УДК 616-002.5-615.371 doi: 10.36422/23076348-2021-9-2-15-21

Возможности тестов *in vitro* в диагностике туберкулеза (обзор литературы)

Е.А. Бородулина[1], Д.А. Кудлай[2,3], Б. Власова[1], А.Н. Кузнецова[1]

[1] Самарский государственный медицинский университет
[2] Государственный научный центр Институт иммунологии Федерального медико-биологического агентства, Москва
[3] Первый Московский государственный медицинский университет им. И.М. Сеченова (Сеченовский Университет)

Potential use of *in vitro* tests in the diagnosis of tuberculosis (literature review)

E. Borodulina[1], D. Kudlay[2,3], B. Vlasova[1], A. Kuznetsova[1]

[1] Samara State Medical University
[2] National Research Center — Institute of Immunology, Federal Medical-Biological Agency, Moscow
[3] I.M. Sechenov First Moscow State Medical University (Sechenovskiy University)

Резюме

Поиск методов, улучшающих раннюю диагностику туберкулезной инфекции, особенно активно ведется в последние два десятилетия. Диагностика латентной туберкулезной инфекции повысит эффективность противотуберкулезных мероприятий. Туберкулез у больных ВИЧ, частота которого среди впервые заболевших возрастает, имеет клинико-иммунологические и патоморфологические особенности, затрудняющие верификацию диагноза. Риск развития туберкулеза у ВИЧ-инфицированных в 30 раз выше, чем в популяции в целом. Диагностика особенно затруднена на стадии выраженного иммунодефицита. В последнее два десятилетия все шире используются IGRA-тесты, имеющие более высокую специфичность, чем туберкулиновые кожные пробы. Представлен обзор литературы сравнения диагностической эффективности тестов T-SPOT.TB и QuantiFERON-TB Gold in-Tube у пациентов с подозрением на активный туберкулез. По данным публикаций у пациентов с ВИЧ при квантифероновом тесте чаще встречаются ложноотрицательные результаты при выраженном снижении количества CD4+-клеток. Чувствительность теста T-SPOT.TB практически не зависит от возраста пациента, тогда как чувствительность QuantiFERON-TB снижается после 30 лет. При проведении теста T-SPOT.TB не отмечается влияние принимаемых пациентом лекарственных препаратов на тест. На основании обзора литературы сформировано предположение, что применение T-SPOT.TB наиболее целесообразно в следующих случаях: когда пациент принимает препараты, угнетающие выработку гамма-интерферона (глюкокортикоиды); когда пациент принимает препараты, снижающие уровень лейкоцитов (группа НПВС — аспирин, парацетамол, кеторол, цитостатики и др.); у детей до 5 лет и лиц пожилого возраста. Представляется перспективным использование T-SPOT.TB в комплексе обследования пациентов с ВИЧ-инфекцией.

Ключевые слова: туберкулез, латентный туберкулез, ВИЧ-инфекция, QuantiFERON-TB Gold, T-SPOT.TB, IGRA-тесты

Summary

The search for methods to improve early diagnosis of tuberculosis has been particularly active in the last two decades. Diagnostics of latent tuberculosis infection will increase the efficacy of anti-tuberculosis measures. Tuberculosis in HIV patients, which is increasingly common in the incident population, has specific clinical, immunological, and pathomorphological characteristics posing challenges to diagnosis confirmation. HIV-infected individuals have a 30-fold risk of tuberculosis compared with the general population. Diagnostic challenges are particularly high at the stage of severe immunodeficiency. In the last two decades, IGRAs, which have a higher specificity versus tuberculin skin tests, have been increasingly used. We present a literature review of studies comparing the diagnostic efficacy of T-SPOT.TB and QuantiFERON-TB Gold in-Tube assays in patients with suspected active tuberculosis. According to literature data, QuantiFERON assay more frequently yields false negative results in HIV patients with markedly decreased CD4+ cell counts. T-SPOT.TB sensitivity is essentially independent of age, whereby the sensitivity of QuantiFERON-TB reduces after the age of 30 years. T-SPOT.TB assay was not found to be affected by drug therapy. Based on this literature review, we assume that the use of T-SPOT.TB assay is most appropriate in the following cases: in patients taking drugs that inhibit gamma interferon production (glucocorticoids); in patients taking drugs that reduce leukocyte levels (NSAIDs: aspirin, paracetamol, Ketorol; also cytostatic agents etc.); in children under 5 years and in elderly subjects. T-SPOT.TB appears to be a promising test within the assessment of HIV-infected patients.

