Anti TNF
Inflammatory Bowel Disease
and infection

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Epidemiology of IBD

• Changed over the past 50 years
• Increase in the incidence of UC and CD
• Initially an increase in cases of UC
• Followed 10-15 years later by CD
• Trend has reached a plateaux in the West
• Ongoing in the developing world: SE Asia
• The incidence in children also increasing

Review. Scand J Gastroenterol 2001
A Critical Review of Epidemiological Studies in Inflammatory Bowel Disease
Gender Differences vs. Ethnicity
n = 1,979  08/2013

Expected
Whites with UC: male = female
Black patients – 60% have UC
Progression of damage and inflammation

Activity in a theoretical patient with Crohn's disease

Pre-clinical  Clinical

Disease onset  Diagnosis  Early disease  Surgery  Fistula/abscess  Stricture

Inflammatory activity

Destructive CD and damage

CD is a chronic progressive and destructive disease

Disease behaviour evolves with time.

Hospitalisations
At 20 yrs:
80% have had surgery
Biologics in IBD

M Hendrick et al
Treatment of Crohn’s Disease with Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (CA2)

Gastroenterology 1995

- Potential to modify natural history
- Rapid healing of the mucosa
- Adalimumab and infliximab available: anti-TNFs
Current approach to IBD therapy

Accelerated step-up Rx: anti-TNF within 3/12
Top down RX: anti-TNF at diagnosis (fistulising CD)

Step-up Rx
- IFX
- AZA 6-MP MTX
- Systemic steroids
- Budesonide (CD)
- Antibiotics (CD) 5-ASA

Top down
Tuberculosis and Anti-TNF Therapy: South African Considerations

WHO Global TB Report 2012

8.7 million new cases of TB
13% HIV co-infected
1.4 million TB deaths
2 billion people with latent TB
Trends in TB Notifications in SA: 1980-2010

Mvusi L., Department of Health, April 2013

Incidence: 2001 993 per 100,000

2011 Mortality: 49 per 100,000

2011 HIV co-infection ± 65%
A descriptive study of Tuberculosis in an inflammatory bowel disease cohort from Cape Town

- Retrospective study of 615 IBD patients
  - History of TB treatment
  - x-ray evidence of TB,
  - histology and microbiology
- 72 patients (11.7%) had TB
  Half occurred before the diagnosis of IBD
  Coloured ethnicity only risk factor for TB

Distribution of IBD and TB Cases per District
n = 1,395

- Cape Flats: 43% IBD, 57% TB
- S Suburbs: 37% IBD, 7% TB
- City: 20% IBD, 6% TB

* Cloete K, Western Cape TB & HIV Programme Report 2006
Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening

- Single centre Spanish study 2000 – 2011
- 423 patients on anti-TNF
- 6.9% tested positive for latent TB → prophylaxis
  - 7 patients (1.6%) developed TB
  - 6 screened negative for TB
  - 1 had a positive TST and developed TB on INH prophylaxis

Only 3 patients restarted anti-TNF therapy at a later stage

Tuberculin Skin Testing (TST)

Sensitivity reduced
- Malnutrition
- Active TB
- Crohn’s disease*
- Immune suppression

Specificity reduced
- BCG vaccination
- Non-TB mycobacteria

In addition
- 2 healthcare visits – 10% drop out
- Variability = SD 3mm
- Boosting

*Verrier Jones J et al Gut 1969
Latent Tuberculosis in Cape Town

- 77 asymptomatic volunteers
- No active TB
- HIV negative

- 66% TST ⊕ cut-off 5mm
- 64% TST ⊕ cut-off 10mm
- 58% TST ⊕ cut-off 15mm
“IGRS’s and TST appeared to have only modest predictive value and did not help identify those who were at highest risk of those who are at risk of progression of disease”
Testing prior to initiating anti-TNF testing

Low prevalence TB

CONCOMITANT MEDICATION
Steroids, biological therapies, Azothiaprine and Methotrexate

DEMOGRAPHIC INFORMATION
BCG vaccination, Residence in a high TB prevalence country

CHEST X-RAY

Positive: nodules, fibrotic scars, calcified granulomas and basal pleura
Negative

