Tuberculin specific T-cell response after intravesical BCG-instillations.

Published: 11-03-2010
Last updated: 06-05-2024

1. Monitoring of cellular (T-cel) specifc immune response in bladder and bloodsamples after intravesical BCG- therapy. 2. Monitoring and comparing T-cell responses after BCG therapy in patients with clinical BCG-related complications to the T-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mycobacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON35614

Source
ToetsingOnline

Brief title
Tuberculin specific T-cell response after BCG-instillations.

Condition

- Mycobacterial infectious disorders
- Bladder and bladder neck disorders (excl calculi)

Synonym
BCG-itis; infection after treatment of bladder carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Laboratorium voor Medische Microbiologie & Immunlogie
Source(s) of monetary or material Support: geen financiering

Intervention

Keyword: BCG-instillation, BCG-itis, Bladder carcinoma, Elispot PPD

Outcome measures

Primary outcome

- Development of reliable and reproducible elispot procedure on cells obtained from the bladder.

- Validation of elispot PPD on bladder lavage fluids

- Determination of the diagnostics and predictive value of Elispot PPD for BCG-related complications.

Secondary outcome

- Which proportion of patients undergoing BCG-installations converts from systemic negatieve reaction to positieve reaction

- Correlation of systemic conversion with disease (BCG-itis)

- Do local reactions correlate with tumoractivity and /or reduction; does the reaction predict the oncologic outcome ?

- Do actual diagnostic procedures give rise to an underestimation of the number of BCG-itis patients and if so, can Elispot-
PPD contribute to earlier identification of patients with BCG-ralated complications.

- Does Elispot PPD have a predictive value for development BCG-therapy related conditions.

Study description

Background summary

Adjuvant immunomodulating therapy by application of Bacille Calmette-Guérin (BCG) fluid as lavage fluid is a common used treatment for patients with superficial bladder carcinoma. The BCG vaccine is based on a viable but attenuated strain of bovine tuberculosis and has been available since the 20th years of the past century. Almost half of the global population has been administered with the vaccine for prevention of severe tuberculosis infections in children. Application of a suspension with BCG-vaccine induces a substantial local cellular immune response with proven antitumor activity.
Ever since BCG-lavages have been applied, patients with superficial bladder carcinoma have a an improved prognosis for recurrence (20-40% reduction). Complications related to bladder lavages are frequent. Fever (75%) and haematuria (24%) are the most predominant side effects. Some of these side effects may be explained by traumatic catheterization or local imuune responses. Because BCG-vaccine contains a live attenuated strain infections are conceivable. This is estimated to occur in approximately 5% of patients with bladder carcinoma treated with BCG-vaccine (3).
Infections may be limited to bladder or prostate but may become manifest elsewhere in the body (lungs, aorta). Clinical symptoms of these infections are often not much specific and may for instance be manifest only by fever. Therefore BCG-infection (BCG-itis) or inflammation after application of BCG may be ranked low in the differential diagnosis.
In literature there is disagreement about the severe side effects of BCG lavages being based on an allergic immune respons or on an actual infection. Both are conceivable because the BCG-vaccine strain may not always be detected in affected organs. In addition, the BCG strain may hard to culture but nevertheless it was demonstrated in ample cases that BCG is frequently present in affected organs.
Hence, diagnosis of these infections may be cumbersome but still these infections require powerful and adequate antimycobacterial therapy.
The Elispot procedure is based on antigen specific T-cell recognition after contact with an (infectious) agent. The PPD-antigen can also be used in the Elispot technique. Previously, we were able to demonstrate that not only cellular immune responses directed to mycobacterium tuberculosis may be identified with PPD-antigen, but also against BCG vaccine and non-tuberculous mycobacteria.

Study objective

1. Monitoring of cellular (T-cel) specifc immune response in bladder and bloodsamples after intravesical BCG-
therapy.
2. Monitoring and comparing T-cell responses after BCG therapy in patients with clinical BCG-related complications to the T-
cell responses in patient without symptoms.

3. To determinatie the potential of measuring PPD-specific T-cell activity for diagnostis and prediction of BCG-therapy
related complications.

Study design

At first a pilot study will be initiated aiming to establish the performance of Elispot PPD on T-cells isolated from urine and/or BCG-lavage. In order to obtain reliable and reproducible IGRA results, these samples must contain sufficient numbers of reactive T-cells. This will provide data about cell reaction in the bladder after BCG-instillations.
Initially 25 patient samples will be tested.
Urine will be drained directly from the bladder through a catheter before administering the BCG-instillation and a portion of midstream urine will be collected for elispot. Subsequently, the empty bladder will be rinsed out with 100 cc NaCl solution. This solution will be collected for elispot. Finally BCG-instillation will be performed.

In phase 2 we will analyse the PPD specific T-cell responses of 50 patients after receiving BCG-instillations. Via a catheter urine will be drained directly from the bladder before administering the BCG-instillation and a portion of midstream urine will be collected for elispot. Subsequently, the empty bladder will be rinsed out with 100 cc NaCl solution. This solution will be collected for elispot. Finally BCG-instillation will be performed.The obtained research data will be related to patient data as documented in the CRF's. By doing this we hope to be able to monitor the basal PPD specific immuunresponses against BCG. Prior to BCG-installations in weeks 0, 1, 2, 3, 4, 5 en 6, blood samples and bladderlavage fluids are analysed on the presence and activity of PPD specific T-cells. After 12 weeks patients attend the urology department for control cystoscopy and blood and bladderlavage fluid will be drawn again for elispot. Plasma and urine will be frozen at -80 C for future IFN-gamma and/or cytokine measurements.

The third study phase aims on specific analysis of patiënts suspected of having infectious BCG-related complications.
Patients will be stratified based on the criteria given in table 1 of the study protocol. We hope to include 20 patients during a 2 years traject and to substantiate the possibility of including 20 patients the study will convert to a multicentre model in which patients from both Diakonessen Hospital Utrecht and St. Antonius Ziekenhuis will be included.
When patients develop complications (as mentioned in the inclusioncriteria) during the regular treatment with BCG-instillations, this traject will be stopped and blood and bladder lavage fluid will be collected. This time point will be regarded as week 0 and will subsequently be repeated after 1, 2, 3, 4, 5, 6 en 12 weeks. In this way hope to gain insight in how immune responses develop in patients with complications after BCG-therapy.

Study burden and risks

n.a.

Contacts

Public
Selecteer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with superficial bladder carcinoma to be treated with BCG-fluid lavages.
Dit betreft patienten met high grade urothelial cell carcinma (G3), multiple PT1 urothelial cell carcinoma, recurrent urothelial cell carcinoma despite intravesical chemotherapy, CIS and age above 18.

Exclusion criteria

under age of 18.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2010
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	11-03-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL28045.100.09