Inflammatory Bowel Disease in Greece

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Topics to be discussed

- Epidemiology
- Clinical behavior
- Treatment
- Outcome
- Conclusions
Data concerning UC were derived from

- Six IBD centers of Greece
- Forty full papers published in the Greek and International literature
- Twenty-five abstracts presented in Greek and International congresses
Total number of patients with UC
1606
Mean follow-up period
9.1 years
Incidence of ulcerative colitis

Number of cases per 100000 population

Epidemiological features


Heraklion  Ioannina  Central  Evoia

Greece  Island
Mean age

40 to 46

Papadatou et al 1991,
Kouvaras et al 1995,
Archimandritis et al 2002,
Tzourmakliotis et al 2000,

Roussomoustakaki et al 2000,
Karamanolis et al 2000,
Kitis et al 2000,
Triantafillidis et al 1998
Sex

Men / Women 1.41:1

Data 1

938 men
668 women

Positive family history

Appendectomy

Percentage of appendectomy

Odds ratio: 0.6
(95% CI: 0.26-1.27)

“Less pronounced association between UC and appendectomy than previous reports”

(Koutroumbakis et al *Dis Colon Rectum* 1999)
Odds Ratio for the development of UC after tonsillectomy

0.95 (95% CI: 0.49-1.82)

(Koutroubakis et al Dis Colon Rectum 1999)
Appendectomy and tonsillectomy have no independent association with the risk of developing UC

(Koutroumbakis et al Dis Colon Rectum 1999)
Extent of disease

- Proctitis: 24.5%
- Sigmoiditis: 12.5%
- Left Colitis: 33.1%
- Total Colitis: 29.9%

Severity of disease

Progression of disease

- 256 cases with a follow-up of 7yrs
- The 10-year cumulative probability of proximal disease extension in patients with proctitis and left sided colitis was 37% and 17% respectively.

(Hatzicostas et al, BMC Gastroenterol 2006)

- 413 cases with a follow-up of 12 yrs
- Evolution to proximal disease: 17%
- Evolution to extensive colitis: 22.5%

Extraintestinal manifestations

No of patients: 1367

Percentage of patients with extraintestinal manifestations

Percentage
### Extraintestinal manifestations

<table>
<thead>
<tr>
<th>Extraintestinal manifestation</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints</td>
<td>66/705 (9.4%)</td>
</tr>
<tr>
<td>Renal</td>
<td>30/661 (4.5%)</td>
</tr>
<tr>
<td>Liver</td>
<td>20/661 (3.0%)</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>21/725 (2.9%)</td>
</tr>
<tr>
<td>Ocular lesions</td>
<td>10/661 (1.5%)</td>
</tr>
</tbody>
</table>
## Oral manifestations

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Controls</th>
<th>Ulcerative colitis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobblestoning</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Lip swelling</td>
<td>0/47 (0%)</td>
<td>1/15 (7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Buccal swelling</td>
<td>0/47 (0%)</td>
<td>1/15 (7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ulcers</td>
<td>0/47 (0%)</td>
<td>1/15 (7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Fissures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>15/47 (32%)</td>
<td>2/15 (14%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Midline</td>
<td>16/47 (34%)</td>
<td>0/15 (0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>0/47 (0%)</td>
<td>4/15 (27%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hairy tongue</td>
<td>0/47 (0%)</td>
<td>1/15 (7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Buccal trauma</td>
<td>0/47 (0%)</td>
<td>3/15 (20%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0/47 (0%)</td>
<td>3/15 (20%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Salivary gland involvement</td>
<td>0/47 (0%)</td>
<td>4/15 (27%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>0/47 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Gingivitis</td>
<td>0/47 (0%)</td>
<td>1/15 (7%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Zervou et al: Annals Gastroenterol 2004*
# Development of colorectal cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>UC patients</th>
<th>CRC cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsaros</td>
<td>1989</td>
<td>144</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Triantafillidis</td>
<td>1998</td>
<td>413</td>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>Karamanolis</td>
<td>2000</td>
<td>248</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Archimandritis</td>
<td>2002</td>
<td>64</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Roussomoustakaki</td>
<td>2000</td>
<td>470</td>
<td>2</td>
<td>0.45</td>
</tr>
<tr>
<td>Katsanos</td>
<td>2005</td>
<td>215</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>1554</strong></td>
<td><strong>18</strong></td>
<td><strong>1.2%</strong></td>
</tr>
</tbody>
</table>
Other malignancies