Keywords: tuberculosis, latent tuberculosis, HIV-infection, QuantiFERON-TB Gold, T-SPOT.TB, IGRAs

Introduction

According to WHO, one third of the world population is estimated to have latent tuberculosis infection. These data were published in 1999, based on the results of tuberculin skin testing. In the last two decades, IGRAs have been increasingly used. They have a higher specificity versus tuberculin skin tests but are not used for the assessment of latent tuberculosis infection prevalence.

Study goal

A review of scientific publications has been conducted to determine the share of *in vitro* tests in the research of options for early diagnosis of tuberculosis.

Study materials and methods

A literature search was conducted using the following databases: Russian Science Citation Index, CyberLeninka, Scopus, Web of Science, MedLine, PubMed. Search keywords included: tuberculosis, HIV infection, QuantiFERON-TB Gold and T-SPOT.TB, IGRAs, latent tuberculosis. A total of 39 papers were reviewed in detail.

Results

A systematic review and meta-analysis of the prevalence of latent tuberculosis infection (LTI) based on IGRA and tuberculin skin testing results published between 2005 and 2018 have been conducted by Cohen A. and Mathiasen D in 2019 [1]. The authors estimated the regional and global prevalence of LTI. In the studies, countries were classified as having a low, intermediate, or high tuberculosis incidence. A pooled estimate has been obtained for each region using a random effects model (a statistical model where the model parameters are random variables). After a preliminary screening of 3280 studies, the authors selected 88 studies from 36 countries based on the results of IGRAs and tuberculin skin tests. The global prevalence of latent tuberculosis was 24.8% based on IGRAs and 21.2% and 24.1% based on tuberculin skin tests with 5-mm and 10-mm infiltrate size cut-offs, respectively. These results correlate with WHO estimates.

In 2011, C. Lai et al. [2] have conducted a study to compare the diagnostic efficacy of T-SPOT.TB and QuantiFERON-TB Gold in-Tube tests in patients with suspected active tuberculosis. From October 2009 to October 2011, a total of 200 patients with suspected tuberculosis were included in the study. Clinical and microbiological characteristics and blood samples for T-SPOT.TB and QFT-GIT testing were collected from 200 subjects. The diagnosis of "tuberculosis" had been confirmed in 98 (49%) of these subjects by mycobacterium tuberculosis detection in culture, a high probability of tuberculosis was found in 18 (9%), and tuberculosis was excluded in the remaining 84 (42%) subjects. The sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of active tuberculosis using T-SPOT.TB testing were 83%, 71%, 81%, and 75%, respectively. For QFT-GIT, the sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of active tuberculosis were 66%, 76%, 80%, and 62%. T-SPOT.TB showed a higher sensitivity and resulted in a lower amount of uncertain results compared with QFT-GIT testing in the diagnosis of active tuberculosis.

In 2012, K. Higuchi and Y. Sekiya [3] conducted a comparison of specificities between T-SPOT.TB and QuantiFERON®-TB Gold in strictly selected Japanese

subjects with a low risk of tuberculosis. Of a total of 111 subjects vaccinated with BCG, one positive result and 110 negative results were obtained using both tests based on global thresholds. Although some meta-analyses have reported a higher specificity for QuantiFERON®-TB Gold versus T-SPOT.TB, their study shows an equally high specificity for both tests in a population with a really low risk of tuberculosis infection.

In 2011, T. Simpson et al. have tested 541 adult immigrants who came to USA from countries with a high tuberculosis prevalence using QFT-GIT [4]. A positive test result was obtained in 24% of subjects. The authors found that QFT-GIT may not provide relevant results in significantly immunocompromised populations.

