Solving the puzzle of Biologic Use in Pediatric IBD

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JANUARY 30, 2018

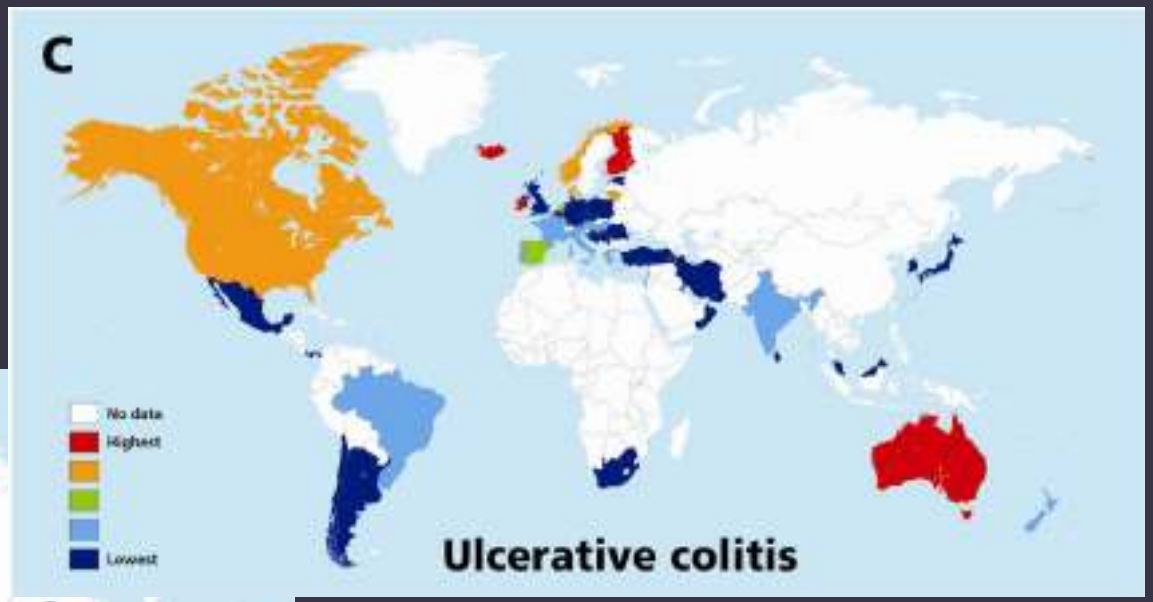
Objectives

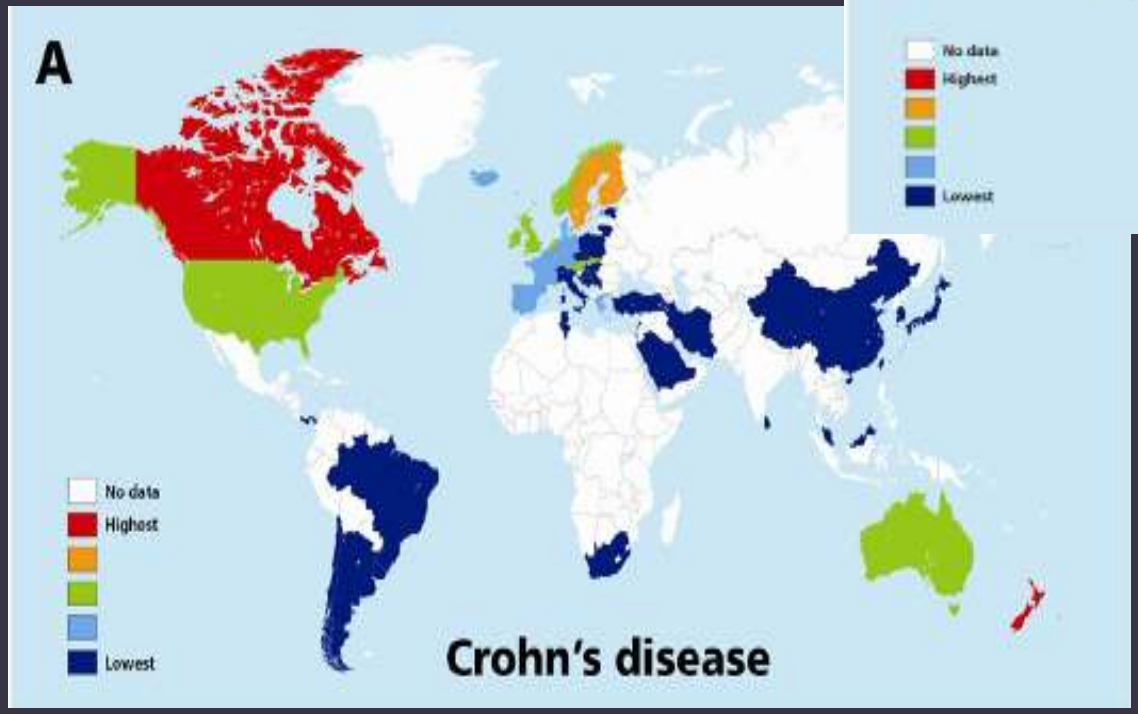
Compare biologic agents; classes, efficacy, and adverse reactions

Examine the use of combination therapy in pediatric IBD

Review therapeutic drug monitoring application to biologic agents and IBD

Evaluate the use of biosimilar agents for treatment pediatric IBD





Incidence of IBD in children living in US

- 2-7 children per 100,00 are affected annually (we are #1)
- 25% of IBD diagnosed annually is in children < 18 y

Corica D. J Clin Gastroenterol 2016; DOI: 10.1097, Lee W, Inflamm Bowel Dis 2016; 22: 2410-7.

Background

Pediatric patients with IBD experience

- Linear growth stunting
- Delay onset of puberty
- Reduced bone mass index

Pediatric patients often have a more rapid, aggressive progression and extensive intestinal involvement

- Example 70-80% of children diagnosed UC present with pancolitis

Biological therapy is used more frequently in adolescents (20%) compared to adults (8%)

Corica D. J Clin Gastroenterol 2016; DOI: 10.1097, Lee W, Inflamm Bowel Dis 2016; 22: 2410-7.

