State of the art treatment in Crohn’s disease (CD)

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Disclosures

Speaker and/or principal investigator for: Abbvie, Celgene, Covidien, Dr. Falk, Ferring Pharmaceuticals, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, Protagonist therapeutics, Receptos, Takeda, Tillotts, Tramedico
Content

• Crohn’s disease (CD) management in the ‘old days’: mainly based on symptoms

• CD management in 2019:
  - Combined treatment goal using objective parameters
  - Top-down treatment in high risk patients
  - Tight monitoring
  - Treat to target
Management of Crohn’s disease (CD) in ‘the old days’

• Treatment intensification mainly driven by symptoms

• But, poor association between clinical remission and endoscopic remission
Management of Crohn’s disease (CD) in ‘the old days’

- Treatment intensification mainly driven by symptoms
- But, poor association between clinical remission and endoscopic remission

Poor association between clinical remission (CDAI<150) and endoscopic remission (no ulcers) \((\text{post-hoc analysis SONIC trial})\)

<table>
<thead>
<tr>
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<th>CDAI &lt;150 at W 26 (n=136)</th>
<th>CDAI &gt;220 at W 26 (n=27)</th>
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<tbody>
<tr>
<td>Mucosal healing</td>
<td>72/136 (53%)</td>
<td>8/27 (30%)</td>
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47% in clinical remission, but with endoscopic disease activity

30% with persistent symptoms, but endoscopic remission achieved

Peyrin-Biroulet et al, presentation at DDW 2013
Choose the right drug at the right time

- Various anti-inflammatory agents are available with different mode of actions & therapeutic options are increasing. But, which drug to choose?

- Holy grail = personalized medicine (predict treatment responses)
Timing of starting anti-inflammatory therapy

Cosnes, et al. Inflamm Bowel Dis 2002
Risk stratification

- Identification of high risk vs low risk patients

  Treatment of high risk patients: ‘hit hard, hit early’

Risk factors:
- Young age
- Smoking
- Extensive small bowel disease
- Peri-anal disease
- Deep ulcers at endoscopy
Risk stratification

- Identification of high risk vs low risk patients

Treatment of high risk patients: ‘hit hard, hit early’

- Phenotypic characteristics in CD may help to choose specific agents:
  - Perianal fistulas → anti-TNF (combo)
  - Significant comorbidity → vedolizumab
  - Extra intestinal manifestations → arthritis (anti-TNF), skin lesions (ustekinumab)
  - Etc.

Risk factors:
- Young age
- Smoking
- Extensive small bowel disease
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- Deep ulcers at endoscopy

Extraintestinal manifestations
- Pregnancy (wish)
- Perianal CD
- Comorbidity: rheumatoid arthritis, psoriasis, etc
- Failed prior biologics

Elderly
- History of infections
- History of cancer
- Anti-drug Ab formation
Risk stratification has therapeutic consequences

Low risk patient

High risk patient

‘hit early & hit hard’
Early combined immunosuppression more effective in preventing CD-related complications

**REACT study**
- RCT
- Outcome: time to first CD complication

Current treatment goal in CD

Clinical remission (using PRO’s) & mucosal healing (objective endpoint)

Based on STRIDE\textsuperscript{1} recommendation (IOIBD\textsuperscript{2} working group) & FDA requirement

\begin{itemize}
\item Mucosal healing $\rightarrow$ better outcomes (i.e. reduced hospitalization and surgery rates and higher remission rates)
\end{itemize}

\textsuperscript{1} STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease
\textsuperscript{2} IOIBD: International Organization for the Study of IBD

Ferrante et al. Validation of endoscopic activity scores in patients with Crohn's post hoc analysis of SONIC. Gastroenterol 2013
Colombel et al. Management Strategies to Improve Outcomes of Patients With IBD. Gastroenterol 2017
Patient Reported Outcomes (PRO’s)

Definition: report of a patient’s health condition directly from the patient (without interpretation by physician)

**PRO types:**
- Symptoms
- Quality of Life
- General well being
- Fatigue
- Workproductivity
- Etc.

*PRO’s for CD*: stool frequency and abdominal pain

*PRO’s for UC*: stool frequency and rectal blood loss
Physicians tend to underestimate disease severity

Online survey in 775 UC patients and 475 physicians, by Schreiber S et al. JCC 2013
Tight monitoring/control
Tight monitoring/ control

CALM (Colombel et al, Lancet 2017)

Compare 2 treatment algorithms in CD patients in achieving mucosal healing by escalating treatment based on symptoms or on symptoms & biomarkers (tight control)
CALM: tight monitoring in CD (using biomarkers)

Tight control in CD using objective markers of disease activity and clinical symptoms to drive treatment decisions.
CALM: higher mucosal healing rates with tight control vs conventional care

Proportion of pts achieving mucosal healing (CDEIS <4 without deep ulcers) at W 48; N=244

Colombel et al, Effect of tight control management on Crohn's disease (CALM): multicentre, randomised, controlled phase 3 trial. Lancet. 2018
Tight monitoring in daily practice

