Clinical evaluation of a serological assay using a monoclonal antibody (TB72) to the 38 kDa antigen of Mycobacterium tuberculosis

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ABSTRACT: We examined an enzyme-linked immunosorbent assay (ELISA) modification of a radioimmunoassay, using the TB72 monoclonal antibody, as a serological test for tuberculosis in a clinical setting.

Sera were obtained from 238 patients with suspected pulmonary tuberculosis, 30 patients treated for tuberculosis, 28 contacts, and 480 random samples from in-patients. Antibody levels were measured as the dilution of serum causing 50% inhibition of binding of the TB72 monoclonal antibody, which binds to an epitope of the 38 kDa antigen specific to the Mycobacterium tuberculosis complex, a positive titre being >3.

Positive antibody titres were present in 21 out of 25 (84%) patients with smear-positive and 22 out of 27 (82%) patients with smear-negative, culture-positive tuberculosis, and 37 out of 41 (90%) patients successfully treated for tuberculosis but without bacteriological confirmation of disease. Three out of 82 (4%) patients with a firm alternative diagnosis to tuberculosis gave a positive result. Serological tests were negative within 2.5 yrs of successful treatment. Patients without a definite diagnosis one year after tuberculosis had been suspected, and those who had received inadequate treatment for tuberculosis, were frequently positive (21 out of 31 and 21 out of 32, respectively). Positive tests concurred with tuberculin reactivity in 8 out of 11 contacts given chemoprophylaxis. Screening of 480 random serum samples gave 22 positive titres, 16 of which were not associated with tuberculosis; none of these 16 had an antibody titre >10.

We conclude that the TB72 test provides additional information in the diagnosis and treatment of tuberculosis. Antibody titres >10 suggest active tuberculosis; titres of 3–10 merit observation.

Several new serological tests for the diagnosis of tuberculosis have been developed in the last decade [1]. Purified antigens and the use of monoclonal antibodies have begun to overcome the problem posed by the broad cross-reactivity of crude extracts from Mycobacterium tuberculosis. However, these tests have been evaluated largely by the use of sera from patients with smear-positive pulmonary tuberculosis [1–6]. In clinical practice, patients with pulmonary tuberculosis are frequently smear-negative (lowest estimate being 46% [7–11]), and treatment is often initiated without the benefit of supporting bacteriological confirmation, in view of the documented progression of smear-negative to smear-positive disease [12, 13]. Few serological tests have been shown to be valuable in the diagnosis of smear-negative disease [3–5, 14, 15]. The initial promise afforded by the purified 19 kDa antigen [3, 15] has faded, in the light of significant geographical variation in the antibody response to this antigen [16].

The competition assay, using a radiolabelled monoclonal antibody (TB72) directed against a species-specific epitope on the 38 kDa antigen of M. tuberculosis, showed a poor sensitivity in patients with smear-negative pulmonary tuberculosis [15]. However, an enzyme-linked immunosorbent assay (ELISA) modification of this radioimmunoassay, using the TB72 monoclonal antibody, had a much increased sensitivity [17] and was valuable in the diagnosis of extra-pulmonary and smear-negative pulmonary tuberculosis [18]. The use of the TB72 monoclonal antibody in an ELISA competition assay appeared to be one of the most sensitive and specific of the serological tests for tuberculosis, and was therefore examined in a clinical setting.

The purpose of this study was to define a role for the ELISA competition assay, using the TB72 monoclonal antibody, in the clinical management of tuberculosis, by testing patients with suspected pulmonary tuberculosis. The true sensitivity and specificity of the test in clinical settings require further evaluation.
practice would become clear, as not all patients tested would prove to have tuberculosis. In addition, random serum samples were also tested, to assess the value of such a serological test in screening for tuberculosis.

**Patients and material**

Two hundred and thirty eight patients with suspected pulmonary tuberculosis agreed to participate in this study, after informed consent, during the period April 1989 to March 1990 (table 1). Patients with documented human immunodeficiency virus (HIV) infection were excluded from the study. Each patient was routinely asked to provide three sputum samples for microbiological examination, in addition to the serum sample. The diagnosis of tuberculosis was made in the absence of microbiological confirmation and with a definite response to treatment, i.e. symptomatic or radiographic improvement.

