LE MALATTIE INFIAMMATORIE CRONICHE INTESTINALI NELL'ANZIANO

I nuovi farmaci biologici: anche nell'anziano?

ANNA KOHN (Roma)
Increasing incidence

**Crohn's disease**

- Adult-onset
- Elderly-onset

**Ulcerative colitis**

- Adult-onset
- Elderly-onset

*FIGURE 1.* Incidence rates of AO and EO CD and UC in the South Limburg area of the Netherlands. Incidence rates were corrected for age, sex, and calendar year.
IBD Prevalence on December 31, 2009 in the Lazio region

Prevalence:
- CD: 91:100,000
- UC: 81:100,000
- 144:100,000

Ulcerative colitis:
- Male: 177:100,000

Di Domenicantonio R et al, DLD 2014
### Disease course of elderly-onset IBD

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>location</td>
<td>more often left sided (E2)</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>less bleeding and abdominal pain</td>
<td>less diarrhoea, abdominal pain and weight loss</td>
</tr>
<tr>
<td>disease behaviour</td>
<td>mostly inflammatory</td>
<td>more likely stable</td>
</tr>
<tr>
<td>extraintestinal manifestations</td>
<td>less common</td>
<td>less common</td>
</tr>
<tr>
<td>cancer risk</td>
<td>Higher risk of NH lymphoma with thiopurine and NMSC with anti-TNF therapy</td>
<td></td>
</tr>
</tbody>
</table>

IBD Epidemiology from a French population-based registry (EPIMAD)

Elderly onset CD

- Inflammatory: 78%
- Strictures: 17%
- Penetrating: 5%

Pediatric onset CD

- Inflammatory: 73%
- Strictures: 23%
- Penetrating: 4%

The risk of IBD-related hospitalization is higher in elderly UC, but not CD patients, than in younger adults.
Conflicting data on the risk of surgery for the elderly IBD.

Study based on administrative data report an increased risk due to a mixed population of elderly with long standing IBD and elderly onset IBD.

Everhov AH et al., Gastroenterology 2018
Nguyen GC Inflamm Bowel Dis 2017

No difference in surgery risk was observed by population-based study
Jeuring FSG et al; Inflamm Bowel Dis 2016
Lakatos PL et al.; J Crohns Colitis 2011

Everhov AH, Gastroenterology 2018
## IBD related surgery: postsurgical mortality and complications

<table>
<thead>
<tr>
<th></th>
<th>Crohns</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>elderly</td>
<td>non elderly</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>4.2</td>
<td>03 **</td>
</tr>
<tr>
<td>infectious complications</td>
<td>16.2</td>
<td>13.6</td>
</tr>
<tr>
<td>cardiac complications</td>
<td>2.3</td>
<td>0.2**</td>
</tr>
<tr>
<td>renal complications</td>
<td>2.2</td>
<td>0.6**</td>
</tr>
<tr>
<td>neurologic complications</td>
<td>0.5</td>
<td>0.1*</td>
</tr>
<tr>
<td>venous thromboembolism</td>
<td>3.1</td>
<td>1.5**</td>
</tr>
</tbody>
</table>

* p<0.05    ** p< 0.01, *** p< 0.001

Bollegala N et al.; Clin Gastroenterol Hepatol 2015

Elderly patients undergoing IBD-related bowel surgery experience a pronounced 5- to 10-fold higher 30-day mortality than younger IBD patients, as well as number of other systemic complications.
Crohn’s disease: Disease activity distribution in each year from diagnosis

- **55%** remission
- **15%** low activity
- **30%** high activity

ECCO Current Practice Position 8

There is no evidence that the efficacy of medical treatment in elderly IBD patients differs from that in younger adult patients

ECCO Current Practice Position 9

All available data indicate a higher risk of serious adverse events with prolonged use of corticosteroids in elderly patients with IBD when compared to younger adult patients

