Anti-TNF medication and tuberculosis

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Why?
Who?
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Blocking TNF has major effect on immune-mediated inflammatory diseases (IMIDs)!

results in increased risk of Mycobacterial infections (Mtb – 25x)…
Who?

IMID patients: RA, IBD (Crohn, CU), psoriasis, Bechterew, …..

Who are candidates for use of TNFα inhibitors:

- Infliximab (Remicade)
- Etanercept (Enbrel)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Golimumab (Simponi)
Miss D

Born in Cabo Verde

2010  uveïtis
2010  M Crohn: immunosuppression, no benefit
2012  Planned to start Adalimumab – what do you do?
How?

1. Select those pre-antiTNF who are at risk for reactivation TB

1A. Exclude / diagnose and treat active TB

2. Start treatment latent TB pre start antiTNF
Diversity of guidelines/statements within Europe

TBNET consensus Statement  Eur Resp J 2010;36:1185-1206

Dutch Statement “Tuberculose en TNF-α blokkerende therapie”
How testing?

- History taking, including results of former TB tests/exposure
- Chest x-ray
- TST/IGRA

- NB Those tested often are under immunosuppression: radiology and TB tests can be false-negative; negative tests do not exclude TB (infection)

- Any positive result is reason to consider latent TB treatment after excluding active TB
- **TBNET Statement:**
  - TST alone not sensitive/specific enough
  - Too little data in pre-antiTNF group to advise IGRA alone
  - TST in non BCG-vaccinated (10 mm) + IGRA

- **European:** TST – IGRA – TST and IGRA +/- boosting

- **Dutch guideline:** TST (10 mm; immunosuppressed: 5 mm) and IGRA
Miss D

Born in Cabo Verde
- Adalimumab
- Chest x-ray (N);
- No latent tb test because of BCG (?)
- Advised to seek help in case of complaints

- X-ray: test for active TB
- history + epidemiology: LTBI
- TST and IGRA
Miss D

- History + epidemiology.....

- How?
- When start adalimumab?
**Guidelines**

- TBNET Statement: 9-12H - 3HR
- European: 2RZ(!)–3R–4R–6H–9H–12H–3HR–4HR
- Dutch guideline: 4HR - 9H – 4R
- When start anti-TNF: 4 wks (TBNET) – 2 months (dutch)
- No preventive treatment for M/XDR TB
2013 1 Year after start adalimumab starts to cough (?) → GP → amoxicillin
2 weeks later: fever and night sweats
Returns to GP: night sweats and fever and a friend (CV) with lung tb….
….GP: public health care will contact you

So she waits…. 
TB under anti-TNF 1-2% all TB (NTR)
…..can be hard to diagnose due to lack of clinical symptoms, lack of radiological signs and false-negative test results…..

What do you do?
Guidelines

Stop anti-TNF
Start tb treatment immediately; maximal effort to achieve microbiology, molecular tests if possible
European = TBNET = dutch

Reactivation or (re)infection?

Median time after start anti-TNF: 13 months…
…clustered with her friend…
Miss D

At 6 weeks TB treatment:
Favorable clinical reaction, normal sensitivity
strain
Starts to complain about her eyes/Crohn, wants to
restart anti-TNF

What do you advise?
Guidelines

Preferably after completing TB treatment

If no complete treatment: at least a favorable clinical reaction on TB treatment and confirmation of sensitive strain; preferably after intensive phase

In life-threatening (neuro-)IRIS consider restart anti-TNF

Clin Infect Dis 2008;47:e83-85
Miss D

Restart adalimumab at 2 months,
very happy…
… even happier when TB treatment
stopped at 6 months….

Ongoing risk under anti-TNF treatment:
- Reinfection
- False-negative test results latent/active TB
- Reactivation in spite of LTBI-treatment (sensitive/resistant strain)
Miss P

Healthy law student, 24, dutch
Weight loss 8 kg/6 weeks, fever, diarrhea, night sweats

GP: appendicitis → hospital GE: extensive ulceration intestines / biopsy: granulomatous reaction → M Crohn
Immunosuppression without benefit $\rightarrow$ infliximab (TST negative)
Further deterioration condition $\rightarrow$ perforation ileum, extensive TB
“everywhere” abdomen + chest. Weeks at ICU, hardly survived.
At 1 year: immense immune reconstitution inflammatory syndrome

At 8 years (2014) after correction AP, aesthetic surgery abdomen, lymph node resections and giving birth to healthy daughter …..persistant pus in the liver (Aur+)

Partner, 2 sisters and mother: active TB


Chest x-ray before start anti-TNF!

TB under anti-TNF can go completely out of control → testing & treating (L)TB to prevent (very nasty) TB!
What we still need….

…a test for viable Mycobacteria in LTBI → optimal testing strategy = optimal selection of patients/optimal PP value for the development of TB under TNF blocking

…knowledge of optimal LTBI treatment pre anti-TNF (use anti-TNF to shorten LTBI treatment??)

…and, last but not least: a test that differentiates latent from active TB
Anti-TNF treatment warrants testing and treating (L)TB pre-start. NB Potential risk of any (cellular) immunosuppressive condition! Ongoing risk under TNF-blocking treatment!

Work up >> latente TB test: A/LO/X + Mx/IGRA, Diversity in testing and treating within Europe

Inform your patient about TB/risks (travelling!) Inform GP!

Primary prophylaxis after excluding active TB if exposure under anti-TNF
• Statement “Tuberculose en TNF-α blokkerende therapie”