- 8 out of 413 patients (2%) developed acute leukemia, lung cancer, cancer of unknown origin, and brain, liver, and bladder cancer (Triantafillidis et al 1998)

- 4 out of 470 patients (0.9%) developed thymoma as well as lung, gastric and liver cancer (Roussomustakaki et al 2000)

- 3 out of 181 patients (1.7%) developed cancer of the uterus breast and prostate (Archimandritis et al 2002)
Coexistence of UC with other diseases

- Renal stones *(Triantafillidis et al 1997)*
- Medullary sponge kidney *(Triantafillidis et al, Ann Gastroenterol 2004)*
- Allergic and atopic reactions *(Triantafillidis et al 1997)*
- Psoriasis *(Mantzaris et al 1993)*
- Asthma *(Mantzaris et al 1993)*
- Sjogren’s syndrome *(Triantafillidis et al It J Gastroenterol 1994)*
- Hemolytic anemia *(Giannadaki et al Am J Gastroenterol 1997)*
- Hyperthyroidism *(Triantafillidis et al Am J Gastroenterol 1990)*
Coexistence of UC with other diseases

- Systemic Lupus Erythematosus (Koutroumbakis et al, Eur J Gastroenterol Hepatol 1998)
- Primary biliary cirrhosis (Koulentaki et al, Dig Dis Sci 1999)
- Eales’ disease (Pomonis et al, Am J Gastroenterol 1989)
- Balamidiasis (Kamberoglou et al, Am J Gastroenterol 1990)
- Sarcoidosis (Archimandritis et al, Hepatogastro-enterology 1992)
- Acute leukemia (Triantafillidis et al, Am J Gastroenterol 1987)
- Varicella infection (Mouzas et al, Am J Gastroenterol 1997)
UC in the elderly

**Course**
Similar to young patients

**Exceptions**
- Smaller number of operations
- No cases of colon cancer
- Increased mortality largely due to other causes except of UC

*(Triantafillidis et al, J Gastroenterol 1999)*
UC and H. pylori

- Low prevalence of infection
- It could be attributed to previous antibiotic treatment

(Triantafillidis et al, Am J Gastroenterol 2003)
Surgical treatment
Proportion of patients operated-on during the follow-up period of 7.2+/−3.5 years

Proportion of patients operated on for UC

Number of patients

(90.9%) (9.1%)
No of petients operated-on for UC

number of patients operated on for UC

years

0 2 4 6 8 11 13 16 20
Indications for surgery

- Poor response to conservative treatment
- Cancer development
- Long duration of disease with lumen stenosis
- Profound hemorrhage
- Toxic megacolon
- Rectovaginal fistula

Percentage

- Poor response to conservative treatment: 66%
- Cancer development: 9%
- Long duration of disease with lumen stenosis: 4%
- Profound hemorrhage: 3%
- Toxic megacolon: 1%
- Rectovaginal fistula: 1%
Type of operation

- Total colectomy with ileorectal anastomosis: 50%
- Permanent ileostomy anastomosis: 30%
- Ileoanal pouch anastomosis: 20%
- Drainage of perianal abscess: 5%
Suicide as an outcome in Greek patients with IBD

- Two male patients (one with UC and one with CD)
- These cases represent a percentage of 0.35% of a total number of 568 patients with IBD seen and followed-up in our institution
- The expected number of suicides in our sample was 0.279
- In our series of patients with IBD the males’ observed suicide rate was 10-fold higher than expected (Greece exhibits extraordinary low suicide rates)

(Triantafillidis et al, Am J Gastroenterol 2002)
Ulcerative colitis in Greece

conclusions

• Epidemiology
  The incidence differs in different parts of the country being relatively lower compared to other European countries. Incidence greater than Crohn’s disease. Significantly larger proportion of men is affected compared to women.