- **Biological care-path** has been introduced at our institute

- Aim: to optimize treatment by systematic monitoring of patients
  - Improve therapeutic efficacy by timely assessment and, if needed, dose adjustment
  - Reduce side effects
  - Discontinue ineffective or unnecessary treatment
  - Manage costs
  - Etc.
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Follow-up timeline (care-path)
‘Treat to target’ approach
Current CD management more and more based on treat to target approach

• Choose an (objective) target that can be measured/ evaluated
Treat to target approach

- Parameters (objective):
  - Biomarkers
  - Drug serum levels (therapeutic drug monitoring (TDM))
  - Endoscopy
  - Imaging
  - Histology

- Goal/ target:
  - Biochemical remission or 50% reduction in CRP/ fecal Calprotectin
  - Achieve therapeutic window (anti-TNFs, thiopurines, vedolizumab, etc.)
  - Mucosal healing
  - Radiological remission
  - Histological remission

- Requires continuous monitoring and therapeutic adjustments (fine-tuning) aimed at achieving specific target
Treat to target approach in CD using therapeutic drug monitoring (TDM)

Little evidence so far that favours TDM-based dosing of IFX in IBD:


- **TAXIT** *(Vande Casteele et al, Trough concentrations of infliximab guide dosing for patients with IBD. Gastroenterology. 2015:1320-9)*
Treat to target approach in CD using therapeutic drug monitoring (TDM)

TAILORIX

- N=122 (biological naive CD pts)
- Induction treatment with IFX + immunomodulator in all pts
- Randomization at W14: (i) dose increase in steps of 2.5 mg/kg based on symptoms and biomarkers or IFX TDM (ii) dose increase in steps of 5-10 mg/kg based on the same criteria (iii) dose increase to 10 mg/kg based on clinical symptoms alone
- Primary outcome: steroid-free clinical remission (CDAI<150) from W22 to W54 & no ulcers at endoscopy at W54 in 33%, 27% and 40% in group (i), (ii) and (iii), resp. (non-sign.)
Treat to target approach in CD using therapeutic drug monitoring (TDM)

**TAXIT**

- N=263 (CD and UC)
- IFX doses were optimized in all pts to reach TL target 3-7 ug/ml
- Next, pts were randomized 1:1 into clinically or TDM based IFX dosing
- Primary end-point (clinical & biochemical remission at 1 yr) was not sign. different between two groups, but TDM based dosing was associated with fewer flares & reduced drug costs
Little evidence so far that favours TDM-based dosing of IFX in IBD:


- **TAXIT** *(Vande Casteele et al, Trough concentrations of infliximab guide dosing for patients with IBD. Gastroenterology. 2015:1320-9)*

- **PRECISION** *(Strik et al, Dashboard driven vs conventional dosing of infliximab in IBD patients: the PRECISION trial. Manuscript submitted)*
PRECISION trial: dashboard driven vs conventional dosing of IFX in IBD

- IBD patients on IFX maintenance treatment
- Clinical remission (HBI ≤4 (CD) or PM score ≤2 (UC)

1:1

Precision dosing group
- Model based dosing (TL = 3 μg/ml)
- Change dose and/or interval

Conventional dosing group
- No changes

Clinical remission After 1 year

- Measurements of IFX serum levels at trough and mid-infusion
- Intervention group: IFX dose (1-10 mg/kg) or interval adjustment (4-12 wk)
Primary outcome PRECISION trial: maintained clinical remission after 1 year

Personalized dosing resulted in higher proportion of pts who maintained clinical remission during 1 yr vs pts who continued treatment without proactive dose adjustments

- Biochemical remission: Calpro <250 µg/g & CRP <0.5 mg/L
- Loss of clinical response: HBI> 4 or PM score> 2 at 2 consecutive visits

(HBI, Harvey Bradshaw Index; PM, partial Mayo score)

First prospective trial demonstrating clinical benefit from personalized IFX dosing in IBD
Clinical and endoscopic response to ustekinumab induction therapy in Crohn's disease: Week 16 interim analysis of the STARDUST trial

STARDUST: T2T approach with USTE in CD

Clinical and endoscopic response to ustekinumab induction therapy in Crohn’s disease: Week 16 interim analysis of the STARDUST trial


- **Aim:** compare clinical and endoscopic outcomes in patients receiving USTE managed with T2T strategy vs standard of care (SoC)

- **At W16,** patients with CDAI reduction ≥70 points were randomized (1:1) into the T2T or SoC arm

- **No data available yet:** week 16 interim analysis submitted to ECCO 2020
Conclusions

• CD management more and more based on pro-active treat to target approach using objective endpoints

• Combined treatment goal in CD: clinical remission (PRO’s) and endoscopic remission

• Important surrogate markers: CRP and FCP
Conclusions

- CD management more and more based on pro-active treat to target approach using objective endpoints
- Combined treatment goal in CD: clinical remission (PRO’s) and endoscopic remission
- Important surrogate markers: CRP and FCP
- CALM: better endoscopic outcomes in tight control group based on symptoms & biomarkers vs only symptoms
- PRECISION: clinical benefit of personalized anti-TNF dosing in IBD using computer algorithm
- STARDUST: treat to target approach with ustekinumab in CD (no data available yet)
Questions?

Thank you