EARLY TREATMENT: IS THERE A WINDOW OF OPPORTUNITY IN IBD?

Antonio Rispo
Gastroenterology
A.O.U. “Federico II” of Naples
The Tale of the Three Brothers

2008
- R.S., male, 26 years
- 30 months of symptoms
- CD diagnosis (A1, L2, B2, p-)
- Ileal extension (40 cm)
- Step-up approach (failure)
- **Surgery**
- AZT after surgery
- AZT-failure
- Anti-TNF alpha (failure)
- **Second surgery**
- Anti-α4β7
- Remission
- **Lemann Index: 13.75**

2012
- E.S., male, 23 years
- 3 months of symptoms
- CD diagnosis (A1, L1, B1, p-)
- Ileal extension (30 cm)
- Early azathioprine (plus steroids)
- AZT-failure
- Anti-TNF alpha
- Anti-TNF alpha-failure
- **Surgery**
- Anti-TNF alpha
- Remission (Rutgeerts i1)
- **Lemann Index: 5.25**

2017
- A.S., male, 15 years
- 2 months of symptoms
- CD diagnosis (A1, L1, B1, p-)
- Ileal extension (30 cm)
- Anti-TNF alpha
- Deep remission (CR, MH, TH)
- **Lemann Index: 0.65**
IS EARLY TREATMENT EFFECTIVE?

LESSON FROM RHEUMATOLOGY

Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis

S M van der Kooij,1 Y P M Goekoop-Ruiterman,1 J K de Vries-Bouwstra,2 M Güler-Yüksel,1 A H Zwinderman,3 P J S M Kerstens,4 P A H M van der Lubbe,2 W M de Beus,6 B A M Gillet,7 H K Ronday,8 T W J Huizinga,1 F C Breedveld,1 B A C Dijkmans,2,4 C F Allaart4

Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial

Paul Emery, Ferdinand C Bredveld, Stephen Hall, Patrick Dunz, David J Chang, Deborah Robertson, Amitabh Singh, Ronald D Pedersen, Andrew SK Koenig, Bruce Friendlich

van der Kooij, Ann Rheum Dis 2009

Emery, Lancet 2008
IS EARLY TREATMENT EFFECTIVE?

LESSON FROM NEUROLOGY

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study

Ludwig Kappos, Mark S Freedman, Chris H Polman, Gilles Edan, Hans-Peter Hartung, David H Miller, Xavier Montalbán, Frederik Barkhof, Ernst-Wilhelm Radü, Lars Bauer, Susanne Dahms, *Vivian Larius, Christoph Pohl, †Rupert Sandbrink, ‡for the BENEFIT Study Group

Figure 2: Kaplan-Meier estimates for the probability of progression on the expanded disability status scale (EDSS) confirmed after 6 months within the 3-year period

Kappos, Lancet 2007
Risk Factors Associated With Progression to Intestinal Complications of Crohn’s Disease in a Population-Based Cohort

KELVIN T. THIA,*§ WILLIAM J. SANDBORN,* WILLIAM S. HARMSSEN,† ALAN R. ZINSMEISTER,† and EDWARD V. LOFTUS, Jr*

18.5% of CD patients experienced complications within 90 days from diagnosis

<table>
<thead>
<tr>
<th>Factors at diagnosis</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>306 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>150 (49.0)</td>
</tr>
<tr>
<td>Female</td>
<td>156 (51.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>35 (11.4)</td>
</tr>
<tr>
<td>A2</td>
<td>172 (56.2)</td>
</tr>
<tr>
<td>A3</td>
<td>99 (32.4)</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>138 (45.1)</td>
</tr>
<tr>
<td>L2</td>
<td>98 (32.0)</td>
</tr>
<tr>
<td>L3</td>
<td>57 (18.6)</td>
</tr>
<tr>
<td>L4</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>L1 + L4</td>
<td>7 (2.3)</td>
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<tr>
<td>L2 + L4</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>L3 + L4</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Penetrating or stricturing complications

Thia, Gastroenterology 2010
Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn’s Disease

Pariente, Gastroenterology 2015
Baumgart, Lancet 2012
Prevalence of Bowel Damage Assessed by Cross-Sectional Imaging in Early Crohn’s Disease and its Impact on Disease Outcome

Gionata Fiorino, Mathilde Morin, Stefanos Bonovas, Cristiana Bonifacio, Antonino Spinelli, Adeline Germain, Valérie Laurent, Camille Zallot, Laurent Peyrin-Biroulet, Silvio Danese