• Extent of the disease
  Proctitis, sigmoiditis or left colitis account for almost 70% of patients

• Progression of the disease
  Proximal extension can be found although in a smaller proportion compared to other European countries

• Positive Family History
  It may be present in a certain proportion of Greek patients with IBD. It differs considerably in different parts of the country

• Type and incidence of extraintestinal manifestations
  Similar to other developed countries

• Rate of colectomy
  Lower compared to other countries

• Indications for colectomy
  Similar to other countries

• Course
  Exacerbations and remissions

• Colorectal cancer development
  It seems to be lower compared to other European countries.

• Causes of death
  Most of them are due to the underlying IBD as well as to other causes
Crohn’s disease
Data were derived from

- Sixteen papers published in the international literature
- Nine papers published in the Hellenic medical literature
- Abstracts presented in Greek and international congresses
- Personal communication
Epidemiological features

Incidence of Crohn’s disease in two geographical areas of Greece

(Manousos et al 1996, Tsianos et al 1994)
The number of new cases of CD referred to gastroenterology departments of teaching hospitals in Greece, tend now to exceed the number of new cases with UC.

More UC patients presented with extensive colitis (pancolitis) compared to those with left-sided colitis.

Family history for IBD at the onset in both ulcerative colitis and Crohn’s disease was low.

Genetic factors

The NOD2/CARD15 mutations are risk factors for CD in Greece. They predict an earlier age at onset and are associated with ileitis.

Gazouli et al Eur J Gastroenterol Hepatol 2004
Genetic factors

Low incidence of mutation was found in the Cretan population

Roussomoustakaki et al, Gastroenterology 2003
Coexistence of a mutation in either the Toll-like receptor 4 or CD14 gene and in NOD2/CARD15 is associated with increased susceptibility for developing CD compared to UC and for developing either CD or UC compared to normal people

Gazouli et al WJG 2005
Appendectomy and tonsillectomy have positive association with the development of Crohn’s disease

(Koutroumbakis et al 1999)
Clinical patterns of CD

- 155 patients
- Men/women ratio: 1.6:1
- Urban dwellers of high socioeconomic level
- Equal anatomic involvement between the three main sites
- At least one extraintestinal manifestation was observed in 42%
- Perianal disease: 21%
- 51% had at least one operation
- Emergency operation was required in 17%
- During the follow-up period of 10 years, 18 pts (12%) died.

(Triantafillidis et al, Digestion 2000)
<table>
<thead>
<tr>
<th>Extraintestinal manifestation</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis/arthralgias</td>
<td>46/155 (30%)</td>
</tr>
<tr>
<td>Angylosing spondylitis</td>
<td>3/155 (2%)</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>4/155 (3%)</td>
</tr>
<tr>
<td>Ocular lesions</td>
<td>6/155 (4%)</td>
</tr>
<tr>
<td>Renal colic/nephrolithitiasis</td>
<td>26/155 (17%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>7/155 (5%)</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>3/155 (2%)</td>
</tr>
</tbody>
</table>

Triantafillidis et al, Hepatogastroenterology 2001
A: January 1996 (normal appearance, before diagnosis of CD), B: June 1996 (slight lip swelling - before the onset of bowel symptoms), C: August 1996 (first diagnosis of CD - gross swelling of the lower lip), D: September 1999 (remission of CD achieved by corticosteroids)
Granulomatous cheilitis


Triantafillidis et al, 2007 (in Press)
Coexistence with other diseases

- Isolated ACTH deficiency (Kalambokis et al J Endocrinol Invest 2004)
- Seropositive rheumatoid arthritis (Georgiadis et al Clin Exp Rheumatol 2003)
- Hidradenitis suppurativa (Roussomoustakaki et al J Gastroenterol 2003)
- Acute idiopathic pancreatitis: Favorable response to Infliximab treatment (Triantafillidis et al, Am J Gastroenterol 2000)

