New guidelines
for screening for tuberculosis
and latent tuberculosis infection
in the pre-immunosuppressive therapy
phase in the Netherlands:
a targeted and stratified approach

European Advanced Course in Clinical TB

November 11th 2019
Paul van der Valk
<table>
<thead>
<tr>
<th>(Potential) conflict of interest</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially relevant company relationships in connection with event (^1)</td>
<td>Company names</td>
</tr>
<tr>
<td>• Sponsorship or research funding (^2)</td>
<td>•</td>
</tr>
<tr>
<td>• Fee or other (financial) payment (^3)</td>
<td>•</td>
</tr>
<tr>
<td>• Shareholder (^4)</td>
<td>•</td>
</tr>
<tr>
<td>• Other relationship, i.e. … (^5)</td>
<td>•</td>
</tr>
</tbody>
</table>
What is the problem?  
→ Case study

- 73 old lady known for 17 years RA
- 2001: start Infliximab without LTBI screening
- 3 months later: fever UO
Case study

• analysis:
  • X-ray chest: NAD
  • Ultra sound liver: vague abnormalities
  • all other investigations + cultures negative

• liverbiopsy:
  • small lymphocytic infiltrates
  • ZN, PCR *M. tbc*, culture TB neg!
Case study

- Continuous febrile 38-39°C
- Active RA? Start prednisolone
- Progressive liver insufficiency

2th liver biopsy:
  PCR *M. tuberculosis* positive
Case study

diagnosis:
infliximab and prednisolon induced (reactivation) of miliary tuberculosis
Death, at autopsy:

multiple ZN positive granuloma in lungs, liver and spleen with central necrosis

culture *M. tuberculosis*
Photomicrographs of Lung Specimens from a Patient with Tuberculosis Who Did Not Receive Infliximab (Panels A and B) and the Index Patient with Tuberculosis Who Did Receive Infliximab (Panels C and D).


No Granuloma Formation, no Apoptosis !!
Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.

Unique problem?

- Vonkeman HE, van der Valk PDLPM: Fatale miliare tuberculose tijdens anti-tumor necrosis factor therapie met infliximab. NTVG 2002;146:1196-1199
- J.M.A. Daniels eo: Tuberculosis complicating Imatinib (Glivec) treatment for CML ERJ 2009;33,3 671-672
- Keizer S ea: Fatale fulminante tuberculose bij Ruxolotinib, JAK1/2-remmer
2001-2014: Need for a guideline!

• The reumatologists did not agree with the pulmonologists about the test procedures.

• So the specialists -like real doctors do- did it all their own way.
Consequence: no structure
Rationale new guideline

- Immunosuppressive therapies with ‘biologicals’ show a rapid rise for more and more indications.

- Risk of latent tuberculosis infection (LTBI) cases progressing into active (life threatening) tuberculosis.
Growth of anti TNF alfa drug use
On the other hand........
## Estimated prevalence of LTBI among Dutch residents born in the Netherlands

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Prevalence LTBI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>&lt;0,1</td>
</tr>
<tr>
<td>2000</td>
<td>0,2</td>
</tr>
<tr>
<td>1990</td>
<td>0,3</td>
</tr>
<tr>
<td>1980</td>
<td>0,5</td>
</tr>
<tr>
<td>1970</td>
<td>0,9</td>
</tr>
<tr>
<td>1960</td>
<td>1,8</td>
</tr>
<tr>
<td>1950</td>
<td>5</td>
</tr>
<tr>
<td>1940</td>
<td>16</td>
</tr>
<tr>
<td>1930</td>
<td>41</td>
</tr>
<tr>
<td>1920</td>
<td>70</td>
</tr>
</tbody>
</table>
Incidence TB and LTBI in the Netherlands
Number of TB-patients on TNF-alfa blockers and percentage of total amount of TB-patients, in NL 2005-2014

Despite strong increase in use, lower incidence
Change in pre-immunosuppression screening policy

- sharp decline in prevalence of LTBI in the Dutch population

- Auguste: moderate predictive value of tests (Mantoux/IGRA)
  
  so:

- potentially unnecessary testing and potentially harmful preventive treatments

Auguste; Health Technol Assess 2016;20(38).
New LTBI screening policy

based upon:

• age
• country of birth
• documented TB contacts and tests in the past
• other risk factors, such as profession and travel history
Stratified approach at risk screening

Candidates for relevant immune-suppressive treatment:

• X-ray of chest
• Questionnaire for risk analysis LTBI: three categories
Two (steps) questionnaire

First step: a main questionnaire:

- age
- country of birth
- documented TB contacts and tests in the past
- other risk factors, such as profession and travel history
If all questions answered in ‘green section’:

Very low risk of tuberculosis or LTBI:

→ start immune-suppressive treatment without Mantoux and/or IGRA testing or consultation of TB-expert.
Strategy main questionnaire

If at least 1 question answered in ‘yellow section’ → Use a more extensive (second) questionnaire

then 2 colour options in the answers:

1. Orange
2. Red
Example: Screening Healthcare workers

<table>
<thead>
<tr>
<th>Question</th>
<th>Ja</th>
<th>Nee</th>
<th>Onbekend</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Werkt patiënt in de gezondheidszorg of heeft patiënt in de gezondheidszorg gewerkt?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Is hij/zij bij indiensttreding getest?</td>
<td>Ja</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Waar is patiënt getest?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Is patiënt getest met een prik of krasje in de arm (tuberculinehuidtest/Mantoux test)?</td>
<td>Ja</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Is patiënt getest met een IGRA (“bloedtest”)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Is patiënt (alleen) getest met een longfoto?</td>
<td></td>
<td>Ja</td>
<td></td>
</tr>
<tr>
<td>f. Was de test positief of negatief?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2 Is patiënt destijds behandeld voor een tuberculose-infectie?           |
| Ja  | Nee | Onbekend |
| Nee |     |          |

Treated for LTBI?
If at least 1 question answered in ‘red’:

Very high risk of tuberculosis or LTBI:

– without testing, (preventive) treatment first

– do not start immune-sup
If at least 1 question answered in ‘orange’:

A medium (possible) risk of tuberculosis or LTBI:

– refer patient to a tuberculosis-expert
– double-testing and preventive treatment if needed
– do not start immune-sup!
Targeted and stratified approach at risk screening for tuberculosis pre-immunosuppression

Classification resulting from the questionnaire:

Three groups of a priori risk of LTBI:
*(very) low risk:
Do no test, no therapy
*(very) high risk:
Preventive treatment without testing
*a medium (possible) risk group:
Double testing and preventive treatment as needed
Authorisation agreed and implementation phase started
Conclusions

• These new guidelines for low incidence for TB countries recommend a targeted and stratified pre-immunosuppression screening policy, using a questionnaire classifying adult candidates in three screening strategies.

• So over- and underdiagnosis in TB screening will be more balanced
Restrictions:

Since the questionnaires are not yet validated, monitoring of this approach on a national level is needed to evaluate the performance of this stratified screening strategy based upon risk analysis.
New guideline