Bowel Damage L.I. > 4.8

142 CD pts

39% of CD patients showed bowel damage at diagnosis
Bowel Damage in Crohn’s Disease: Direct Comparison of Ultrasonography-based and Magnetic Resonance-based Lemann Index

Antonio Rispo, MD, PhD,* Nicola Imperatore, MD,* Anna Testa, MD, PhD,* Pierpaolo Mainenti, MD,† Giovanni Domenico De Palma, MD,‡ Gaetano Luglio, MD,§ Simone Maurea, MD,‖ Olga Maria Nardone, MD,* Nicola Caporaso, MD,* and Fabiana Castiglione, MD*

Bowel Damage L.I. > 4.8

71 CD pts

Rispo, Inflamm Bowel Dis 2017
WHAT IS EARLY CD?

TIME

B1

B2

B3
Development of the Paris Definition of Early Crohn’s Disease for Disease-Modification Trials: Results of an International Expert Opinion Process

Laurent Peyrin-Biroulet, MD, PhD,1 Vincent Billioud, MD,1 Geert D’Haens, MD, PhD,2 Remo Panaccione, MD,3 Brian Feagan, MD,4 Julian Panés, MD,5 Silvio Danese, MD, PhD,6 Stefan Schreiber, MD, PhD,7 Haruhiko Ogata, MD, Toshifumi Hibi, MD, PhD,8 Peter D.R. Higgins, MD,9 Laurent Beaugerie, MD, PhD10, Yehuda Chowers, MD11,12, Edouard Louis, MD, PhD13, Flávio Steinwurz, MD14, Walter Reinisch, MD15, Paul Rutgeerts, MD, PhD16, Jean-Frédéric Colombel, MD17, Simon Travis, MD18 and William J. Sandborn, MD19

Table 3. Paris criteria defining early Crohn’s disease for use in disease-modification trials (evidence level D)

<table>
<thead>
<tr>
<th>Component</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>≤18 months after diagnosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>No previous or current use of immunomodulators and/or biologics</td>
</tr>
<tr>
<td></td>
<td>Previous or current use of 5-aminosalicylate and/or corticosteroids permitted</td>
</tr>
</tbody>
</table>

Approximately 20% of patients with newly diagnosed CD present with bowel damage (4). These patients should be included in disease-modification trials in order to evaluate prevention of damage progression in patients with early CD, even though the primary focus of early CD trials is likely to be the stratum of patients without preexisting bowel damage. Only perianal fistu-
IS EARLY TREATMENT EFFECTIVE?

LESSON FROM CHILDREN
A Multicenter Trial of 6-Mercaptopurine and Prednisone in Children With Newly Diagnosed Crohn’s Disease

JAMES MARKOWITZ,* KATHY GRANCHER,* NINA KOHN,† MARTIN LESSER,† FREDRIC DAUM,* and THE PEDIATRIC 6MP COLLABORATIVE GROUP

Markowitz, Gastroenterology 2000
Impact of early thiopurines on surgery in 2770 children and young people diagnosed with inflammatory bowel disease: a national population-based study

V. Chhaya*, R. C. G. Pollok*, E. Cecil†, V. Subramanian‡, V. Curcin§, A. Majeed† & S. Saxena†
Comparison of Adult and Pediatric Biologics Trial Results

**Infliximab**

- **UC**
  - ACT Placebo
  - ACT 1
  - T72

- **CD**
  - ACCENT1 placebo
  - ACCENT1
  - REACH

**Adalimumab**

- **CD**
  - CHARM placebo
  - CHARM
  - IMAGINE

- **UC**
  - ULTRA2 placebo
  - ULTRA2
  - Pediatric trial (ongoing)

% 1 year remission

- Placebo
- Adults
- Pediatrics

J Pediatr Gastroenterol Nutr 2016
Biologics Delay Progression of Crohn’s Disease, but Not Early Surgery, in Children


1442 CD pts
Prediction of complicated disease course for children newly diagnosed with Crohn’s disease: a multicentre inception cohort study


913 CD pts
IS EARLY TREATMENT EFFECTIVE?

LESSON FROM R.C.Ts.
(SUB-GROUP, SECONDARY END-POINT AND/OR POST-HOC ANALYSES)
Early Azathioprine Therapy Is No More Effective Than Placebo for Newly Diagnosed Crohn’s Disease