Positive > 5 mm
Negative < 5 mm

GAMMA INTERFERON ASSAY

Positive
Negative

Latent Tuberculosis Infection

Prophylaxis
Isoniazid for preventing tuberculosis in the non-HIV infected person

Method
- 11 trials involving 73,375 patients
- Broad spectrum of patients
- INH prophylaxis 6 and 12 months vs. Placebo
- Outcomes active TB, TB death, INH toxicity

Results
- 60% reduction in active TB over 2yrs
- Treat 35 6 months to prevent 1 case of active TB
- 1 in 200 will develop drug induced hepatitis

Smieja M, Marchetti C, Cook D rt al Cochrane Database Syst Review 2010
Treatment of latent TB infection in HIV infected persons

• Method
  – 12 trials, 8,578 participants
  – TB preventative Rx vs. Placebo
  – Participants could be TST positive or negative

• TB prophylaxis a 32% lower risk of active TB
  – RR 0.68, 95% CI 0.54 to 0.85

• Benefit similar with all TB prophylaxis regimes used.

Akolo, Adetifa, Sheperd et al  Cochrane Database Syst Review 2010
The recommendations in SARAA?

“Treatment choice for latency”
- INH - RIF combination x 3 months
- INH alone for 6 to 9 months.

- Combination
  - Rifampicin - INH for 3 months is advised in certain circumstances only.
Anti-TNF and Hepatitis

• Hepatitis B
• Worsening
  – those with evidence of active viral replication,
• Reactivation
  – those who had evidence of quiescent infection
  – Incidence <2%
  – Fulminant hepatic failure

Hepatitis C  No risk
Serious Infection Risk with Anti-TNF

- Infection requiring intravenous antibiotics or hospitalization.
- This rate expressed as patient-years of follow-up.
  - 42/100,000 in the anti-TNF group
  - 32/100,000 in the naive group.
- Greatest Risk
  - the over 60’s
  - first 6 months of treatment
  - Corticosteroid therapy
Perianal Disease and Infection Risk
MRI Abscess
Suspected sepsis in the surgical candidate

- Assess for collections.
  - Aspiration
  - Drain
    - Image guided or surgical.
- Clinical and further imaging
  - Confirm the resolution
- Prior to Biological Therapy.
151 urgent colectomies
  only 17 had received infliximab
  • Complications rate
  • 37% who received infliximab
  • 27% in those who did not. no difference

  • Five patients who received additional cyclosporin and anti TNF had an 80 % complication rate.
• 72 patients
  – 33 who underwent a 1-stage procedure
  – 39 who had a 2-stage surgery.
• In the 2-stage group (12 months prior to surgery)
  – 17 had previous infliximab therapy
• Complication rates
  – total infectious, non-infectious and pelvic sepsis
  – similar for infliximab and the naive patients.
Risk of Surgery
Dutch Cohort Urgent and Elective

- 72 patients
  - 33 who underwent a 1-stage procedure
  - 39 who had a 2-stage surgery.
- 1-stage group anti-TNF (7 months before surgery)
  - 21 anti-TNF patients
    - five developed pelvic sepsis
  - 12 naive group.
    - No pelvic sepsis
- Non-infectious complications.
  - Also commoner in those receiving anti-TNF
Risk of Surgery
Danish National Study

- Over 10 years
- 2293 surgery for Crohn’s disease
- 214 of whom were exposed to anti TNF therapy.
- No increase
  - death
  - abscess drainage
  - anastomosis leakage
  - reoperation within 30 days.

Nørgard BM, Nielsen J, Qvist N. et al. Pre-operative use of anti-TNF-alpha agents a nationwide cohort study Aliment Pharmacology Therapeutics 2013
Over 10 years
2293 surgery for Crohn’s disease
214 of whom were exposed to anti-TNF therapy.

Sub-analyses
No increased risks when anti-TNF agents were given within 14 days prior to surgery

Nørgard BM, Nielsen J, Qvist N. et al. Pre-operative use of anti-TNF-alpha agents a nationwide cohort study Aliment Pharmacology Therapeutics 2013
Surgery and Anti-TNF

• Adopt a cautious approach
• Elective surgery
  – longest window possible without anti-TNF therapy
• Salvage surgery
  – be vigilant for complications surgery is required when these drugs fail when used for salvage therapy.
Conclusion

- Treatment paradigms
- Risks
  - The TB Risk
    - Prophylaxis
- Exclude infection prior to use.
- Vigilant for infection when surgery performed.
- Need a medical gastroenterologist