Immunosuppression in an endemically TB infected environment

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Dr Choon Jin Ooi
MBBS, FAMS, FRCP (Edin.)
Inflammatory Bowel Disease Centre
Singapore General Hospital
Estimated tuberculosis incidence rates, 1997

- Infected: 2 billion
- Active: 20 million
- Incident: 8.4 million
- Deaths: >2 million

Range of rates (per 100,000):
- <10
- 10 - 24
- 25 - 49
- 50 - 99
- 100 - 249
- ≥250
- No estimate
Outline

- Tuberculosis infection in Asia-Pacific
- IBD - an emerging disease in Asia-Pacific
- Immunosuppression & TB
- Strategies to diagnose & manage LTBI/active TB
- Immunosuppression unmasking TB
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Tuberculosis - Epidemiology

• More than 50% of TB occurs in Asia-Pacific
• Ten out of 22 high TB burden countries are in Asia Pacific - India, China, Indonesia, Bangladesh, Pakistan, Philippines, Vietnam, Thailand, Myanmar & Cambodia
Tuberculosis

- Among those with TB and HIV, 22% live in South East Asia
- Multi-resistant TB is emerging
Tuberculosis in India

- India has the highest TB cases world-wide ~ 30%
- WHO estimates one in two adults infected
- 0.5M die each year in India alone
Tuberculosis - Management Issues

- Inappropriate management
- Multi resistance
- Co-infection with HIV
- Insufficient DOTS provision
- Treatment non-compliance
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The emergence of inflammatory bowel disease in the Asian Pacific region
Qin Ouyang, Rakesh Tandon, Khean-Lee Goh, Choon Jin Ooi, Haruhiko Ogata and Claudio Fiocchi

Recent findings
A progressive rise in the incidence and prevalence of inflammatory bowel disease is discernible in most Asian Pacific countries, more so for ulcerative colitis than Crohn disease. Some ethnic differences are notably evident, as Indians suffer more inflammatory bowel disease than Chinese or Malay. Age of onset and gender are similar to those of Western patients, as are the distribution and extent of disease which, however, tends to be clinically less severe than in European and North American patients. A family history is occasionally elicited, whereas smoking and appendectomy appear to have the same impact on inflammatory bowel disease as seen in the West.
Japan - 1985-2001

Figure 1. Increasing cumulative number of ulcerative colitis and Crohn's disease patients in Japan during a 17-year period according to the national registry maintained by the Ministry of Health, Labor and Welfare of the Japanese government.
South Korea - 1985-2000

Ulcerative colitis

Crohn’s disease

Incidence / 100,000


Prevalence of IBD in Singapore

- **Ulcerative Colitis**
  - Tan 1992: 8.6/100,000
  - Lee 2000: 6.0/100,000
  - Ooi 2005: ~17/100,000

- **Crohn’s Disease**
  - Tan 1992: 1.3/100,000
  - Lee 2000: 3.6/100,000
  - Thia 2006: 7.2/100,000
Prevalence Trends in Singapore

Per 100,000

- CD
- UC


1.3 3.6 7.2 8.6 6 6.8 17 7.2

CD
UC
IBD Prevalence across countries

North America: Olmstead MN '01
Europe: Copenhagen '87
Europe: UK '95
Asia: Punjab India '99
Asia: Japan '91
Asia: China '00
Asia: Singapore '00
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Per 100,000

UC CD
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Immunosuppression

- Steroids
- Azathioprine/6-mercaptopurine
- Methotrexate
- MMF
- Biologics - anti-TNF antibody
Steroids & TB


- 11 patients described
- Indications for immunosuppressive therapy were varied, but all patients received high doses of corticosteroids with azathioprine in addition in 2 cases and chlorambucil in a third.
- The diagnosis was delayed in all cases because of suppression of symptoms, so that 4 patients died, 3 directly as a result of tuberculosis
Steroids & TB


- A clear policy of investigation and, if indicated, chemoprophylaxis is necessary for all patients with long-term immunosuppressive therapy.