Using these data, the type of tuberculosis (TB) was classified (table 1) as: smear-positive TB (and culture-positive for *Mycobacterium tuberculosis*, n=25); smear-negative TB (also culture-positive, n=27); or probable TB (i.e. treated by the attending physician as tuberculosis in the absence of microbiological confirmation and with a definite response to treatment, n=41). A firm alternative diagnosis to tuberculosis was achieved in 82 patients. This left 31 patients in whom no definite diagnosis was made, and 32 patients with previous tuberculosis who had received a form of treatment in the past (children were not asked to provide samples).

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>Ps</th>
<th>Age*</th>
<th>Asian:Caucasian</th>
<th>Samples taken</th>
<th>Smear-positive</th>
<th>Culture-positive</th>
<th>PPD-positive</th>
<th>Treated</th>
<th>TB72-positive</th>
<th>% patients</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive TB</td>
<td>25</td>
<td>33 (17–68)</td>
<td>0.4</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>NT</td>
<td>100</td>
<td>72 (84)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear-negative TB</td>
<td>27</td>
<td>50 (19–78)</td>
<td>0.6</td>
<td>52</td>
<td>67</td>
<td>30</td>
<td>0</td>
<td>100</td>
<td>7/8</td>
<td>100</td>
<td>56 (82)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable TB</td>
<td>41</td>
<td>50 (22–79)</td>
<td>0.6</td>
<td>56</td>
<td>41</td>
<td>37</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>13/16</td>
<td>100</td>
<td>73 (90)†</td>
<td></td>
</tr>
<tr>
<td>No definite diagnosis</td>
<td>31</td>
<td>57 (16–82)</td>
<td>0.5</td>
<td>37</td>
<td>38</td>
<td>16</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>3/4</td>
<td>0</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Previous TB with inadequate treatment</td>
<td>32</td>
<td>66 (16–82)</td>
<td>0.2</td>
<td>47</td>
<td>41</td>
<td>35</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>14 (44)†</td>
<td></td>
</tr>
<tr>
<td>Firm alternative diagnosis</td>
<td>82</td>
<td>59 (18–86)</td>
<td>0.3</td>
<td>41</td>
<td>35</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NT</td>
<td>0</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

*= median (range). The age distribution reflects the local population. Paucibacillary tuberculosis is more common in Asians than Caucasians [7]. The taking of sputum samples is only recorded if ≥3 samples were taken and were judged to be adequate (i.e. not saliva) by the microbiologists. Bronchoalveolar lavage (BAL) was routinely taken from both upper lobes. Other samples sent for microbiological examination were pleural fluid, pleural biopsies and lymph node aspirates. Some patients submitted several samples for bacteriological analysis and others none. +: PPD-positive/PPD-tested. †: Serum samples were obtained from all those treated for tuberculosis; several patients who had been negative for the TB72-test became positive and the final sensitivity has, therefore, been recorded in parentheses. **: seven patients had smear-positive nontuberculous mycobacterial disease (four with *Mycobacterium xenopi* and three with *Mycobacterium kansasii*); three additional patients from whom unidentified mycobacterial species were grown were also negative for the TB72-test. TB: tuberculosis; PPD: purified protein derivative; pts: patients. NT: not tested.
was taken may be used for scientific research, unless they oppose such use. From these sera, 480 samples were taken at random, their code number recorded, and antibody to the TB72 epitope measured. Tracing the patient number from the code number, clinical records were examined in all except four, and the final diagnosis noted; no patient provided more than one sample for hepatitis B testing, so that each sample represented a single patient. These samples were collected during May and June 1990.