ECCO Current Practice Position 11

Elderly IBD patients treated with TNF inhibitors for IBD have an increased risk of severe infection compared with younger patients

European Crohn’s and Colitis Organisation
Topical Review on IBD in the Elderly

Andreas Sturm,a Christian Maaser,b Michael Mendall,c Dimitrios Karagiannis,d Pantelis Karatzas,e Nienke Ipenburg,f Shaji Sebastian,g Fernando Rizzello,h Jimmy Limdi,i Konstantinos Katsanos,j Carsten Schmidt,k Steven Jeuring,l Francesco Colombo,m Paolo Gionchetti,n

Sturm A et al., J Crohns Colitis 2016
The elderly are less likely to receive biological agents or IMM. This may be secondary to concerns for risks for infection and cancer; or may reflect that the elderly do have more comorbidities and polypharmacy making the use of more medications riskier.
Advanced Age Is an Independent Risk Factor for Severe Infections and Mortality in Patients Given Anti–Tumor Necrosis Factor Therapy for Inflammatory Bowel Disease

MARIO COTTONE,* ANNA KOHN,† MARCO DAPERNO,‡ ALESSANDRO ARMUZZI,‡‡ LUISA GUIDI,‡ RENATA D’INCA,‡
FABRIZIO BOSSA,‡ ERIKA ANGELUCI,** LIVIA BIANCONE,** PAOLO GIONCHETTI,** SANDRO ARIZZONE,‡†
CLAUDIO PAPI,** WALTER FRIES,** SILVIO DANESI,** GABRIELE RIEGLER,**‡† MARIA CAPPETTO,**‡‡
FABIANA CASTIGLIONE,§§ VITO ANNESE,§§ and AMBROGIO ORLANDO*

### Table

<table>
<thead>
<tr>
<th></th>
<th>95 elderly patients treated with biologics</th>
<th>190 adult matched controls treated with biologics</th>
<th>190 elderly controls not treated with biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts n°</strong></td>
<td>UC</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>Male/female</td>
<td>37</td>
<td>58</td>
<td>74</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>71 (65-81)</td>
<td>71 (65-84)</td>
<td>38 (17-64)</td>
</tr>
<tr>
<td>Remission n° (%)</td>
<td>22 (59.5)</td>
<td>38 (65.5)</td>
<td>42 (56.7)</td>
</tr>
<tr>
<td>Maintenance n° (%)</td>
<td>12 (32.4)</td>
<td>39 (67.2)</td>
<td>24 (32.4)</td>
</tr>
<tr>
<td>Comorbidity n° (%)</td>
<td>35 (94.5)</td>
<td>44 (75.8)</td>
<td>4 (5.4)</td>
</tr>
<tr>
<td>Deaths (n°)</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Severe Infections (n°)</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Cancer (n°)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Steroids (n°)</td>
<td>36</td>
<td>54</td>
<td>72</td>
</tr>
<tr>
<td>antiTNF+AZA/MTX n° (%)</td>
<td>7 (19)</td>
<td>15 (26)</td>
<td>17 (23)</td>
</tr>
</tbody>
</table>

Data from: M Cottone et al., Clin Gastroenterol Hepatol 2010
Malignancy and mortality during the follow up in IBD cases: ≥ 65 yrs anti TNF as compared with controls

Lobaton T et al., Aliment Pharmacol Ther 2015
Efficacy of anti-TNF therapy

Clinical response at short term (10 weeks) &
Clinical response at long term (≥ 6 months)

Lobaton T et al., Aliment Pharmacol Ther 2015
Therapeutic Galaxy in IBD

Cytokine Receptors
- CCX-025 GSK
- CCX282-B GSK
- ZP1848 Zealand
- RDP 58 Genzyme
- laquinimod Teva / Active Biotech
- Tofacitinib Pfizer