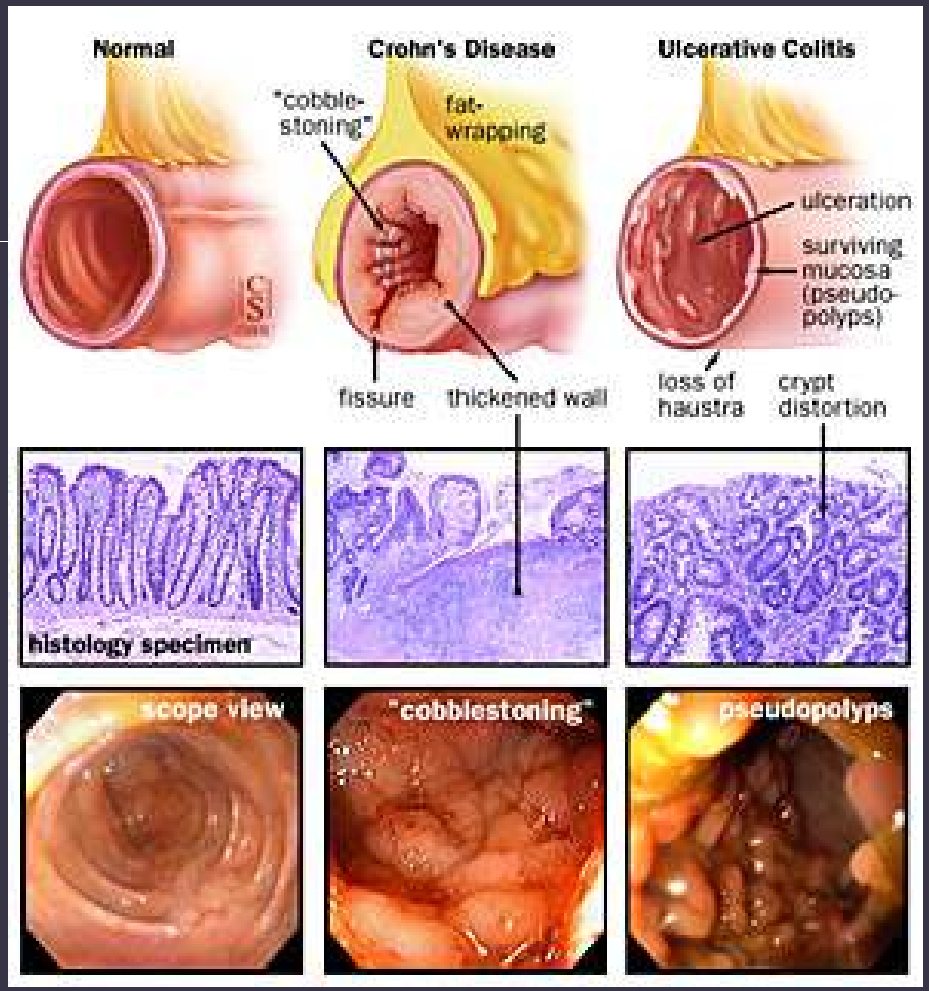
Types of IBD

Crohn's Disease	Ulcerative Colitis
Male = Female	Male
↓ Growth velocity 50%	↓ Growth velocity 3-10%
	families
Any part of the gastrointestinal tract	Colon
Entire thickness of bowel wall	Limited to mucosa
Skip lesions or patches	Continuous

