Biologicals in clinical practice: Anti-TNF inhibitors, vedolizumab, or ustekinumab: which to use and when?

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Disclosures

• Consulting fees: AstraZeneca, AbbVie, Delenex, Ferring Pharmaceuticals, Janssen, Merck-Serono, MSD, Nestlé Health Sciences, Pfizer, Takeda, UCB Pharma, and Vifor.
• Lecture fees: AbbVie, Ferring Pharmaceuticals, Janssen, Hospira, MSD, Pfizer, Takeda, UCB Pharma, and Vifor.
• Research grants: MSD and Takeda, UCB pharma.

Crohn’s disease and ulcerative colitis are progressive diseases

Crohn’s disease and ulcerative colitis are heterogeneous

- Various disease phenotypes
  - Clinical presentation
  - Disease location
  - Disease behaviour
  - Extra-intestinal manifestations
- Difficulties in prediction
  - Disease progression and complications
  - Individual response to therapy
  - Lack of predictive biomarkers
- Multiples genetic and environmental factors implicated
- Multiples cellular and molecular mechanisms involved

Predictors of Progressive Disease Course in Crohn’s Disease

Classical treatment strategies do not accommodate the phenotypic, genetic and pronostic diversity of IBD

These strategies were limited to the use of anti-TNF agents and not goal-oriented

Adapted from Pariente B et al. Inflamm Bowel Dis 2011;17(6):1415-22
**The treat-to-target concept applied to IBD**

[Diagram showing the treat-to-target concept with stages: baseline assessment, assessment, control of intestinal inflammation, target achievement, and maintenance of target.]


**Effect of Tight Control Management on Crohn’s Disease (CALM) - study design**

Adults with moderate to severe CD randomized to treat-to-target approach versus management based on clinical symptoms


**Choosing the first Biological Therapy in IBD**

- Can we compare the efficacy of the various biologics?
  - Difficult in the absence of head-to-head studies
  - Speed of action? Durable efficacy? Are they similar for most patients?
  - Are they specific situations in which one biologic should be preferred?
  - Are the risks of the same magnitude for all biologics?
  - Which one is the safest?
  - Similar immunogenicity?
  - Should one mechanism of action be avoided in some situations?
  - What about patients’ preferences?
    - Practical aspects
    - Perceived differences in efficacy and risks

**Systematic Review and Network Meta-analysis of First-line Therapies in Crohn’s Disease**


**Comparative Efficacy of Biologics for Mucosal Healing in Ulcerative Colitis - Meta-analysis**

Choosing the first Biological Therapy in IBD

- Can we compare the efficacy of the various biologics?
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  - Speed of action? Durable efficacy? Are they similar for all drugs?
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Cyclosporin or infliximab? The CYSIF study

Composite primary endpoint: Treatment failure

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Fistulizing Crohn’s Disease

- Present DH, et al (1999): (IFX W0,2 and 6)
  - Closure of at least 50% of fistulas for at least 4 weeks in 56–68% of patients compared with 26% treated with placebo (p=0.002).
  - Closure of all fistulas was achieved in 38–55% on infliximab.
- ACCENT II trial (2004)
  - Week 14 responders to the induction regimen
  - 39% of patients who received infliximab maintenance therapy had complete closure of all draining fistulas at week 54.

Infliximab in Fistulizing Perianal CD

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  - Closure of at least 50% of fistulas for at least 4 weeks in 56–68% of patients compared with 26% treated with placebo (p=0.002).
  - Closure of all fistulas was achieved in 38–55% on infliximab.
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  - Week 14 responders to the induction regimen
  - 39% of patients who received infliximab maintenance therapy had complete closure of all draining fistulas at week 54.
Adalimumab in Fistulizing Perianal CD

- CHARM (2007)
  Subgroup analysis in patients with draining fistulas at baseline showed complete fistula healing in 33% of adalimumab treated patients versus in 13% for placebo (p<0.05)

In OLE of this trial, sustained healing was observed in 96% at 2 years follow-up.

GEMINI 2: Vedolizumab in Crohn’s Disease

- Maintenance Phase: Closure of Draining Fistulae

Fistula Resolution (100% Reduction) at Week 8 Among Randomized Patients with Open, Draining Fistulas at Baseline in Pooled data from CERTIFI, UNITI-1 and UNITI-2

Medication Safety and Dosing in Pregnancy

Lack of placental transfer of certolizumab pegol during pregnancy: CRIB, a prospective, pharmacokinetic study
Choosing the first Biological Therapy in IBD

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  - Difficult in the absence of head-to-head studies
  - Speed of action? Durable efficacy? Are they similar for all drugs?
  - Do all biologics need a combination with an immunosuppressors?
  - Are they specific situations in which one biologic should be preferred?

- Are the risks of the same magnitude for all biologics?
  - Which one is the safest?
  - Similar immunogenicity?
  - Should mechanism of action be avoided in some situations?

- What about patients’ preferences?
  - Practical aspects
  - Perceived differences in efficacy and risks

Systematic Review and Network Meta-analysis of First- and Second-line Therapies in Crohn’s Disease

Choosing the first Biological Therapy in IBD

- Can we compare the efficacy of the various biologics?
  - Difficult in the absence of head-to-head studies
  - Speed of action? Durable efficacy? Are they similar for all drugs?
  - Do all biologics need a combination with an immunosuppressors?
  - Are they specific situations in which one biologic should be preferred?

- Are the risks of the same magnitude for all biologics?
  - Which one is the safest?
  - Similar immunogenicity?
  - Should mechanism of action be avoided in some situations?

- What about patients’ preferences?
  - Practical aspects
  - Perceived differences in efficacy and risks

Optimizing Selection of Biologics in IBD: Development of an Online Patient Decision Aid

Survey of CD patients (n=346): relative importance of biologic attributes

- In summary - The choice of first biologic in IBD
  - Comparison in terms of efficacy
    - Difficult in absence of head-to-head studies
    - Some differences in onset of action, durability and immunogenicity but patients selection and tests differ across studies
  - Comparison in terms of risks
    - Risks are probably reduced with the newer drugs
    - The clinical situation matters (pregnancy)
  - The choice of biologic should be based on a case by case evaluation
    - Decision should be shared with the patient
  - The ideal situation would be a personalized approach based on biomarkers to design a treatment targeting the disease mechanisms at play in each patient.
Personal Approach on First Biologic Choices in IBD

- **First choice**
  - Infliximab
  - **Other anti-TNFs**
  - Vedolizumab
  - **Extra-intestinal manifestations**
  - All other Biologics

- **Safety**
- Pregnancy

- **First choice**
  - Anti-TNFs
  - Ustekinumab
  - Vedolizumab
  - All other anti-TNFs

- **First choice**
  - Ustekinumab
  - Vedolizumab
  - Other anti-TNFs
  - **Complicated CD**