The future of IBD therapeutic research

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The future of IBD therapeutic research

• Disease modification

• Personalization
Crohn’s disease as a progressive disease

Disease initiation; Expansion of auto-inflammatory process

Digestive damage (Lémann index)

Sub-clinical inflammation

Early disease

Inflammatory activity (CDAI, CDEIS, CRP)

Late disease

Surgery

Stricture

Fistula/abscess

Diagnosis

Goal of treatment in IBD: Blocking disease progression and damage

- Disease initiation; Expansion of auto-inflammatory process
- Sub-clinical inflammation
- Early disease
- Late disease
- Digestive damage (Lémann index)
- Inflammatory activity (CDAI, CDEIS, CRP)

Diagnosis

- Stricture
- Fistula/abscess
- Surgery
Goal of treatment in IBD:
Blocking disease progression and damage

Disease onset
Diagnosis
Early disease
The future of IBD therapy

- Access and reimbursement pressures will increase
- Especially for drugs with “limited” efficacy
- Just because it is approved won’t mean it will get reimbursed

We have to show something more than a “p-value” and a PI!
Disease modification: the model of RA

The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis

The upper and lower lines indicate the upper and lower limits, respectively, of the 95% confidence interval.

The upper and lower lines indicate the upper and lower limits, respectively, of the 95% confidence interval for joint damage progression.

Strategy trials in RA: what did we learn?

- Value of intensive treatment adjusted according to quantitative data (Treat to target)
- Benefits of early therapy (Window of opportunity)
- Value of a quantitative index monitored frequently for rational intensification of therapy (Tight control)
- Strategy is more important than the agent to treat
- Long term studies needed to best illustrate the benefit
Disease modification trials in IBD: What do we need?

- Disease-modifying drugs
- Treat to target
- Tight control
- Early intervention
- Long term endpoints
- Selected patients
Therapeutic targets in UC

Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target

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The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) group, under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), has developed 12 recommendations for treating to target in Crohn’s disease (CD) and ulcerative colitis (UC).

Clinical/patient-reported outcomes and endoscopic remission are recommended in clinical practice for both CD and UC.

The implementation of these recommendations in clinical practice has the potential to change disease course and improve quality of life.
Tight-control through monitoring is necessary to reach the target.

Tight control and monitoring
(patient management programme)

Adapted from Pariente B, et al. Inflamm Bowel Dis 2011
Close monitoring of CRP and faecal calprotectin predicts clinical relapse after infliximab withdrawal

Sub-analysis of the STORI study (in patients with CD in remission)

- In relapsers:
  - Higher median CRP and calprotectin during follow-up
  - Sudden and pronounced increase in CRP and calprotectin during 4 months prior to relapse

- CRP of 6.1 mg/L and calprotectin of 305 µg/g best for prediction of relapse

Early intervention is key to prevention of progression

Diagnosis

\[ \text{Disease initiation; Expansion of auto-inflammatory process} \]

\[ \text{Sub-clinical inflammation} \]

\[ \text{Early disease} \]

\[ \text{Late disease} \]

\[ \text{Stricture} \]

\[ \text{Fistula/abscess} \]

\[ \text{Surgery} \]

\[ \text{Window of opportunity} \]

\[ \text{Digestive damage (Lémann index)} \]

\[ \text{Inflammatory activity (CDAI, CDEIS, CRP)} \]

Early Intervention: RISK Cohort

Increased Effectiveness of Early Therapy With Anti–Tumor Necrosis Factor–α vs an Immunomodulator in Children With Crohn’s Disease

N = 204 patients included with propensity score matching

Corticosteroid-Free Clinical Remission at 1 Year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF vs IM</td>
<td>1.41 (1.14-1.76)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Anti-TNF vs no early immunotherapy</td>
<td>1.57 (1.23-1.99)</td>
<td>0.0002</td>
</tr>
<tr>
<td>IM vs no early immunotherapy</td>
<td>1.11 (0.83-1.48)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Early Anti-TNF in children produced better clinical outcomes at 1 year

Walters TD et al. Gastroenterology 2014
Early Intervention: REACT Trial

Early combined immunosuppression for the management of Crohn’s disease (REACT): a cluster randomised controlled trial