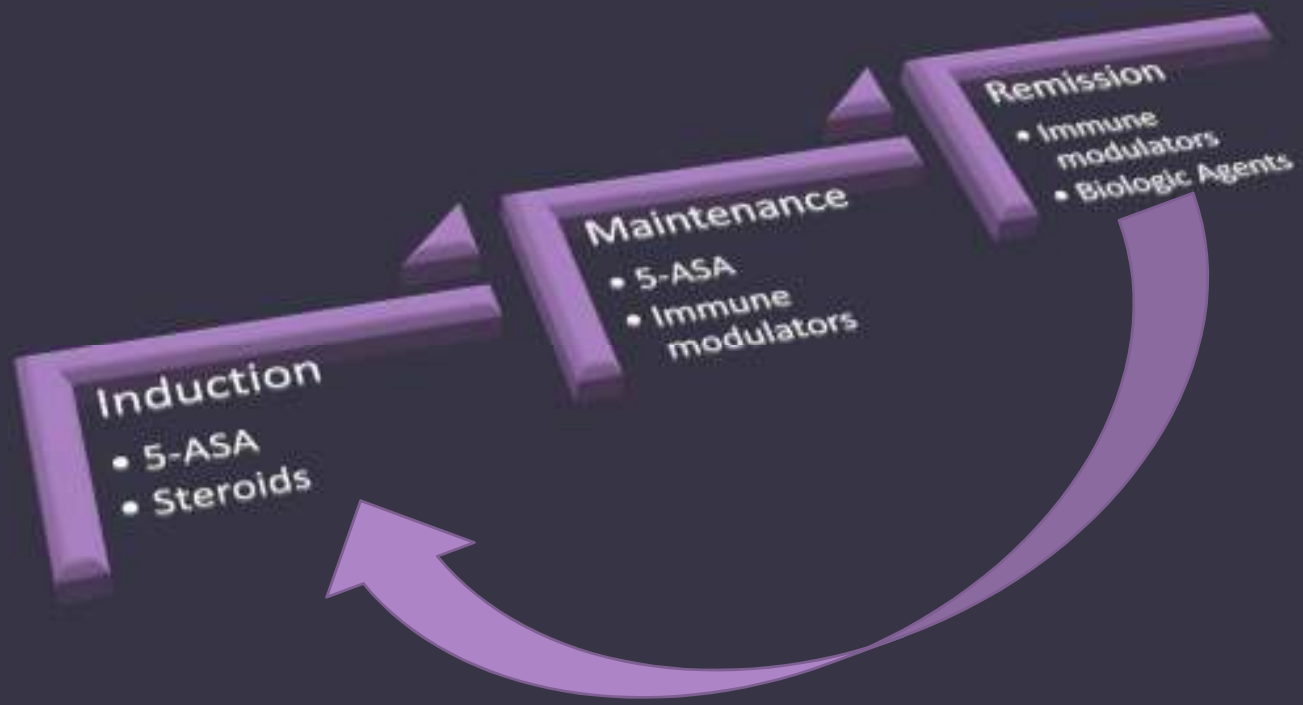
Indeterminate colitis

Overlapping features

10% of pediatric patients



Treatment Strategy



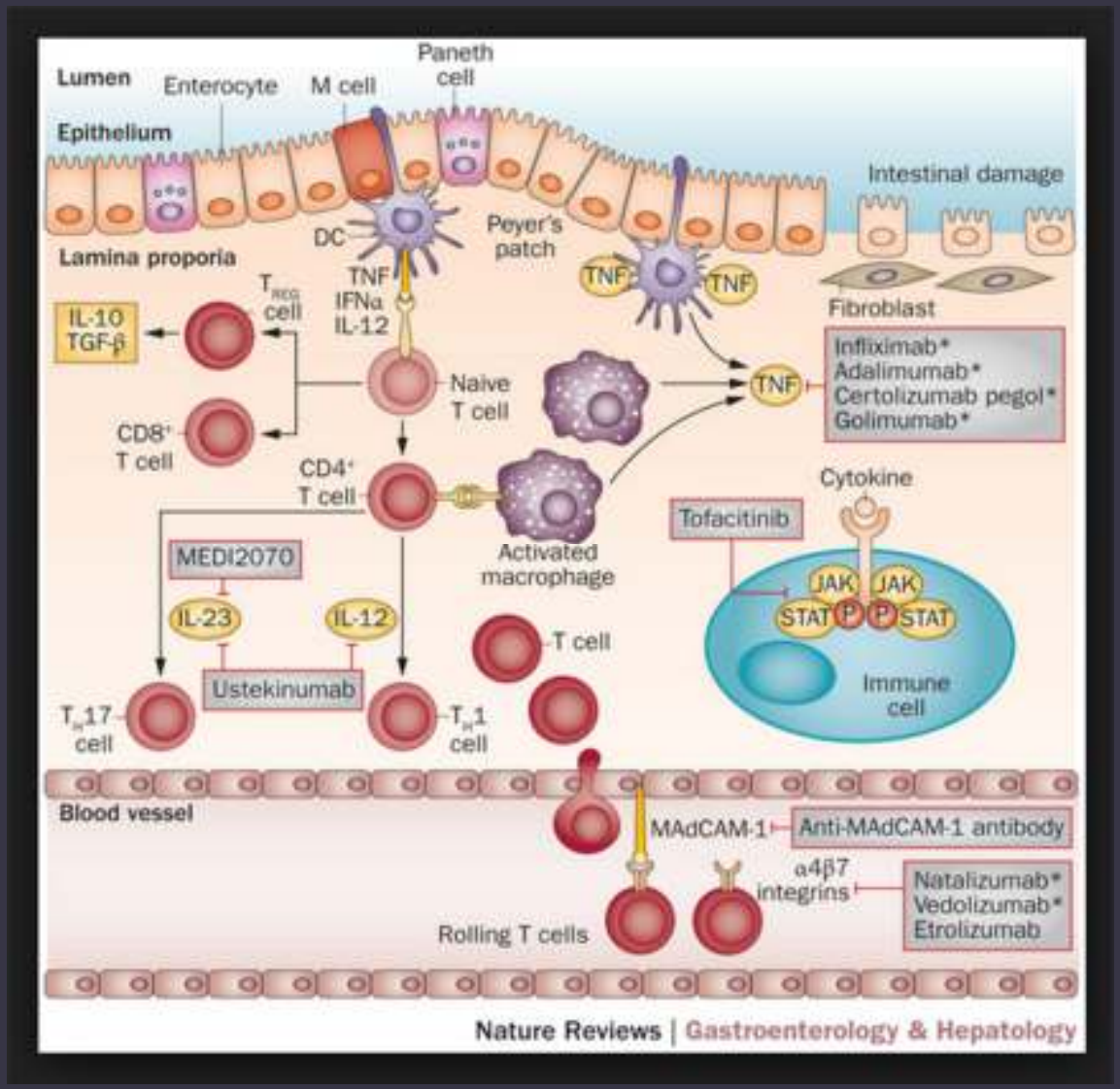
Goals of Treatment

1. Induce and maintain clinical remission
2. Achieve normal growth
3. Provide the best quality of life
4. Promote psychological health
5. Minimize toxicity
6. Achieve mucosal healing endoscopically

Therapies for Moderate to Severe IBD

Anti-Tumor Necrosis Factor-α Agents

- Bind to the Fc-receptor on both types of TNF and neutralize
  - Transmembrane TNF-α on cell surfaces
  - Soluble TNF-α floating around
- Induces apoptosis of monocytes and T-cells
- Block antibody dependent cell mediated cytotoxicity
- Complement dependent cytotoxicity



de Bie, C. Inflamm Bowel Dis. 2012; 18:981-998. Danese S, Nat Rev Gastro and Hep 12, 2015

Medication	Induction	Maintenance	Manufacture
Anti-Tumor Necrosis Factor α (A-TNF)			
Infliximab (Remicade®) IFX	5mg/kg IV @ 0, wk 2, wk 6	5mg/kg IV q 8 wk	Janssen Biotech, 2006
Adalimumab(Humira®) ADA	≥6 y, 17- 40 kg • 80mg SC on D 0, then 40mg SC on D15, D29 ≥40kg • 160mg SC D 0, then 80mg SC on D15, D29 Ulcerative colitis • 100mg/m^2 SC (max.160mg), then 50mg/m^2 SC (max. 80mg) on D15, then 25mg/m^2 SC (max. 40mg)	<40kg • 20mg SC q14 d ≥40kg • 40mg SC q14 d Ulcerative colitis • 25mg/m SC q14 d	AbbVie, 2012
Certolizumab pegol (Cimzia®) CER	400mg SC D0, wk 2, wk 4	400mg SC q month	UCB, 2008
Golimumab(Simponi®) GOL	Ulcerative colitis 200mg SC D0, 100mg SC wk2	100mg SC q 4 wk	Janssen Biotech, 2013

de Bie,. Inflamm Bowel Dis. 2012; 18:981-998. Corica D. J Clin Gastroenterol 2016; DOI: 10.1097,