- A high index of suspicion for tuberculosis must be maintained with regular clinical and radiological review.
In our centre, where there are 450 UC and 140 CD patients on the registry, at least one have been diagnosed with TB so far.

- **Azathioprine dosed at 2.5 mg/kg BW along with prednisolone 5 mg om**
- **Presented with cough for 2 weeks**
- **Suspected on CXR and confirmed on BAL**
Mycophenolate Mofetil

• MMF seem more potent
• Risk of TB activation appear higher


Biologics - anti-TNF therapy


- 147,000 patients received infliximab as of May 29, 2001

- 70 reported cases of tuberculosis after treatment with infliximab, for a median of 12 weeks.

- 40/70 had extrapulmonary disease (17 had disseminated disease, 11 lymph node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningeal, enteric, paravertebral, bone, genital, and bladder disease).
- 64/70 were from countries with a low TB incidence.
Biologics - anti-TNF therapy


• Before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease
## Anti-TNF and TB

**TABLE. Characteristics of 12 cases of reported tuberculosis (TB) disease in patients receiving tumor necrosis factor-alpha (TNF-α) antagonist therapy — California, January 2002–August 2003**

<table>
<thead>
<tr>
<th>Patient age (yrs)</th>
<th>Reason for TNF-α antagonist therapy</th>
<th>Site of TB disease</th>
<th>Foreign born</th>
<th>Other TB risk factors</th>
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<tr>
<td>55</td>
<td>Rheumatoid arthritis</td>
<td>Lung, supraclavicular node</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
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<td>64</td>
<td>Rheumatoid arthritis</td>
<td>Lung, pericardium</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Prednisone</td>
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<td>Rheumatoid arthritis</td>
<td>Disseminated</td>
<td>Yes</td>
<td>Yes</td>
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<td>41</td>
<td>Psoriatic arthritis</td>
<td>Kidneys</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
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<td>70</td>
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Morbidity & Mortality WR, CDC. Aug 6, 2004
Anti-TNF and TB

- TB occurs within 3 cycles of treatment, with a median of 12 weeks
- Most TB occurred in extra pulmonary sites
- TB rates in US patients treated was 6 times that of untreated patients

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Strategies to exclude LTBI/active TB

• Careful history & physical examination
• Tuberculin Testing & Adjunctive Tests
• Chest X-Rays
• Diagnostic Microbiology & Resistance Testing
Careful history & examination

- History of TB exposure, infection, or disease
- Demographic factors (e.g., country of origin, age, ethnic or racial group, occupation) that may increase the patient’s exposure to TB or to drug-resistant TB
- Exclude other medical conditions, especially HIV infection
Tuberculin Testing

- Immunologic basis for the tuberculin reaction.
- Infection with *M. tuberculosis* produces a delayed-type hypersensitivity reaction.
Tuberculin Testing

- Previous BCG vaccination.
- Tuberculin reactivity can be caused by BCG vaccination.
- Reactions of $\geq 20$ mm of induration are not likely caused by BCG.
Tuberculin Testing

- HIV infection and cutaneous anergy
- Anergy testing in IBD patients with immunosuppressives

QuantiFERON®-TB Gold (QFT-Gold)

- On May 2, 2005, QFT-Gold (Cellestis Ltd, Victoria, Australia), received approval from U.S. FDA in diagnosing *Mycobacterium tuberculosis* infection, including both latent tuberculosis infection (LTBI) and tuberculosis (TB) disease

*MMWR, CDC. Dec 16, 2005*
QuantiFERON®-TB Gold

- ELISA test detects the release of IFN-γ in whole blood from sensitized persons when incubated with synthetic peptides simulating two proteins in *M. tuberculosis*: early secretory antigenic target--6 (ESAT-6) and culture filtrate protein--10 (CFP-10)

- Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains, QFT-G is expected to be more specific for *M. tuberculosis*.