Methods

Antibody measurement (TB72-test)

Epitope-specific antibody was measured using a competition assay; antibody titres were defined as the serum dilution giving 50% inhibition of binding of the monoclonal antibody (MoAb). Polystyrene microtitre plates (flat-bottomed, Immulon M129B; Dynatech, Billingshurst, Sussex) were coated with a soluble extract of Mycobacterium tuberculosis H37Rv (MTSE), prepared as previously [14], at 10 µg·ml⁻¹ and 50 µl·well⁻¹ overnight at 4°C in a humidified atmosphere. The plates were washed once with phosphate buffered saline (PBS) containing 0.05% Tween 20 (PBSTM), and then nonspecific binding was blocked with 200 µl·well⁻¹ 3% skimmed milk in PBSTM for 1 h at 37°C. The plates were inverted and shaken to remove the blocking solution, and 25 µl of human serum, diluted 1:3 for the initial screening, and 1:5, 1:25, 1:125 and 1:625 for analysis of selected positive samples, in 3% milk PBST was added to duplicate wells, and incubated for 1 h at 37°C. Without washing, 25 µl of the TB72 monoclonal antibody, diluted in PBSTM to give 90% of maximum binding in wells without competing serum, was added to each well. Plates were agitated for 30 s on a Dynatech microtitre Varishaker, and incubated at 37°C for 2 h. Plates were then washed thoroughly with six washes of PBST over 30 min and patted dry. Fifty microlitres of affinity-purified goat anti-mouse immunoglobulin G (IgG) conjugated with horseradish peroxidase (BioRad Laboratories), diluted 1:3,000 in PBSTM was added to each well and incubated for 37°C for 1 h. Plates were washed six times with PBST, and 75 µl of 0.1 M citrate buffer (pH 5.1), containing 0.1 mg·ml⁻¹ tetramethyl benzidine and 0.01% hydrogen peroxide (30% w/v), was added to each well. Colour development occurred after 15 min, and the reaction was stopped by the addition of 0.5 M sulphuric acid. Absorbance was measured at 450 nm in a Titertek Multiskan spectrophotometer. Each plate contained wells where competing serum had not been added (high control), and wells that had been coated with PBS rather than MTSE (low control). The absorbance of the low control was subtracted from all wells, and if a value >0.05 was obtained the plate was considered unsatisfactory. Samples where there was >10% difference in absorbance between duplicate wells were repeated. The high control reached a mean absorbance of 0.773 optical density (OD) units (range 0.665–1.162 OD units). Each plate included a known positive patient with smear-positive pulmonary tuberculosis (serum diluted 1:25, 1:125 and 1:625), to confirm that inhibition of binding had taken place in that plate, and a negative sample from a BCG-vaccinated healthy control (used undiluted and at 1:3 and 1:9) the values of which served as a check for the high control. Any serum diluted 1:3 with an absorbance less than half the high control was defined as positive; antibody titres from positive samples tested at four log5 dilutions were calculated by interpolation as that dilution causing 50% inhibition of binding of the monoclonal antibody.

Statistical analysis

The sensitivity, specificity and positive and negative predictive values of the TB72 test were calculated using the method described by Toman [19]. The χ²-test with Yates' correction was used to measure the significance of differences in frequency.

Results

In patients with smear-negative, culture-positive pulmonary tuberculosis the positive rating (sensitivity) obtained with the TB72 ELISA competition assay was similar to that in patients with smear-positive TB (table 1). Furthermore, serum taken at the first out-patient visit was positive for the TB72-test on average 40 days (range 19–89 days) before sputum obtained either at the same time or from subsequent appointments gave a positive culture for M. tuberculosis (fig. 1). As treatment was initiated in 21 out of 27 patients the moment either sputum and/or bronchial washings had been obtained, this delay in bacterial culture was rarely significant, although two patients with a positive TB72-test were lost to follow-up by the time a positive culture was reported. Positivity was unaffected by age or ethnic origin.

Forty four patients were treated for tuberculosis without any bacteriological confirmation of disease; a firm alternative diagnosis was made in three. The TB72-test was as frequently positive in this group of patients as in those who had been culture-positive (table 1); two of three with a firm alternative diagnosis had a negative TB72-test. The serological test using the TB72 monoclonal antibody was also frequently positive in a group of patients without a definite diagnosis one year after tuberculosis had been suspected. Comparison of these two groups of patients showed that a decision to start antituberculous chemotherapy was based on a clinical assessment of the probability of tuberculosis: patients with several features of tuberculosis were more likely to be treated than those with merely a chronic cough and an abnormal chest radiograph compatible with tuberculosis (fig. 2).