JULIÁN PANÉS, ANTONIO LÓPEZ–SANROMÁN, FERNANDO BERMEJO, VALLE GARCÍÁ–SÁNCHEZ, MARIA ESTEVE, YOLANDA TORRES, EUGENI DOMÉNECH, MARTA PIQUERAS, MARÍA GOMEZ–GARCÍA, ANA GUTIÉRREZ, CARLOS TAXONERA, and MIQUEL SANS, for the AZTEC Study Group

AZTEC TRIAL

131 CD pts

Panes, Gastroenterology 2013
Early Administration of Azathioprine vs Conventional Management of Crohn’s Disease: A Randomized Controlled Trial

JACQUES COSNES, ANNE BOURRIER, DAVID LAHARIE, STÉPHANE NAHON, YORAM BOUHNIK, FRANCK CARBONNEL, MATTHIEU ALLEZ, JEAN–LOUIS DUPAS, JEAN–MARIE REIMUND, GUILLAUME SAVOYE, PAULINE JOUET, JACQUES MOREAU, JEAN–YVES MARY, and JEAN–FRÉDÉRIC COLOMBEL, for the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID)

132 CD pts
Early Administration of Azathioprine vs Conventional Management of Crohn’s Disease: A Randomized Controlled Trial

JACQUES COSNES, ANNE BOURRIER, DAVID LAHARIE, STEPHANE NAHON, YORAM BOUHNIK, FRANCK CARBONNEL, MATTHIEU ALLEZ, JEAN-LOUIS DUPAS, JEAN-MARIE REIMUND, GUILLAUME SAVOYE, PAULINE JOUET, JACQUES MOREAU, JEAN-YVES MARY, and JEAN-FRÉDÉRIC COLOMBEL, for the Groupe d’Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID)

**Graph:**

- **Proportion of patients given immunosuppressants (%):**
  - **Early azathioprine**
  - **Conventional management**

- **Months after randomization:**
  - 0
  - 12
  - 24
  - 36

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Early aza.</th>
<th>Conv. m.</th>
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<tbody>
<tr>
<td>65</td>
<td>64</td>
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<td>59</td>
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<td></td>
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</table>

132 CD pts
Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn’s disease: an open randomised trial

Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn’s disease: an open randomised trial

Step-Up: Conventional Management (corticosteroids, followed in sequence by AZA and IFX)

Top-Down: Combined Immunosuppression (3 infusions of IFX, 5 mg/kg at wks 0, 2, and 6, with AZA)

Complete Absence of Ulcerations at yr 2

<table>
<thead>
<tr>
<th>Patients Without Lesions, %</th>
<th>Step-up</th>
<th>Top-down</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.4</td>
<td>73.1</td>
</tr>
</tbody>
</table>

P = .0028

StepUp vs TopDown TRIAL

D’Haens, Lancet 2008
"Deep remission" defined as complete mucosal healing and clinical remission (CDAI <150)
Early combined immunosuppression for the management of Crohn’s disease (REACT): a cluster randomised controlled trial

STEROID-FREE CLINICAL REMISSION

Khanna, Lancet 2015
Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy (REACT2)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01898307

Recruitment Status: Active, not recruiting
First Posted: October 2, 2012
Last Update Posted: October 23, 2016

Sponsor:
University of Western Ontario, Canada

Outcome Measures

Primary Outcome Measures:
1. Risk of CD-related complications at one-year, measured at the practice level [Time Frame: 12 months]
   CD-related complications include (1) CD-related surgeries and non-surgical CD events (such as disease flare, bowel obstruction, and bowel damage events (such as symptomatic bowel obstruction, fistula, abscess and CD related hospitalizations and 2) complications and hospitalizations related to CD medications or procedures.

Secondary Outcome Measures:
1. Risk of CD-related complications at 6 months. [Time Frame: six months]
   CD-related complications include (1) CD-related surgeries and non-surgical CD events (such as disease flare, bowel obstruction, and bowel damage events (such as symptomatic bowel obstruction, fistula, abscess and CD related hospitalizations and 2) complications and hospitalizations related to CD medications or procedures.

Other Outcome Measures:
1. Proportion of patients at one year who are in Deep Remission without disease progression [Time Frame: twelve months]
   Disease progression is defined as the de novo development of strictures or fistula, the occurrence of an intra-abdominal abscess, or surgery for CD (resection, bypass, stricturoplasty).
IS EARLY TREATMENT EFFECTIVE?