In 2016, W. Bae et al. have conducted a retrospective study to review health records of tuberculosis patients tested using QFT-GIT or T-SPOT.TB from February 2008 to December 2013 [5]. Their goal was to establish how test sensitivity changes with age. Positive results obtained with both tests were confirmed using bacteriological and PCR methods. The QFT-GIT group included 192 tuberculosis patients, 76 (39.6%) of which had active pulmonary tuberculosis; the T-SPOT.TB group included 212 tuberculosis patients, 143 (67.5%) of which had active pulmonary tuberculosis. The overall sensitivity was 80.2% for QFT-GIT and 91.0% for T-SPOT.TB. QFT-GIT and T-SPOT.TB sensitivities according to age groups were the following:

- <29 years, 93.3% (QFT-GIT) and 96.7% (T-SPOT.TB);
- 30–49 years, 86.5% (QFT-GIT) and 94.7% (T-SPOT.TB);
- 50–69 years, 73.8% (QFT-GIT) and 87.5% (T-SPOT.TB);
- >70 years, 68.3% (QFT-GIT) and 85.7% (T-SPOT.TB).

Thus, T-SPOT.TB was shown to have a higher overall sensitivity (91.0%) versus QFT-GIT (80.2%). Both tests showed a statistically significant reduction in sensitivity with increasing age. The magnitude of reduction in sensitivity was higher for QFT-GIT compared with T-SPOT.TB.

E. Chiappini, F. Bonsingori et al. (2012) have conducted a review of studies assessing the efficacy of IGRAs in pediatric practice [6]. A literature search was performed in Medline, EMBASE, and Cochrane databases using several keywords and standard terminology for papers published until January 27, 2011. The quality of the studies was assessed based on MOOSE checklist and the results of adequate studies have been pooled. Sixty-seven pediatric studies (study population ranging from 14 to 5244 children) were analyzed. ESAT-6 and CFP-10 tests have been carried out in 11 studies. QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold In-tube (QFT-G-IT), and T-SPOT.TB assays have been performed in many studies [7–9]. Sensitivity for active tuberculosis ranged from 51 to 93% for QuantiFERON-TB Gold and QuantiFERON-TB Gold In-tube assays, and from 40 to 100% for ESAT-6 and CFP-10 assays, which demonstrates that a negative IGRA result does not exclude tuberculosis. Combining tuberculin skin test and IGRA results increased the diagnostic sensitivity. The rate of indeterminate results varied greatly (0 to 35%). Most of the studies in children younger than 5 years or immunocompromised children showed over 4% of indeterminate results. Higher rates of discordance were reported in BCG-vaccinated versus non-BCG-vaccinated children. Studies in children younger than 5 years and immunocompromised children, as well as studies with serial IGRA testing showed conflicting results. The authors consider that combined use of tuberculin skin test and IGRAs may increase diagnostic sensitivity but interpretation of conflicting results remains a challenging issue.

In 2018, Abubakar I and Drobiniewski F. have conducted a study to assess the prognostic value of interferon-gamma assays QuantiFERON® Gold in Tube (QFT) and T-SPOT.TB and tuberculin skin test in predicting the development of active tuberculosis in high-risk groups [10]. A total of 9610 high-risk subjects were included in the study from 54 centers in London, Birmingham, and Leicester in the UK. In this cohort, 4861 subjects (50.6%) were tuberculosis contacts and 4749 (49.4%) were migrants. Study participants were followed up for an average of 2.9 years (21 days to 5.9 years). Ninety-seven of 9610 subjects developed active tuberculosis (1.0%). The medical assessments included T-SPOT.TB, QFT, and tuberculin skin testing. The results of all three tests were obtained for 6380 subjects, 77 (1.2%) of which developed active tuberculosis during the study. The results showed that a positive T-SPOT.TB result is a significantly better predictor of progression to active tuberculosis than the other assays. The probability of developing active tuberculosis was 8.8-fold higher in subjects with positive T-SPOT.TB results than in those with negative results. Also, the annual incidence of active tuberculosis in participants with positive T-SPOT.TB results was 13.2 per 1000 persons. The positive predictive value of T-SPOT.TB assay proved to be 28% higher versus QFT assay for all the 6380 tested subjects and at least 20% higher compared with any other assay: T-SPOT.TB=4.2%, QFT=3.3%, tuberculin skin test with a 15-mm infiltrate size cut-off=3.5%, tuberculin skin test with a 5-mm infiltrate size cut-off=2.2%, and tuberculin skin test with a 10-mm infiltrate size cut-off=2.7%. Distinctive results were obtained in different groups. The positive predictive value of a positive T-SPOT.TB result was higher in the group of tuberculosis contacts (4.8%) versus the group of migrants. However, the positive predictive value of T-SPOT.TB assay was 38% and was shown to be higher than the predictive value of QFT assay and tuberculin skin test. Authors showed that a positive tuberculin skin test result with a 5-mm infiltrate size cut-off has a significantly lower predictive value versus all the other tests, and a positive T-SPOT.TB result is the best predictor of latent tuberculosis progressing to active tuberculosis.

