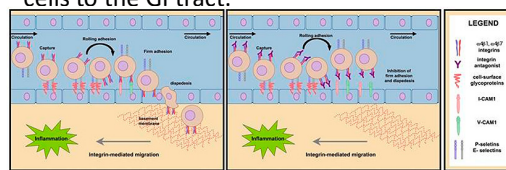
- The best predictor of pregnancy outcome in IBD is the health of the mother.
- Recent study of 1050 pregnant IBD patients
 - Unexposed, azathioprine, anti-TNF biologics or combination therapy
 - Congenital abnormality in 4%
 - About the same as non-IBD pregnancy
 - No difference between groups

Anti-TNF Drugs in Pregnancy

- No difference between drug exposure groups in development milestones of infant up to 12 months
- No increased risk of infection if breastfed
- 35% increased risk of infection in infant at 12 months in combination treated patients versus no exposure
- Discuss stopping or continuing IBD medications with your GI and OB doctors.

Anti-integrin

- Integrins are proteins that help white blood cells move to different parts of the body
- $\alpha 4\beta 7$ is an integrin that moves white blood cells to the GI tract.



Anti-integrin

- Vedolizumab (Entyvio®)
- FDA Approval
 - Moderate to Severe Crohn’s in adults
 - Achieving remission, mainly maintenance
 - Moderate to Severe ulcerative colitis in adults
 - Induction and maintenance
- Dosing
 - Given intravenously over a 30 minute infusion
 - Induction: 300mg on week 0,2, and 6
 - Maintenance: 300mg every 8 weeks

Anti-integrin

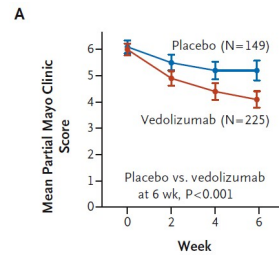
- Advantages
 - Minimal to no increased infection risk
- Disadvantages
 - Slow onset (especially Crohn’s)
 - Must be given in clinic/hospital

Vedolizumab - Effectiveness

- Ulcerative colitis
 - Response by week 8 in 47%, Remission in 17%
 - Among responders, at one year durable response in 57%
 - Among responders, at one year remission in 42%

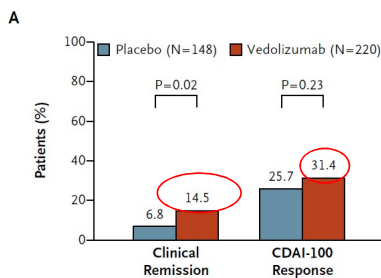
Vedolizumab - Effectiveness

- Relatively quick onset in UC



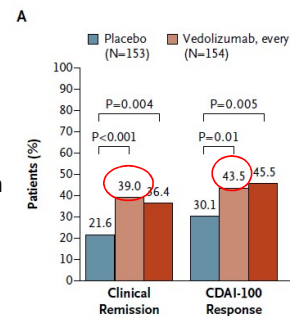
Vedolizumab - Effectiveness

- Crohn’s disease – week 6



Vedolizumab - Effectiveness

- Crohn’s disease – one year among responders
- Onset of action much slower than in ulcerative colitis, up to 3 months



Vedolizumab - Safety

- Crohn's disease

Event	Placebo (N=301)	Vedolizumab (N=814)
	no. (%)	
Adverse event		
Crohn's disease exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Back pain	12 (4.0)	38 (4.7)
Any serious adverse event	46 (15.3)	199 (24.4)
Any serious infection†	9 (3.0)	45 (5.5)
Any cancer‡	1 (0.3)	4 (0.5)

Vedolizumab - Safety

- Ulcerative Colitis
- Very little known in pregnancy

Event	Placebo (N=275)	Vedolizumab (N=620)
	no. of patients (%)	
Headache	28 (10.2)	80 (12.9)
Ulcerative colitis	58 (21.1)	97 (15.6)
Nasopharyngitis	26 (9.5)	80 (12.9)
Upper respiratory tract infection	21 (7.6)	52 (8.4)
Arthralgia	25 (9.1)	56 (9.0)
Nausea	19 (6.9)	38 (6.1)
Abdominal pain	10 (3.6)	35 (5.6)
Anemia	16 (5.8)	35 (5.6)
Fatigue	10 (3.6)	33 (5.3)
Cough	13 (4.7)	36 (5.8)
Any serious adverse event	37 (13.5)	77 (12.4)
Any serious infection†	8 (2.9)	12 (1.9)
Any cancer	3 (1.1)§	1 (0.2)§