Thirteen of the 21 patients with a positive TB72-test but without a definite diagnosis had chest radiographs with soft apical shadowing and/or hilar lymphadenopathy,
suggesting active tuberculosis; five had bronchiectasis, of whom one had been investigated for tuberculosis in 1947 and another had bilateral upper lobe disease without aspergillus precipitins; one had an apical granuloma; and two had fevers associated with haemoptysis. Further chest films were obtained at subsequent visits to the chest clinic (median 4 months, from presentation range 1–33 months,) and only two showed any radiographic improvement. Three patients died, but postmortem examinations were not obtained because of the risk of tuberculosis. A final assessment of these patients was made in June 1993 (median follow-up 38 months, range 33–45 months) in 9 out of 18 surviving patients who were still at the same address; one had received treatment for gastrointestinal tuberculosis.

Eighty two patients with suspected pulmonary tuberculosis gained a firm alternative diagnosis other than tuberculosis, but three (4%) were positive for the TB72-test. All three had lung cancer causing cavitation in the upper lobes of the lung and, although lavage specimens failed to grow Mycobacterium tuberculosis, concurrent tuberculosis could not be confidently excluded as postmortem studies were declined.

Patients with possible reactivation of previous tuberculosis, who had been "treated" either by artificial pneumothoraces or an inadequate course of antituberculous chemotherapy, were often positive for antibody to the TB72 epitope (table 1). The majority (17 out of 21) of those with a positive TB72-test had chest radiographs showing soft apical shadows, and a new lesion was apparent in three. By contrast, of patients who had not received adequate treatment for tuberculosis and who had no antibody to the TB72 epitope [11], six had a chest radiograph with densely calcified opacities, one had received a right upper lobectomy for tuberculosis, and another had a normal chest radiograph having had tuberculosis.
mediastinal lymphadenopathy as a child. No patient who had received a full course of antituberculous chemotherapy more than 2.5 yrs ago was positive for antibody to the TB72 epitope. Patients who had completed treatment in the past 2 yrs occasionally gave a positive TB72 test, but in 2 out of 17 this coincided with recurrent disease.

Twenty eight adult contacts were tested for the presence of antibody to the TB72 epitope. Twelve gave a positive tuberculin reaction, and all, except for one Caucasian who had been a contact of a patient with renal tuberculosis, received chemoprophylaxis with isoniazid. Eight of these 11 were positive for the TB72-test. One contact was positive for the TB72-test, but was tuberculin-negative and did not receive chemoprophylaxis.

Twenty two of 480 sera obtained at random from inpatients at the London Chest Hospital were positive for the TB72-test. Clinical records were traced for all those with a positive TB72-test, but were unavailable for four patients with a negative antibody test. Of the 22 with antibody to the TB72 epitope, one was receiving treatment for a tuberculous pleural effusion (and had been previously included among the 238 patients with suspected pulmonary tuberculosis), one had untreated tuberculosis, one was a contact, two had clinical features consistent with tuberculosis but were smear and culture-negative, and a sixth had a pleural effusion in 1961, the cause of which was not known. The incidence of tuberculosis in this part of London is 54.7 per 100,000 (London Research Centre, Royal London Hospital), and the majority of adults >40 yrs of age, who have not received BCG-vaccination, give a positive tuberculin response. However, the remaining (16 out of 22) positive tests may be termed "false-positives", in that none was considered to require treatment for tuberculosis, and none were notified as having tuberculosis in the following year. "False-positive" antibody titres in these 16 were between 3 and 10 (96% specificity). There were no false-negative results. When used as a screening test for tuberculosis the TB72-test, therefore, gave a positive predictive value of possibly 27% (assuming six patients had tuberculosis), and a negative predictive value of 100%. These compare with a positive predictive value of 92% (94%, if post-treatment samples are included) and a negative predictive value of 81% (90%, if post-treatment samples are included) derived from the culture-positive tuberculosis group and those with a "firm alternative diagnosis".