LESSON FROM COHORT STUDIES
Early intervention in Crohn’s disease: towards disease modification trials

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study design</th>
<th>Intervention/control</th>
<th>Early CD definition</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safroneeva et al (2015)</td>
<td>Prospective observational cohort</td>
<td>Early use of anti-TNF and/or immunomodulators</td>
<td>24 months</td>
<td>Development of complications</td>
</tr>
<tr>
<td>Kwak et al (2014)</td>
<td>Retrospective cohort</td>
<td>Early immunomodulator use versus conventional therapy</td>
<td>6 months in the ET group</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>Kim et al (2016)</td>
<td>Retrospective study</td>
<td>Early immunomodulator use versus conventional therapy</td>
<td>6 months in the ET group</td>
<td>Need for surgery</td>
</tr>
<tr>
<td>Nuij et al (2015)</td>
<td>Retrospective cohort</td>
<td>Early anti-TNF versus conventional step-up approach</td>
<td>≤16 months</td>
<td>IBD-related complications</td>
</tr>
</tbody>
</table>

Danese, Gut 2017
Crohn’s disease prognosis and early immunomodulator therapy: Results from the CONNECT study

Bun Kim,* † Jae Hee Cheon,* Hyun Jin Moon,* Yi Rang Park,* Byong Duk Ye, † Suk-Kyun Yang, † Geom Seog Seo, † Byung Ik Jang, ‡ You Sun Kim, † Joo Sung Kim,** Dong Soo Han, †† Young-Ho Kim, ††† and Won Ho Kim*
The Role of Thiopurines in Reducing the Need for Surgical Resection in Crohn’s Disease: A Systematic Review and Meta-Analysis

Sukhdev Chatu, MD¹, Venkataraman Subramanian, MD², Sonia Saxena, MD³ and Richard C.G. Pollok, FRCP, PhD¹

<table>
<thead>
<tr>
<th>Group by</th>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Hazard ratio 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Study population</td>
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<tr>
<td>1.00</td>
<td>Vernier-Massouille</td>
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<tr>
<td>1.00</td>
<td>Pooled (population)</td>
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<td>0.44</td>
<td>0.93</td>
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<tr>
<td>2.00</td>
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<td>0.52</td>
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<td>2.00</td>
<td>Pooled (hospital based)</td>
<td>0.57</td>
<td>0.45</td>
<td>0.73</td>
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<tr>
<td>Overall</td>
<td>Pooled (combined)</td>
<td>0.59</td>
<td>0.48</td>
<td>0.73</td>
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</tr>
</tbody>
</table>

1= population-based study
2= hospital tertiary referral-based studies

Favors thiopurine no effect
ECCO statement 8C

Early treatment with thiopurines [EL2] is associated with reduced risk of first surgery. Treatment with anti-TNF reduces the risk of surgery [EL2]
Transmural Healing Evaluated by Bowel Sonography in Patients with Crohn’s Disease on Maintenance Treatment with Biologics

Fabiana Castiglione, Anna Testa, MD, Matilde Rea, MD, Giovanni Domenico De Palma, Maria Diaferia, MD, Dario Musto, MD, Francesca Sasso, MD, Nicola Caporaso, and Antonio Rispo, MD

Transmural Healing at 2 Years

140 CD patients

Castiglione, Inflamm Bowel Dis 2013

<table>
<thead>
<tr>
<th></th>
<th>BIOLOGICS</th>
<th>THIOPURINES</th>
<th>$p$</th>
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<tbody>
<tr>
<td>BWT at BS</td>
<td>6.0±2.8 vs 4.0±1.2*</td>
<td>6.2±2.5 vs 5.8±1.7^</td>
<td>*&lt;0.01</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>^n.s.</td>
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</tbody>
</table>
CONCLUSIONS:
IS THE EARLY TREATMENT OF EARLY CD REALLY EFFECTIVE?

- Early treatment of early CD could avoid bowel damage (reducing complications, surgery and hospitalizations) BUT the evidence is not yet strong.

- At now, early treatment should be offered to CD patients with prognostic factors for disabling disease (e.g. deep ulcers, rectal CD, extensive involvement of small bowel, paediatric CD, familial aggregation ?).

-“Strategic” R.C.Ts. focused on the early treatment of early disease (in accordance with Paris definition) are needed to really evaluate our window of opportunity for treating CD.
GRAZIE PER L’ATTENZIONE...

...my window of opportunity...