Immunomodulators
- Rifaximin EIR AlphaWessermann
- NN8555 Novo Nordisk
- Tofacitinib Pfizer
- Adalimumab AbbVie
- Certolizumab pegol UCB
- Remestemcel-L Osiris
- PDA-001 Celgene Cellular
- Cellerix Cellerix
- OvaSave TXCell

JAK Inhibitors
- laquinimod Teva / Active Biotech
- Tofacitinib Pfizer

Cell Therapies
- HSCT

IL Inhibitors
- TNF-α Inhibitors
- IL Inhibitors

Adhesion Molecules Inhibitors
- Debiaerse Neovacs
- Natalizumab Elan/Biogen Idec
- Vedolizumab Millenium / Takeda
- Infliximab Centocor
- Golimumab MSD - Merck
- AMG 827 Amgen
- PF 05230900 Pfizer
- PF-547659 Pfizer
- AIN 457 Novartis
- ELND-004 Elan/Biogen Idec
- PF-05230900 Pfizer
- Neovacs
- Neovacs
- Neovacs
- Neovacs
- Neovacs
- Neovacs

Infliximab Centocor
- Natalizumab Elan/Biogen Idec
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- Neovacs
- Neovacs
- Neovacs
- Neovacs

Adapted from Danese S. Gut 2012;61:918-32
Lymphocytes migration and retention of T cells in Gut mucosal tissue


decreased lymphocyte migration & inhibition of homing of lymphocytes to the gut

anti-adhesion therapies

vedolizumab
etrolizumab
natalizumab
Vedolizumab induction and remission in moderate to severe UC - GEMINI I

**Week 6**

- Response: Placebo (n=149) 25%, VDZ300 mg (n=225) 47%
- Remission: Placebo (n=149) 5%, VDZ300 mg (n=225) 17%
- Mucosal healing: Placebo (n=149) 25%, VDZ300 mg (n=225) 41%

**Week 52**

- Clinical remission at 52 weeks: Placebo (n=126) 15.9%, VDZ300 mg every 8 weeks (n=122) 41.8%, VDZ300 mg every 4 weeks (n=125) 44.8%
- Durable clinical response (at 6 and 52 weeks): Placebo (n=126) 23.8%, VDZ300 mg every 8 weeks (n=122) 56.6%, VDZ300 mg every 4 weeks (n=125) 52%
- Mucosal healing at 52 weeks: Placebo (n=126) 19.8%, VDZ300 mg every 8 weeks (n=122) 51.6%, VDZ300 mg every 4 weeks (n=125) 56%

Efficacy of Vedolizumab in UC and CD patients stratified by age: from the GEMINI trials

### UC

<table>
<thead>
<tr>
<th>Age, y</th>
<th>UC patients in clinical response at week 6, n/N (%)</th>
<th>Difference from PBO, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>PBO: 11/53 (20.8), VDZ: 44/86 (51.2)</td>
<td>30.4 (15.2, 45.6)</td>
</tr>
<tr>
<td>35 to &lt;55</td>
<td>PBO: 25/78 (32.1), VDZ: 50/107 (46.7)</td>
<td>14.7 (0.7, 28.7)</td>
</tr>
<tr>
<td>≥55</td>
<td>PBO: 2/18 (11.1), VDZ: 12/32 (37.5)</td>
<td>26.4 (-2.5, 52.6)</td>
</tr>
</tbody>
</table>

### CD

<table>
<thead>
<tr>
<th>Age, y</th>
<th>CD patients with enhanced clinical response at week 6, n/N (%)</th>
<th>Difference from PBO, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>PBO: 21/87 (31.3), VDZ: 31/111 (27.9)</td>
<td>-3.4 (-17.3, 10.5)</td>
</tr>
<tr>
<td>35 to &lt;55</td>
<td>PBO: 14/83 (22.2), VDZ: 32/96 (33.3)</td>
<td>11.1 (-2.8, 25.1)</td>
</tr>
<tr>
<td>≥55</td>
<td>PBO: 3/18 (16.7), VDZ: 6/13 (46.2)</td>
<td>29.5 (-6.4, 60.6)</td>
</tr>
</tbody>
</table>