A-TNF α Agents

IFX
- Most studied within the group
- Administered as an IV infusion
  - Can be associated with AIR (acute infusion reactions) 9.3%
- Screen QT prolongation
- No response by wk 14 consider discontinuation

ADA
- Administered as subcutaneous injection (at least 2 shots up to 4)
- Available as pen-injector kit for home use
- Decrease levels of cyclosporine and warfarin

CER
- Administered as subcutaneous injection (2 shots)
- Missing dose, administer if ≥ 1 wk prior to next dose
- Nausea in 11%
- Agent with the highest risk for infection (OR 4.7)

GOL
- UC only
- Administered as subcutaneous injection (2 shots)
- Auto-injector pen will click when shot is complete
- Intravenous formulation is **not** used for IBD*

Dulai, P. Inflamm Bowel Dis 2013; 19: 2927-36. Lexicomp

Cost of A-TNF α Therapy

Medication	How supplied	Cost	$ Induction	$ Maintenance*
Infliximab	100mg, vial lyophilized powder	$ 1,285.78	35kg = $ 7,714.68 50kg = $ 11,572.02	$ 7,714.68 $ 11,572.02
Adalimumab	Prefilled Syringe 10mg/0.2ml, 20mg/0.4ml, 40mg/0.8ml Pen-Injector Kit (set of 2) 40mg/0.8ml	$ 2,458.24 $ 2,458.24 per kit	80mg = $ 4,916.48 160mg = $ 9,832.96	$ 29, 498.88 $ 29, 498.88
Certolizumab	200mg, vial lyophilized powder Prefilled syringe (set of 2) 200mg/ml Starter Kit (set of 6) 200mg/ml	$ 4,212.18 $ 4,212.18 per kit	$ 12,636.54 $ 4,212.18	$ 25, 273.08
Golimumab	Auto-injector pens 50mg/0.5ml 100mg/ml 50mg/4ml, vial for injection	$ 4,573.42 $ 5,259.44 $ 1,752.90	$ 21, 037.76	$ 31, 554.00

Efficacy of Anti-TNF α Therapy

Growth

- IFX improves linear height, growth velocity
  - **REACH** study height z-scores improved by 0.5 @ 50 weeks
  - Independent of steroid dose reduction or progress through puberty
    - Benefit the most
      - Patients on steroids and with 1 year delay in bone age
      - Patients prior to puberty or early in puberty

de Bie, C, Escher J, de Ridder L. Antitumor Necrosis Factor Treatment for Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2012; 18:981-998.
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Efficacy of Anti-TNF α Therapy

Remission CD

- IFX shown to maintain remission 80% of patients @ 3 years
  - **REACH** Trial
- ADA shown to maintain remission > 50% of patients @ 1 year
  - **IMAgINE** Trial included IFX failures
  - 30% of patients with fistulas had closure at 1 year

Colectomy in UC

- IFX maintain long-term response in 55% patients with severe UC flare refractory to steroids
- IFX maintain 2 year response in 22% of patients with steroid dependence
- Delay the need for colectomy by 1 year

Lee W, Briars L, Lee T, Calip G, Suda K, Schumock T. Top-down Versus Step-up Prescribing Strategies for Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016; 22: 2410-7.

Efficacy of Anti-TNF-α Therapy

Health Insurance Claims Data

- Retrospective
- Cohort ≤ 24 y newly diagnosed
- n= 3295

- Top-down had higher rate of discontinuation of Anti-TNF at 24 months
  - 43% vs 37% p= 0.034

Medication Use	Overall Users	Top-down Strategy	Step-Up Strategy	
Corticosteroids	69.9%	32.5%	94.2%	p =0.0001
Thiopurine	38.6	13.5	54.8	p =0.0001
5-Aminosalicylates	52.4	17.3	75.1	p =0.0001

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Adverse Effects of Anti-TNF-α agents

Class black box warning

- Increase risk of infection
  - Opportunistic infections, reactivation of latent virus or TB
  - Especially during combination therapy
- Increase risk of cancer
  - In children and adolescents particularly after 30 months of therapy

DEVELOP Registry

- Long term safety IFX, 20 years
- Rate of malignancy with combination therapy
  - 0.11/100 patient years vs 0/100 patient years $p < 0.05$

Lee W, Briars L, Lee T, Calip G, Suda K, Schumock T. Top-down Versus Step-up Prescribing Strategies for Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016; 22: 2410-7. Cozijnsen M, Escher J, Griffiths A, Turner D, de Ridder L. Benefits and Risks of Combining Anti-tumor Necrosis Factor with Immunomodulator Therapy in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis 2015; 21: 951-61.

Adverse Effects of Anti-TNF-α agents

Acute Infusion Reactions (AIR)

- Mediated by antibodies to Anti-TNF-α agent
- Pre-medication will not prevent initial AIR but can mitigate repeat reactions
- Previous AIR (83% will experience AIR on subsequent infusions)

Managing Severe Infusion Reactions

- Anaphylaxis change to another Anti-TNF-α agent
- Oral/facial angioedema change to another Anti-TNF-α agent

Corica D, Romano C. Biologic Therapy in Pediatric Inflammatory Bowel Disease A Systemic Review. J Clin Gastroenterol 2016; DOI: 10.1097 accessed 10/05/16.