- Acute pancreatitis may precede the clinical manifestations of Crohn’s disease (Triantafillidis et al, Am J Gastroenterol 2003)
- Inflammatory fibroid polyp of the small bowel (Triantafillidis et al, Ann Ital Chir 2005)
- Idiopathic fibrosing pancreatitis (Potamianos et al, Eur J Gastroenterol Hepatol 2000)
Crohn’s disease in the elderly

- Terminal ileum: the most common site of involvement
  - Acute presentation: significantly more common compared to the young group
  - Higher rate of complications including acute abdomen
- Significantly fewer elderly patients were operated-on for perianal disease

(Triantafillidis et al, Dig Liver Dis 2000)
Defense mechanisms in Greek patients with IBD

- Crohn’s disease patients presented a different and more immature defensive profile than patients with ulcerative colitis.

- Psychologically more mature patients with IBD had lower rates of relapses and surgical operations.

(Hyphantis TN, Triantafillidis JK, J Gastroenterol 2005)
Factors associated with Crohn’s disease evolution

- The cumulative probability of change in disease behavior in B1 patients was 44% at 10 years after diagnosis.

- Smoking and non-colonic disease (no L2) were associated with behavioral change in B1 patients.

  (Chatzicostas et al BMC Gastroenterol 2006)
Medical treatment

- Ornidazole in the treatment of active Crohn’s disease
  *(Triantafillidis et al, Am J Gastroenterol 1988)*

- Ornidazole in the treatment of active Crohn’s disease: short-term results
  *(Triantafillidis et al, It J Gastroenterol 1996)*

- Ornidazole in the prevention of recurrence of Crohn’s disease
  *(Triantafillidis et al, It J Gastroenterol Hepatol 1998)*

- Absence of toxicity of ornidazole after a 10-year continuous daily use for Crohn’s disease (case report)
  *(Triantafillidis et al Am J Gastroenterol 2001)*
## Indications for surgery

<table>
<thead>
<tr>
<th>Indication</th>
<th>Small</th>
<th>Large</th>
<th>Small &amp; Large</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive ileus</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>17 (11%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Poor response to medical treatment</td>
<td>6</td>
<td>3</td>
<td>17</td>
<td>26 (17%)</td>
<td></td>
</tr>
<tr>
<td>Severe hemorrhage</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Perianal fistulae</td>
<td>3</td>
<td>8</td>
<td>12</td>
<td>23 (15%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>10 (6%)</td>
<td></td>
</tr>
<tr>
<td>Bowel perforation</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Erroneous diagnosis of appendicitis</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>9 (6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>8</td>
<td>12</td>
<td>29 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

*(Triantafillidis et al, Hepatogastroenterology 2001)*
# Type of operation

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Small bowel</th>
<th>Large bowel</th>
<th>Small &amp; Large bowel</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterectomy &amp; end-to-end anastomosis</td>
<td>30</td>
<td>5</td>
<td>23</td>
<td>58 (48%)</td>
</tr>
<tr>
<td>Ileorectal anastomosis</td>
<td>0</td>
<td>6</td>
<td>7</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Drainage of abdominal abscess</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Drainage of perianal abscess</td>
<td>4</td>
<td>9</td>
<td>11</td>
<td>24 (20%)</td>
</tr>
<tr>
<td>Erroneous diagnosis of appendicitis</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9 (7%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>46</strong></td>
<td><strong>25</strong></td>
<td><strong>51</strong></td>
<td><strong>122</strong></td>
</tr>
</tbody>
</table>

*(Triantafillidis et al, Hepatogastroenterology 2001)*
Other characteristics of patients operated-on for CD

- Emergency operation: 17%.
- Significant differences in the number of operations performed in the three groups of patients with CD (small, large and small and large bowel involvement).
- Perioperative morbidity: 16%
- No perioperative mortality
- Evolution to cancer during the follow-up period: 3 cases (2%)

Triantafillidis et al, Hepatogastroenterology 2001
Some of the clinicoepidemiological characteristics of the disease are in accordance with those reported from the western as well as the neighbouring Mediterranean countries. However, other parameters such as the higher incidence of the disease in males, the low incidence of familial clustering, and of perianal disease, underline the importance of environmental, and genetic factors on the evolution of the disease.

Crohn’s disease in Greece

Conclusions
Thank you