February 1st 2019,
10th Gastro Foundation Weekend for Fellows; Spier Resort Centre, Stellenbosch

Treat to target in IBD

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### Set the target... Decide the treatment... Assess the target... Reach the target

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- **What**: treatment adaptation and optimisation until the target is reached
- **Why**: the treatment of a chronic disease for which there is no cure requires a treat-to-target approach

The question is: how to define the target and what is the optimal strategy to reach it
Treat to target concept in IBD

Treat-to-target recommendations in Crohn’s disease

the target has 2 dimensions: Quality of Life and intestinal healing

Composite endpoint

Clinical/PRO remission
- Defined as resolution of abdominal pain and normalisation of bowel habit
  - Assessed at minimum of 3 months during active disease
  - Patients’ individual goals should also be addressed

AND

Endoscopic remission
- Defined as resolution of ulceration
  - Should be assessed within 6–9 months after start of therapy
  - When endoscopy cannot adequately evaluate inflammation, assess resolution of inflammation by cross-sectional imaging

Adjunctive measures

- **Biomarkers**: CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring CD
- **Histology**: histologic remission is not considered a target

CRP, C-reactive protein; PRO, patient-reported outcome

Treat-to-target recommendations in ulcerative colitis

the target has 2 dimensions: Quality of Life and intestinal healing

Composite endpoint

Clinical/PRO remission AND Endoscopic remission

Clinical/PRO remission

Defined as resolution of rectal bleeding and normalisation of bowel habit
- Should be assessed at minimum of 3 months during active disease
- Patients’ individual goals (e.g., QoL, mood disorders, fatigue, work productivity) should also be addressed: normalisation of QoL as ultimate goal

Endoscopic remission

Defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy (Mayo 0–1)
- Should be assessed within 3–6 months after start of therapy

Adjunctive measures of disease activity that may be useful in selected cases

- **Biomarkers**: CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring UC
- **Histopathology**: is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility

CRP, C-reactive protein; PRO, patient-reported outcome; QoL, quality of life
So, how to apply Treat-to-target in daily practice?

1. Tailor and define the target with the patient
2. Adapt the treatment strategy and the monitoring to the risk of disease progression and complications
3. Optimize benefit/risk and benefit/cost
4. Proceed step by step, re-assess and redefine target

Set the target... Decide the treatment... Assess the target... Reach the target

the target has 2 dimensions: Quality of Life and intestinal healing
CALM: primary endpoint at 48 weeks after randomisation

Mucosal healing (CDEIS <4) and no deep ulcerations

Higher rates of mucosal healing and no deep ulceration observed in early CD when treating to a target of biomarker levels (CRP and faecal calprotectin), compared with symptom-driven clinical management.

CDEIS: Crohn's disease endoscopic index of severity

Higher rates of mucosal healing and deep remission observed in early CD when treating to a target of biomarker levels (CRP and faecal calprotectin), compared with symptom-driven clinical management.
Potential benefits and risks of “treat to target”

Benefits

Improved outcomes through better disease monitoring
Disease modification: reduction of damage

Risks

Unrealistic targets: Mucosal healing only achieved in 40% of patients: Rapid rotation of drugs possible, frustrated patients, frustrated physicians
Over-treatment: cost and safety
Increased complexity of treatment algorithms
Risk of immunogenicity
Added risk from endoscopic procedures or invasive tests
Mucosal healing: Lack of a “common definition”

“Working definition” for mucosal healing:
- UC: Mayo score of ≤1
- CD: absence of ulcers >5 mm

Alternative: quantitative endpoints (CDEIS, SES-CD, UCEIS)
- More responsive to change
- Complex as a treatment goal, not realistic in daily practice

Evidence for the working definition for mucosal healing?
- Association with relevant long-term outcomes
- No evidence for treating to these goals
Mucosal healing rates in recent clinical trials in CD

- Endoscopic remission CALM (Adalimumab) 45.9%
- Endoscopic remission in all segments CALM (Adalimumab) 29.5%
- Complete endoscopic remission CALM (Adalimumab) 18%
- Mucosal healing IM-UNITI (Ustekinumab) 17.2%
- Durable endoscopic healing Vedolizumab 29%
- Complete mucosal healing; SES-CD is 0 FITZROY (Filgotinib) 4%

% of patients treated:

- Rutgeerts P et al. UEGW 2016 #OP 104
- Noman et al, J Crohns Colitis. 2017 Sep 1;11(9):1085-1089.
People with good intentions *make* promises. People with good character *keep* them.

- Unknown

A promise made is a debt unpaid.
Changing treatments too early due to “unmet targets”
Does current medical therapy prevent intestinal damage?

Incident IBD cases South-Limburg Area; Population-based IBD cohort with >93% coverage
«Biologic cohort»: 1999 – 2011 (Follow up until 2014)

Similar risk to develop fibrosis in the pre- and biological era

1. Steuring, et al. DDW2015, #79 (Oral)
Treat to target in other diseases: Always beneficial?

- 2015 ADA/EASD position statement on treatment of T2D: therapy should be escalated every 3 months if patients do not achieve target HbA1c ¹
- A study of more than 40,000 T2D patients in 5 European countries and in the US, reveals that only 8.1% reached target at 3 months ²
- More recent RCTs and meta-analyses have shown no difference of intensive glycemic control vs. a conventional approach (an HbA1c level of approximately 8.0% ³,⁴
- In contrast, a 2- to 3-fold increase in the risk of hypoglycemia with intensive treatment was found ³,⁴
- Hypoglycemia is associated with cardiovascular events, cognitive impairment, fractures, death, and decreased quality of life. ⁵,⁶

¹ Diabetes Care. 2015;38:140-149
² Diabetes Obes Metab. 2017; DOI:10.1111/dom.12927
“Treat to target” must be individualized

- Mucosal healing only achieved in 40% of patients: Rapid rotation of drugs possible, frustrated patients, frustrated physicians
- Risk of over-treatment: risk/benefit studies are missing
- Increased complexity of treatment algorithms/too rapid rotation of drugs
- Added risk from endoscopic procedures or invasive tests
- Treat to target is seen now more critical also in other diseases

- Treatment target need to be individualized!!!
Thank you for your attention

head-to-head studies

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