Adverse Effects

Loss of response (LOS)

- Related to formation of antibodies
  - Increases clearance and lowers serum concentrations
- Patients on ADA were 10 times more likely to not be in remission if antibodies were detected OR 10.15 (3.9-26.4 p< 0.0001)
- Over come by dose intensification
  - Increase dose ± shorten interval

1, 3

Adverse Effects of Anti-TNF-α agents

Risk Factors for Antibody Development

- Female
- ≤ 5 y
- Immunosuppressive therapy for < 4 months
- Episodic treatment
  - Insufficient exposure to drug

Development of Antibodies occurs in 38% of patients (IFX or ADA)

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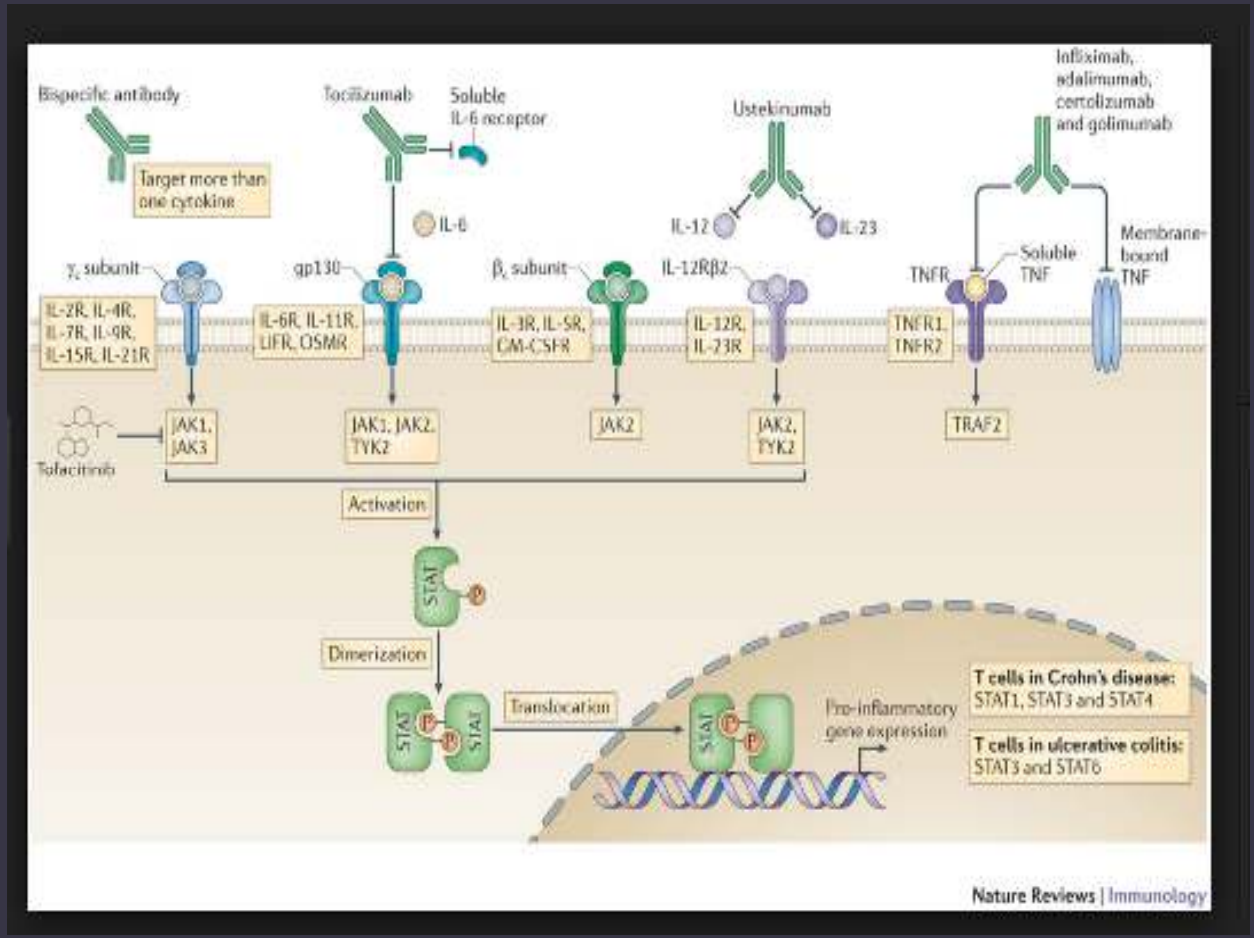
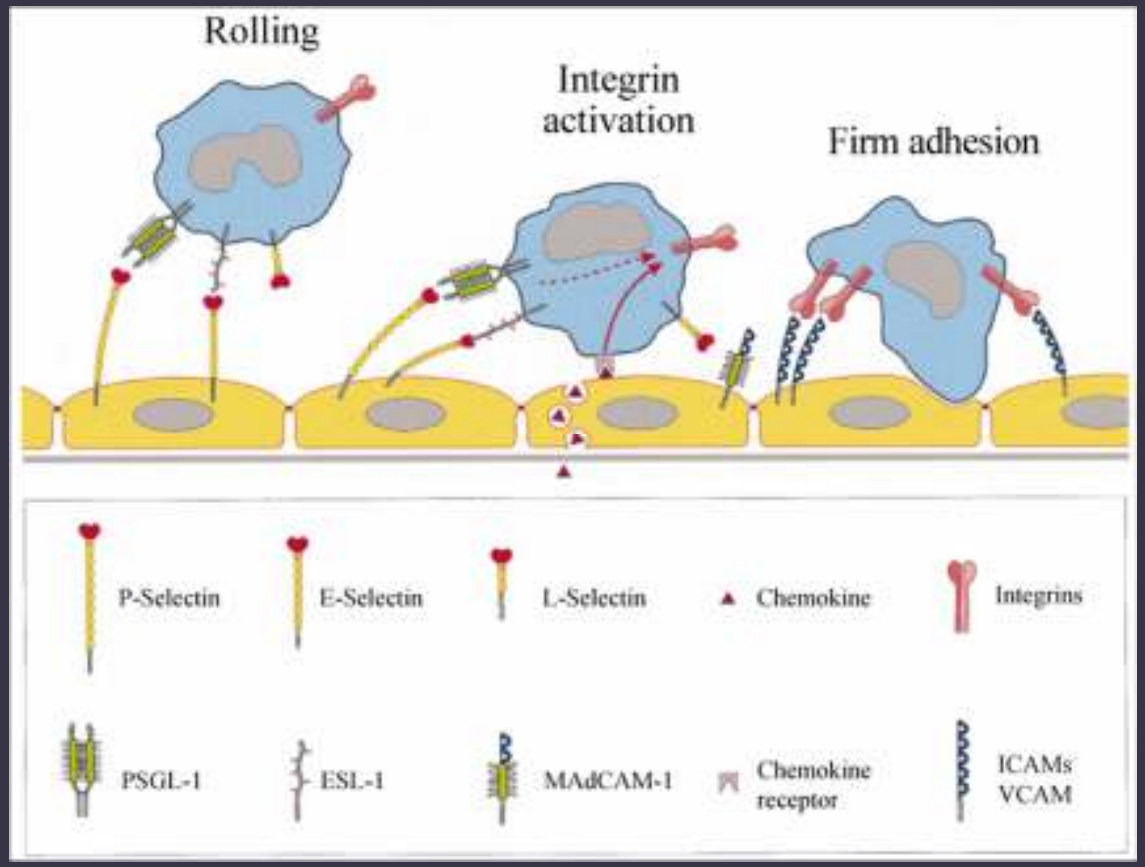
IL Inhibitors