Anti-IL12/23

- Hormones that activate white blood cell inflammation.
- Ustekinumab blocks two hormones with similar parts.

a

Intracellular signaling

b

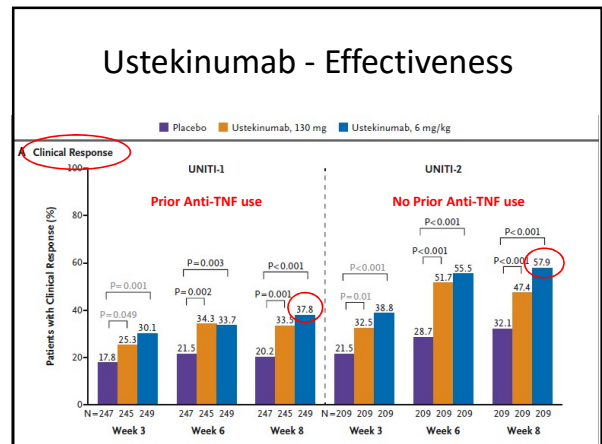
No signal

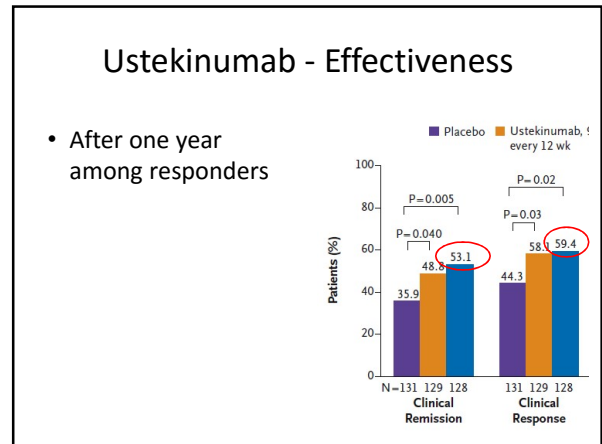
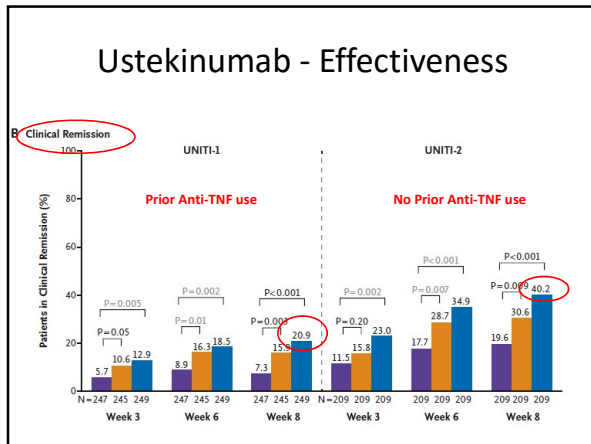
Anti-IL12/23

- Ustekinumab (Stelara®)
- FDA Approval
 - Moderate to Severe Crohn's disease
- Dosing
 - Induction: Single intravenous infusion based on weight
 - Maintenance: 90mg (one syringe) injection every 8 weeks

Anti-IL12/23

- Advantages
 - Mainly given at home with infrequent injections
- Disadvantages
 - Your insurance will not want to pay for this





- ### Ustekinumab - Safety
- Must be tested for tuberculosis prior to starting
 - No obvious increase in serious infections
 - Slight increased risk of nasopharyngitis
 - Very little known about pregnancy

- ### Biologic Drugs can stop working
- Patient's body forms antibodies against the drug
 - Bodies immune response to a protein that shouldn't be there
 - Can be measured with infliximab or adalimumab
 - Increasing dose may regain response (temporary)
 - Often need to change to different drug

- ### How can you prevent forming antibodies against a biologic?
- Take doses on schedule
 - Less likely to occur if the amount of drug in the bloodstream doesn't reach zero
 - Restart drug with full initial dosing when a break in dosing occurs
 - Simultaneous use of azathioprine (or similar medications)
 - Often recommended when switching to new biologic

Questions?