Discussion

The sensitivity of the ELISA competition assay using the TB72 monoclonal antibody in patients with smear-negative, culture-positive pulmonary tuberculosis was similar to that in patients with smear-positive disease. A slightly higher sensitivity of 70% in smear-negative and culture-positive pulmonary tuberculosis had been obtained by other workers using the same assay [18]. This compares well with the results of other serological assays (table 2). An increase in sensitivity with treatment was noted. Although, at first sight, the 19 kDa antigen would appear to be the most valuable reagent in the diagnosis of smear-negative tuberculosis [3, 15], significant geographical variation in antibody titres to this antigen in control samples makes it less attractive [16]. Healthy control sera from India, Indonesia and Europe do not show geographical variation in antibody levels to the TB72 epitope of the 38 kDa antigen of M. tuberculosis (unpublished data).

The decision to treat patients for tuberculosis was clearly made on clinical grounds. Thus, in patients who were treated, but in whom there was no microbiological confirmation of disease, there was at least one symptom or sign of tuberculosis in addition to an abnormal chest radiograph. Antibody titres >10 were not found when screening patients for tuberculosis, and this level of antibody could be valuable in deciding which patient without bacteriological confirmation of tuberculosis should be treated.

Table 2. – Serological tests in patients with smear-negative pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Patients Tested n</th>
<th>Sensitivity %</th>
<th>Controls Tested* n</th>
<th>Specificity %</th>
<th>[Ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB72 epitope (38 kDa antigen)</td>
<td>68</td>
<td>66 (87)i</td>
<td>556</td>
<td>97</td>
<td>This study</td>
</tr>
<tr>
<td>Lipoarabinomannan</td>
<td>27</td>
<td>70</td>
<td>117</td>
<td>92</td>
<td>[18]</td>
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<tr>
<td>30–32 kDa antigen</td>
<td>32</td>
<td>19</td>
<td>125</td>
<td>100</td>
<td>[5]</td>
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<tr>
<td>16</td>
<td>17</td>
<td>35 (60)i</td>
<td>221</td>
<td>95</td>
<td>[4]</td>
</tr>
<tr>
<td>19 kDa antigen</td>
<td>13</td>
<td>62</td>
<td>39</td>
<td>95</td>
<td>[3]</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>58</td>
<td>39</td>
<td>95</td>
<td>[15]</td>
</tr>
<tr>
<td>TB23 epitope (19 kDa antigen)</td>
<td>27</td>
<td>30</td>
<td>77</td>
<td>98</td>
<td>[18]</td>
</tr>
<tr>
<td>14 kDa antigen</td>
<td>13</td>
<td>54</td>
<td>39</td>
<td>95</td>
<td>[14]</td>
</tr>
<tr>
<td>TB68 epitope (14 kDa antigen)</td>
<td>27</td>
<td>15</td>
<td>77</td>
<td>98</td>
<td>[18]</td>
</tr>
<tr>
<td>67</td>
<td>67</td>
<td>14</td>
<td>79</td>
<td>95</td>
<td>[14]</td>
</tr>
</tbody>
</table>

*: the control groups for assessing specificity included healthy tuberculin-negative, healthy tuberculin-positive and healthy BCG-vaccinated subjects, patients with other lung disease, and patients with suspected pulmonary tuberculosis in different proportions. Significantly, variation within the control groups was observed in some instances, i.e. higher antibody levels to lipoarabinomannan were noted for patients with histoplasmosis compared to patients with other lung disease [6], and higher titres to the TB68 epitope in BCG-vaccinated compared to nonvaccinated controls [14]. †: after treatment TB: tuberculosis; BCG: bacille Calmette-Guérin.
Previous data using the same antibody test have shown that 29% of patients with smear-positive tuberculosis and 56% of patients with smear-negative culture-positive pulmonary tuberculosis had antibody titres between 3 and 10 [18]. The considerable numbers of patients with tuberculosis and antibody titres between 3 and 10 would suggest that patients with these lower antibody titres still merit continued observation.