- Monoclonal antibodies blocks the activity of IL -12 and 23 by antagonizing P40 receptor subunit



Integrin Receptor Antagonists

- Monoclonal antibodies binding to α4β7 integrin molecule on the surface of lymphocytes preventing the ability to bind to MadCAM-1 receptors on endothelium in GIT.
- This inhibits migration of lymphocytes to inflamed tissue



Trendowski M. Cel Dev Biol 2104; 3:137

IL inhibitor and integrin receptor antagonists

Medication	Induction	Maintenance	Manufacture
Interleukin 12 and 23 inhibitors (IL 12, 23 Inhibitors)			
Ustekinumab (Stelara®) UST	Crohn's [14] 90mg SC D0, wk 4 Adults ≤ 55 kg 260mg IV* 55-85 kg 390mg IV > 85 kg 520mg IV	90mg SC q 8 wk 90mg SC q 8 wk	Janssen Biotech, 2016
Integrin receptor antagonist (inhibit T-Lymphocyte migration)			
Natalizumab (Tysobri®) NAT	300mg IV q 4 wk	300mg IV q 4 wk	Biogen, 2008
Vedolizumab (Entyvio) VED	300mg IV D0, wk 2, and wk6	300mg IV q 8 wk	Takeda, 2014

IL inhibitor and integrin receptor antagonists

UST

- Administered as an IV infusion during induction (filter)
- Subcutaneous administration during maintenance
- Medication guide from FDA

VED

- Administered IV infusion over 30 minutes
- Reconstituted solution stable for 4 hours in refrigerator
- Discontinue if no benefit @ wk 14
- Contains mouse and hamster proteins
- Headaches, joint aches, N, fever >10%

NAT

- Administered as IV infusion
- REMS, CD-TOUCH prescribing program
- Progressive multifocal leukoencephalopathy if John Cunningham virus antibody +
- MONOTHERAPY
  - Taper CS
  - IM off at least 3wks prior
- Discontinue if no benefit @ 12 weeks, on CS @ 6 months
- Do NOT re-treat patients with hypersensitivity reactions
- Headache 11%

Efficacy

Ustekinumab

- Limited data in pediatric patients
- Case series n=4
  - One patient responded and needed dose adjustment q7wk
- Adult data
- Induction of remission 18.3% failing anti-TNF-α therapy no different compared to placebo
- Of responders
  - 41.7% maintenance at 22 wk
  - 30.6% steroid free at 22 wk

Vedolizumab

Significant improvement occurs later in therapy (14 wk)

- n= 21 pediatric IBD
- Response
  - wk 6 32%
  - wk 22 58% (2 UC, 9 CD)
- Able to wean steroids or remain off steroids in 7 of 21 patients