### UC patients in clinical remission at week 52, n/N (%)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>VDZ/PBO(^a) (18.5)</th>
<th>VDZ/PBO(^\text{b}) (33.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>10/54 (18.5)</td>
<td>34/101 (33.7)</td>
</tr>
<tr>
<td>35 to &lt;55</td>
<td>8/50 (12)</td>
<td>58/110 (52.7)</td>
</tr>
<tr>
<td>≥55</td>
<td>4/22 (18.2)</td>
<td>15/36 (41.7)</td>
</tr>
</tbody>
</table>

### CD patients in clinical remission at week 52, n/N (%)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>VDZ/PBO(^a) (20.5)</th>
<th>VDZ/PBO(^\text{b}) (37.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>15/73 (20.5)</td>
<td>65/173 (37.6)</td>
</tr>
<tr>
<td>35 to &lt;55</td>
<td>13/65 (20.0)</td>
<td>42/112 (37.5)</td>
</tr>
<tr>
<td>≥55</td>
<td>5/15 (33.3)</td>
<td>9/23 (39.1)</td>
</tr>
</tbody>
</table>

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Yajnik V et al., Adv Ther 2017
Adverse events by age < 65 years and ≥ 65 years

from the Gemini 1 and 2 trials

Yajnik V et al., Adv Ther 2017
IL-12 and IL-23 pro-inflammatory cytokines sharing p40 subunit

Ustekinumab

Koutruba L et al., Ther Clin Risk Manag 2010
i.v. Ustekinumab induces response and remission in patients with moderately to severely active CD refractory to anti-TNF or conventional therapy.

s.c. Ustekinumab maintained remission in patients who had clinical response to induction therapy.
**TNF Inhibitors**
- **IFX, ADA, GOLIMUMAB**
- **UC & CD**
- Fast onset
- Loss of response in 1/3 of cases
- Very effective on EIM
- Increased risk of severe infection in elderly IBD
- Infusion related reactions (iv), opportunistic infections, melanoma, NMSC, demyelinating disorders, psoriasis, aggravation of heart failure*
- Rarely, non infectious hepatitis & reduced blood cells count
- Increased risk of severe infection in elderly IBD
- Chest X-ray, TB skin tests, IFN-γ release assay (Quantiferon), HBV testing
- Inactivated trivalent influenza vaccine, Pneumococcal vaccine (PCV 13)
- Cardiological and neurological evaluation

**Integrin Inhibitors**
- **Vedolizumab**
- **UC & CD**
- Delayed therapeutic effect
- Persistent efficacy
- Moderately effective on EIM
- Suitable for UC patients at risk of infections as first line
- Nasopharyngitis
- Infusion related reactions, psoriasis (uncommon)
- Favorable safety profile
- Limited data in the elderly
- Cardiological and neurological evaluation

**Anti IL12-IL 23 mab**
- **Ustekinumab**
- **CD**
- Fast onset
- Persistent efficacy
- Effective on EIM
- Suitable for CD patients at risk of infections as first line
- Nasopharyngitis
- Infusion related reactions (uncommon)
- Favorable safety profile
- No data in the elderly
- Cardiological and neurological evaluation
- Inactivated trivalent influenza vaccine, Pneumococcal vaccine (PCV 13)
when making management decisions in the elderly IBD

“ageism” should be avoided

focus on functional status and comorbidities

avoid emergent surgeries

more frequent clinical assessment

Safety Issues

Greater mortality risk for severe disease
Higher post operative mortality

Infections & related serious complications more common

High risk of SAE and worse outcome with continued steroid use

Management optimization

Rapid decision-making

Fast onset therapy in acute severe disease

In severe disease overcome the limited evidence on drugs and choose the treatment as in adult IBD

Avoid drugs association
Safety screening better at diagnosis