The tuberculin test fails to distinguish active from healed tuberculosis and exposure to tubercle bacilli from nontuberculous mycobacterial disease, and diminishes with age [21]. In these circumstances, the TB72-test fared well. Many patients with pulmonary tuberculosis who had been inadequately treated in the past gave a positive test, while those who had completed a full course of anti-tuberculous chemotherapy more than 2.5 yrs ago were negative. The 38 kDa protein of M. tuberculosis is secreted by metabolically active bacilli [22]. Thus, in patients where live bacilli were present, antibody levels would have been continually boosted by the secretion of the 38 kDa antigen, whereas in patients where tubercle bacilli had been killed, an exponential decline in antibody levels to the TB72 epitope would be expected. Radiographic features associated with a greater likelihood of reactivation [23, 24] were present in patients with a positive TB72-test; dense calcified opacities were present in patients with untreated tuberculosis, but no antibody to the TB72 epitope. Now that reactivation is increasingly responsible for active tuberculosis [7], the combination of the TB72-test with a typical chest radiograph might be particularly helpful in the early diagnosis of recurrent tuberculosis.

Approximately 15% of patients with suspected pulmonary tuberculosis had no definite diagnosis after one year. Although a small group, these patients remain a problem to the attending physician. Of nine patients who were alive and could be traced three or more years after their initial presentation, one had extrapulmonary tuberculosis treated at another hospital. Positive antibody tests were common in patients with bronchiectasis, and might reflect a tuberculous aetiology. Bronchiectasis is associated with hypergammaglobulinaemia due to nonspecific B-cell stimulation. Antibody to the 38 kDa antigen may, therefore, have been maintained above the cut-off titre by such nonspecific stimulation. The data from patients with previous tuberculosis which was inadequately treated suggest that the radiographic abnormalities in many of the patients with a positive TB72-test but without a definite diagnosis could presage reactivation.

An immunological test based upon the response to an antigen secreted by living tubercle bacilli may have an advantage over deoxyribonucleic acid (DNA) probes, by distinguishing active disease (when there are sufficient numbers for the host response to cause tissue damage), from infection (when organisms are present but are either contained by cell-mediated immunity or too few to elicit any host response), or from the presence of nonviable bacilli. The incidence of false-positive reactions in healthy controls using the polymerase chain reaction (PCR) and specific DNA probes has been high [25]. One study has addressed the diagnostic problem of smear-negative and culture-negative tuberculosis using PCR to detect mycobacterial DNA, but conclusions cannot be drawn from the clinical data provided [26].

A monoclonal antibody-based test has the advantage of a potentially limitless supply of a standard reagent, which compares well with the difficulties of extracting pure antigens from complex mixtures of either the native organism or the vector for recombinant proteins. The TB72-test employed reagents commonly used in a diagnostic laboratory, with only one additional step compared to conventional serology, and was used in a hospital environment. The cost of the test is likely to be cheaper than other ELISA techniques (hepatitis B serology costs £0.93 per test when there are 6,000 tests per year, and cytomegalovirus (CMV) immunoglobulin M (IgM) £2.50 per test for 200 tests per year, Brompton Hospitals), as materials can be made in the laboratory (the soluble extract of M. tuberculosis), or are available through the World Health Organization (TB72 monoclonal antibody). By comparison, 1 ml of tuberculin for Mantoux testing costs £2.22 (British National Formulary (BNF)) and the DNA technique currently available costs US$33.33 per isolate [27].

In conclusion, the clinical role for the TB72-test in the diagnosis of tuberculosis is becoming clearer. In the majority of patients with smear-negative tuberculosis, a decision to start specific treatment will continue to be made on clinical grounds, after appropriate samples have been sent for microbiological testing. Where there is doubt, an antibody titre >10 to the TB72 epitope will be useful confirmation. In patients with evidence of untreated or poorly treated tuberculosis, in whom symptoms and a chest radiograph suggesting reactivation, an antibody titre >10 to the TB72 epitope would indicate treatment, while those with titres 3–10 need close observation. The TB72-test may have a role in contact tracing, as there would be no requirement for the subject to return at a specified interval, as is the case with tuberculin testing, and this is the subject of further study. The role of serological testing in patients with HIV infection is also under investigation.

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References