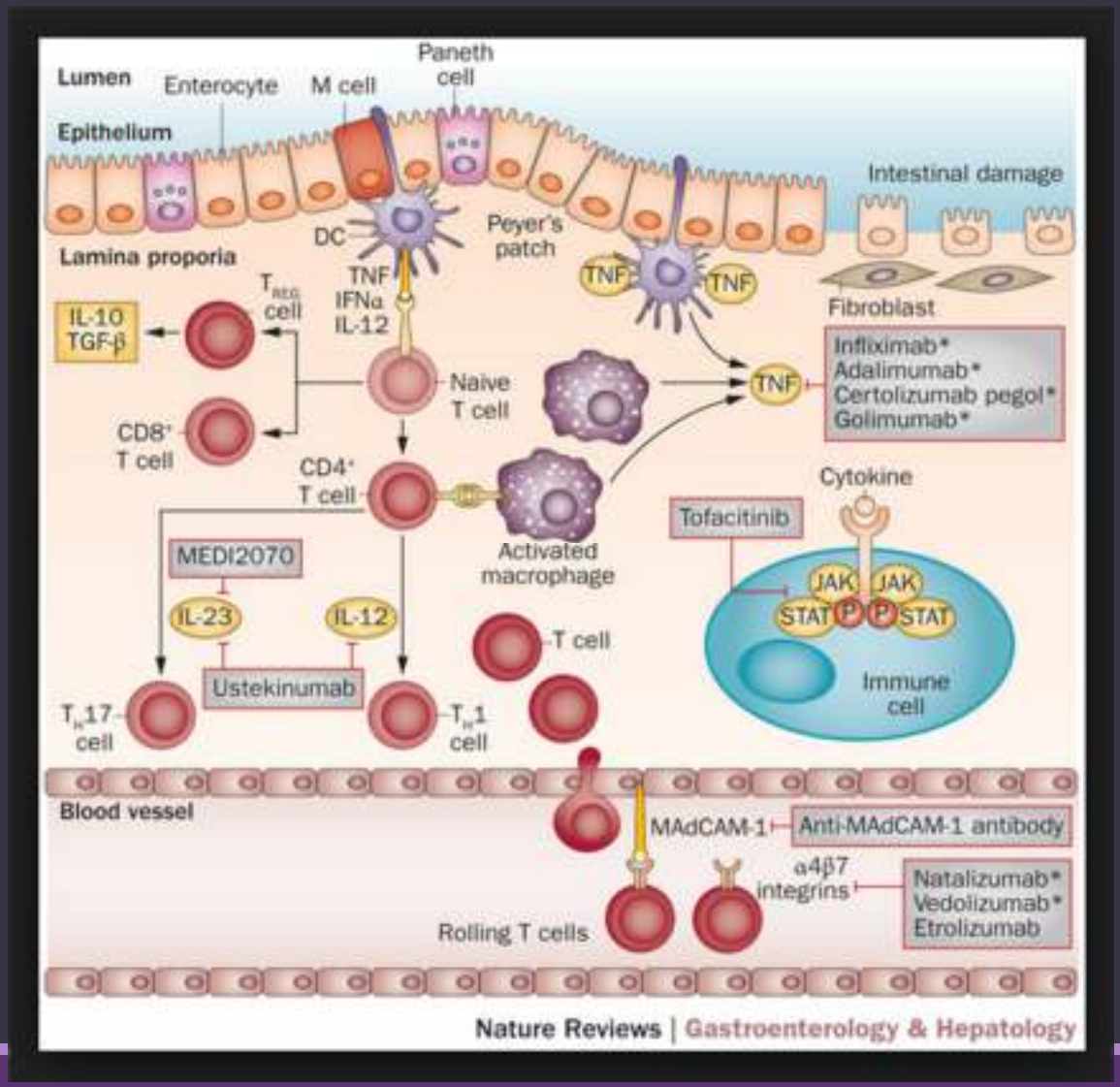
Efficacy

Natalizumab

- Limited data in pediatrics
- n= 9 with Crohn's ages 14-20y
  - Failed anti-TNF α agent
  - Immune suppression was stopped 3 wk prior
  - 5 on prednisone
- Results
  - 4 achieved remission at wk 10 and wk 20
  - 3 of 5 weaned off prednisone by wk 10
- Transitioned all patients to vedolizumab

Comparison cost of IL inhibitor and integrin receptor antagonists

Medication	How supplied	Cost	$ Induction	$ Maintenance
Ustekinumab	130mg, vial for injection Prefilled Syringe 45mg/0.5ml 90mg/ml	 $ 10, 608.26 $ 21, 216.53	$ 42, 433.06	$ 63, 649.59
Vedolizumab	300mg, vial for injection	$ 6,014.11	$ 18, 042.33	$ 18, 042.33
Natalizumab	300mg, vial for injection	$ 6,956.40	$ 6,956.40	$ 34, 782.00



Danese S, Nat Rev Gastro and Hep 12, 2015

Combination Therapy

Unclear if combination therapy is better than monotherapy

- *Combination therapy Anti-TNF + immune modulator*
- In pediatric patients with Crohn's
  - Not difference in maintenance of remission, endoscopy score, need to optimize regimen
- Pediatric patients with UC
  - No difference in 8 and 54 wk remission, mucosal healing rates, or colectomy rates at 3, 6, 12 and 24 months

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Cozijnsen M, Escher J, Griffiths A, Turner D, de Ridder L. Benefits and Risks of Combining Anti-tumor Necrosis Factor with Immunomodulator Therapy in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis 2015; 21: 951-61.

Combination Therapy

Combination therapy may be considered for induction

- Benefit to reach remission is modest
  - Related to increased serum levels of Anti-TNF agent and decrease immunogenicity
- Patients with high risk for disease complications may benefit from combination therapy
  - Growth retardation
  - Formation of strictures
  - Need for surgery
- Immune modulator (thiopurine) is discontinued once in maintenance

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Combination Therapy

Adverse effects associated with combination therapy

- Higher malignancy rate compared to monotherapy
  - Related to thiopurine use not only in combination but at anytime during treatment
- More serious infections in anti-TNF + thiopurine group compared to anti-TNF alone
  - 6.2/100 vs 3.5/100 patient years $p < 0.05$
  - Neutropenia/leukopenia occur more frequently during combination therapy

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Therapeutic Drug Monitoring

Drug Concentrations

- Good check for absorption, exposure and compliance
- Identify a maximum concentration correlating with efficacy
- Correlation to efficacy has been established (continuing)
- Optimization of Anti-TNF therapy may allow for monotherapy or decrease time spent on combination therapy

Anti-drug Antibody Concentrations

- Prevent unnecessary use of combination therapy
- Determine the need for dose intensification or change in therapy

Jossen J, Dubinsky M. Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Curr Opin Pediatr 2016; 28: 620-5.

Therapeutic Drug Monitoring

Studies have demonstrated….

- Formation of anti-drug antibodies correlates with lower serum levels
- Association between higher serum levels and response to induction and length of remission
- Subtherapeutic levels and low anti-drug antibodies managed with dose escalation improves outcomes more compared to changing therapy
- Proactive TDM resulted in 86% of patients remaining on IFX at 5y compared to 52% monitored traditionally
- Using algorithmic approach in patients with failure due to antibodies decreased cost by 56% while sustaining outcomes

Joosse M, Samsom J, van der Woude J, Escher J, van Gelder T. The Role of Therapeutics Drug Monitoring of Anti-Tumor Necrosis Factor Alpha Agents in Children and Adolescents with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015: 21: 2214-2221.

TDM and fit for pediatrics

Overcoming effects of anti-drug antibodies on loss of response

- Low titers of antibodies (1:100) can be over come by dose modification
  - Increase dose and/or decrease frequency
  - Prevents inadvertently changing therapy prematurely
- 50% of patients will lose response over time

Joosse M, Samsom J, van der Woude J, Escher J, van Gelder T. The Role of Therapeutics Drug Monitoring of Anti-Tumor Necrosis Factor Alpha Agents in Children and Adolescents with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015: 21: 2214-2221.

Therapeutic Drug Monitoring

Predictive of sustained response

- IFX serum levels at 14 weeks predictive of sustained remission at 54 weeks in CD
  - 3mcg/ml PPV 64%
  - 4mcg/ml PPV 76%
  - 7mcg/ml PPV 100%
- Patients with UC in remission at 54 wk
  - IFX serum levels at week 14
    - 4.7mcg/ml patients in remission compared to 2.6mcg/ml patients not in remission p= 0.03

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Therapeutic Drug Monitoring

IFX “therapeutic range” (3-7mcg/ml)

- 3mcg/ml prevents flares and need for rescue therapy
- > 7mcg/ml associated with efficacy plateau

ADA serum levels at 14 weeks

- 6.5 mcg/ml associated with mucosal healing
- ≤ 4.2 mcg/ml associated with NOT healing mucosal
- Serum levels (4.85-5.9mcg/ml) correlate with remission OR 2.6 (1.79-3.77) $p < 0.0001$

Dulai P, Singh S, Casteele N, Boland B, Sandborn W. How Will Evolving Future Therapies and Strategies Change How We Position the Use of Biologics in Moderate to Severely Active Inflammatory Bowel Disease. Inflamm Bowel Dis 2016; 22: 998-1009.