- Open-label cluster randomized trial in Belgium and Canada

- Randomly assigned community gastroenterology practices to either:
  - Early combined immunosuppression algorithm (22 practices, n=1084)
  - Conventional management (18 practices, n=898)

- **Primary outcome**: corticosteroid-free clinical remission at 1 year at the practice level

- Secondary outcome: Proportion of patients with major adverse outcomes at 2 years (surgery, hospitalization, major complication)
Early intervention: REACT trial (CD)

aHBI ≤4 without steroids

Complications

Surgery

HR (95% CI) = 0.73 (0.61, 0.87)
p = 0.001

HR (95% CI) = 0.69 (0.50, 0.97)
p = 0.031

Patients in remission:

- Early combined immunosuppression
- Conventional management


REACT: Randomised Evaluation of an Algorithm for Crohn's Treatment; HBI: Harvey Bradshaw Index; NS: not significant; HR: hazard ratio
The effect of early response to treatment on 5-year follow-up of radiographic progression in the CAMERA study (rheumatoid arthritis)
Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn’s Disease

First experience with the Lemann index

**Figure 1.** Median (IQR, range) of Lémann Index values in 95 patients who had 3 morphologic evaluations after a diagnosis of Crohn’s disease.
Disease modification trials in IBD: What do we need?

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The future of IBD therapeutic research

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• Personalization
We anticipate that over the next 5 years, the one dose fits all strategy will not likely yield the clinical results required to justify “traditional” biologic drug pricing in currently served indications.
Taking into account patient’s prognosis

Assessing prognosis at an early stage is essential for the development of an appropriate management plan.

- **Indolent**
  - Avoid intensive therapy, immunosuppression, adverse events

- **Aggressive**
  - Assure early intensive therapy to avoid complications
Which prognostic factors to use?

Clinical (age, extent, behaviour, symptoms)

Endoscopic (mucosal healing)

Imaging

Genetic (>100, primarily NOD2/CARD15)

Serological and laboratory markers (CRP, ASCA, ANCA, OmpC)

Fecal (calprotectin)

ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: anti-Saccharomyces cerevisiae antibodies; OmpC, outer membrane protein C precursor
A Web-based tool to display individualised CD predicted outcomes based on clinical, serologic and genetic variables.

Predictive tool prospectively collected from 695 CD patients.

Model for high-risk 57 year old male patient with high probability of disease complication.

Taking into account parameters that impact response with Biologic Agents

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>Patients with shorter disease duration respond better regardless of the disease and the mAb</td>
</tr>
<tr>
<td>Patient weight</td>
<td>Heavier patients fair worse regardless of the disease and the mAb (even with drugs dosed by weight like IFX)</td>
</tr>
<tr>
<td>Therapy history</td>
<td>Patients with biologicals experience achieve poorer results regardless of the disease and the mAb</td>
</tr>
<tr>
<td>Disease severity and PK/PD</td>
<td>Disease severity as measured by “biomarkers” impacts PK and PD of mAbs and subsequent response</td>
</tr>
<tr>
<td>Biomarkers of inflammation</td>
<td>Patients with multiple elevated baseline biomarkers of inflammation are less likely to achieve and sustain a clinical response</td>
</tr>
<tr>
<td>Biomarker kinetics</td>
<td>Patients who “normalize” biomarker levels (e.g., CRP) are more likely to achieve and sustain a clinical response</td>
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<tr>
<td>Early drug AUC</td>
<td>Patients who achieve greater early drug concentration and AUCs are more likely to achieve and sustain a clinical response</td>
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<tr>
<td>Drug concentration maintenance</td>
<td>Patients who maintain adequate drug concentration are more likely to sustain a clinical response</td>
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</table>

*Univariate analyses*
Taking into account predictors of response to therapy
EX: Etrolizumab phase II

- Etrolizumab maximally occupied β7 receptors in the colonic mucosa and on circulating CD4+ and CD8+β7+ T lymphocytes, and CD19+β7+ B lymphocytes at both doses, with a corresponding specific increase in intestinal homing CD4+β7+ T lymphocytes in the peripheral blood.

Clinical remission according to baseline colonic biopsy αE levels

Conclusion

- Opportunity to transform the therapeutic strategy in IBD
- X Challenges: early patients, multiple selection criteria, long term follow-up, cost...