*MMWR, CDC. Dec 16, 2005*
QuantiFERON®-TB Gold

- Reaches 90% sensitivity for active TB infection
- May be even better for diagnosis for LTBI
Chest X-rays
Chest X-rays
Diagnostic Microbiology & Resistance Testing

- Acid-fast-bacilli (AFB) on a sputum smear or other specimen
- Culture be done on all specimens, regardless of AFB smear results
- For all patients, the initial *M. tuberculosis* isolate should be tested for drug resistance
BOX. Recommendations for screening, diagnosis, and treatment of latent TB infection (LTBI) and tuberculosis (TB) in patients administered or scheduled to receive tumor necrosis factor-alpha (TNF-α) antagonists

- Screen patients for risk factors for *Mycobacterium tuberculosis* and test them for infection before initiating immunosuppressive therapies, including TNF-α antagonists. Risk factors include birth in a country where TB is prevalent or history of any of the following: residence in a congregate setting (e.g., jail or prison, homeless shelter, or chronic-care facility), a positive tuberculin skin test (TST) result, substance abuse (i.e., injection or noninjection), health-care employment in settings with TB patients, and chest radiographic findings consistent with previous TB (1).
- Diagnosis and treatment of LTBI and TB disease should be in accordance with published guidelines (1–3).
• Test to exclude TB disease before starting treatment for LTBI (1, 2).

• Start treatment for LTBI before commencing TNF-α blocking agents, preferably with 9 months of daily isoniazid (1, 2).

• Consider treating for LTBI in patients who have negative TST results but whose epidemiologic and clinical circumstances suggest a probability of LTBI.

• Pursue TB disease as a potential cause of febrile or respiratory illness in immunocompromised patients, including those receiving TNF-α blocking agents.

• Consider postponing TNF-α antagonist therapy until the conclusion of treatment for LTBI or TB disease.
Other recommendations


Risk of hepatitis: 280/100,000 for 6 months of Isoniazid
Isoniazid for LTBI

• Strategies to treat latent TB infection that are tailored to the at-risk population can effectively and safely lessen the likelihood of active TB in patients treated with TNF antagonists.

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Crohn’s disease

Ileo-caecal valve

Terminal ileum

Descending colon
TB

Caecum
Is it Crohn’s disease? Is it TB?
Crohn’s disease - Sites

- Terminal ileum / cecum
- Colon
- Small bowel
- Rectosigmoid +/- another
- Stomach / duodenum + another
- Others

% of patients

Ooi et al, UEGW 2004
TB gut - Sites

Ooi et al, UEGW 2004

% of patients

- Rectum
- Colon
- TI/cecum+SB
- TI/cecum+colon
- TI/cecum

0 10 20 30 40 50 60
Histopathology - Patient B

Large, fused granulomas
Histopathology - Patient B

Fibrosis of muscularis propria - resected specimen
TB gut - extra GI involvement

- Extra-abd LN
- Pulmonary (old)
- Pulmonary
- None

% of patients (Ooi et al. UEGW 2004)
Is it Crohn’s disease? Is it TB?

- Very real diagnostic dilemma
- Immunosuppression may unmask the ‘real’ diagnoses
- Close monitoring if using immunosuppression where there is initial doubt in the diagnosis
Summary

- IBD is emerging in Asia-Pacific where TB is endemic
- Meticulous work-up and high index of suspicion required to diagnose LTBI/active TB
- High endemicity of TB compounds the diagnostic dilemma in CD diagnosis & the use of immunosuppression
Summary - Chemoprophylaxis in Asia

- Identifying high risk groups
- Type of immunosuppression - steroids, anti-TNF agents
- Type of chemoprophylaxis & toxicity profile
- Future evolution of Quantiferon-GOLD for diagnosis of LTBI
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  – Dr. Teh Lip Bin
  – Dr. Widjaja Luman

• National University of Singapore
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• Raffles Hospital
  – Dr. Jean Ho

• Singapore General Hospital
  – Prof. Ng Han Seong
  – A/Prof. Chow Wan Cheng
  – Dr. Kelvin Thia
  – Dr. Ling Khoon Lin
  – Colorectal Polyposis Group