Paul s, Moreau AC, Del Tedesco E, Rinaudo M, Phelip J, et al. Pharmacokinetics of Adalimumab. Inflammatory Bowel Diseases: A Systemic Review and Meta-analysis. Inflamm Bowel Dis 2014; 20: 1288-1295.

Therapeutic Drug Monitoring

Other biologic agents with serum concentrations correlated to outcomes

- CER and endoscopic response @ wk 10
  - CER ≥ 20 mcg/ml during maintenance 70% achieved remission
- GOL concentrations @ 6wk and efficacy
- VED (7.5 -11 mcg/ml) @ 46wk associated with remission in CD
- USE optimal serum concentrations are being determined

Jossen J, Dubinsky M. Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Curr Opin Pediatr 2016; 28: 620-5

Dulai P, Singh S, Casteele N, Boland B, Sandborn W. How Will Evolving Future Therapies and Strategies Change How We Position the Use of Biologics in Moderate to Severely Active Inflammatory Bowel Disease. Inflamm Bowel Dis 2016; 22: 998-1009.

Biosimilars

Biosimilars are the generic version of proprietary biologic agents. True or False

Companies producing biosimilars must prove the absence of clinically meaningful difference to achieve biosimilar status from the FDA. True or False

Biosimilar status means the biosimilar and the origin product may be therapeutically interchanged. True or False

Use of biosimilars to treat IBD has been estimated to reduce treatment related cost by 20% . True or False

Sieczkowska J, Jarzebicka D, Meglicka M, Oracz G, Kierkus J. Experience with Biosimilar Infliximab (CT-P13) in Paediatric Patients with Inflammatory Bowel Disease. Ther Adv Gastroenterol 2016; 9: 729-735.

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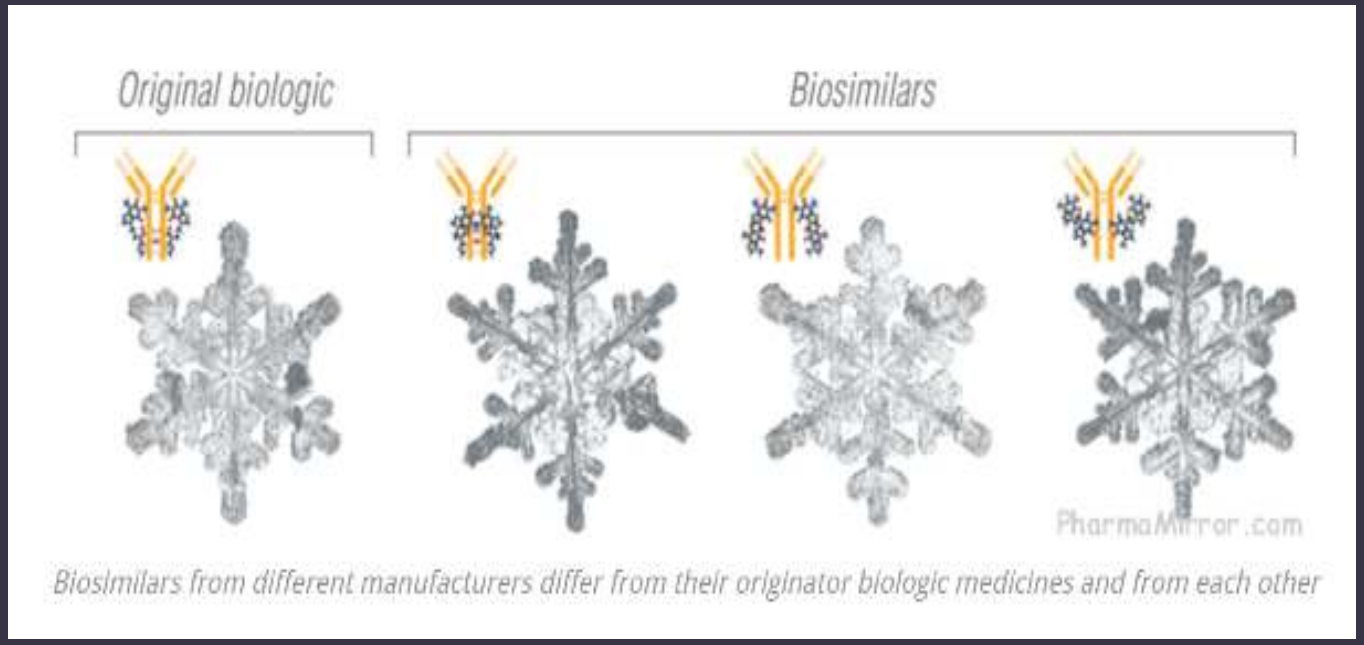

Biosimilars from different manufacturers differ from their originator biologic medicines and from each other

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Biosimilars

Experience in pediatric IBD

- IFX biosimilar CT-P13 (Inflectra)
- 39 pediatric patients
  - 32 with CD and 7 with UC all in remission on IFX
  - Changed to Inflectra because of IFX shortage
- Remained in remission at early follow up

Place in Therapy

- Do not switch patients to biosimilar agents if current regimen is effective

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Biosimilars

CT-P13 used for induction therapy

- n= 36 pediatric patients with CD
- CT-P13 5mg/kg at weeks 0, 2, and 6

Results

- 86% experienced a clinical response
- 67% experienced remission after three doses
- AIR occurred in 1 patient leading to discontinuation

Conclusion

- Induction with CT-P13 in children with CD is effective. Profile is similar to IFX

Sieczkowska-Golub J, et al. JPGN 2017; 65: 285-88.

Biosimilars

Available in US

- Amjevita (biosimilar to ADA)
- Inflectra (biosimilar to IFX)

In the Pipeline

- CER
- UST

Conclusions

Biologicals are improving outcomes in pediatric patients with IBD.

Optimization of therapy will include monitoring serum concentrations of medication, anti-drug antibodies, and precise timing of combination therapy.

The use of biosimilars in pediatric patients with IBD is taking shape becoming widely used in European countries.

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