In 2011, Santin M., Muñoz L., and Rigau D. have conducted a search in MEDLINE, Cochrane, and Biomedicine databases to identify articles published between January 2005 and July 2011, which assessed the diagnostic value of QuantiFERON®-TB Gold In-Tube (QFT-GIT) and T-SPOT.TB assays in HIV-infected adults [11]. The search identified 38 studies which included a total of 6514 HIV-infected subjects. The sensitivity and specificity for detecting tuberculosis was 61% and 72% for QFT-GIT assay and 65% and 70% for T-SPOT.TB assay, respectively. The cumulative incidence of active tuberculosis was 8.3% for QFT-GIT and 10% for TSPOT.TB in subjects with initially positive results (one study for each test). Authors concluded that IGRAs are not accurate enough to confirm or exclude active tuberculosis in HIV-infected adults. In their opinion, the predictive value of these assays for the development of active tuberculosis is low. Most studies suggest that the results of such testing are not sufficient to establish an accurate diagnosis [12–18].

Since the beginning of the 21st century, tuberculosis and HIV coinfection has been an increasingly pressing issue [19, 20]. According to the World Health Organization, approximately 208,000 people died from HIV-associated tuberculosis in 2019, and the percentage of reported TB patients who had a documented HIV test result was 69%, up from 64% in 2018 [21].

Tuberculosis detection in HIV-positive patients poses unique challenges. Persistent fever is sometimes the sole manifestation of tuberculosis. Lung lesions are not always visible on photofluorography. Tuberculosis often involves the central nervous system causing signs of meningitis and meningoencephalitis [22]. In 80–94% of patients with severe immunodeficiency, tuberculin reaction becomes negative when $CD4^+$ lymphocyte counts fall below 200 cells/μL [23].

No "gold standard" test is currently available in the world for the diagnosis of latent tuberculosis infection in HIV-infected individuals. Positive results of both skin immunological tests and *in vitro* assays do not allow to reliably differentiate latent and active tuberculosis. They only attest the presence in the body of memory cells which have previously came in contact with mycobacterium tuberculosis and react to its repeated inoculation. However, it cannot be determined when the immune system encountered the pathogen: recently or many years ago. With that said, various immunological tests have certain advantages and drawbacks, which must be taken into account in specific situations [24].

Diaskintest®, developed based on recombinant tuberculosis allergen, has been used in Russia since 2010. It contains two antigens: ESAT-6 and CFP-10, which are components of virulent Mycobacterium tuberculosis strains and are absent in the BCG vaccine strain. Since, unlike tuberculin, this product contains only two antigens, it has higher sensitivity and specificity for diagnosing latent tuberculosis infection in HIV-negative individuals [25-31]. Unfortunately, clinical studies assessing the diagnostic value of intradermal Diaskintest in HIV-infected patients showed that, although it has a high specificity of up 100%, its sensitivity reduces with the decrease of CD4+ lymphocyte counts. This means that in severe immunodeficiency, when CD4+ lymphocyte counts drop below 200 cells/μL, Diaskintest and tuberculin skin test prove uninformative, because the immune system is severely compromised in HIV-infected patients and cannot react to the test [32].

QantiFERON-TB Gold and T-SPOT.TB assays, which are IGRAs (interferon gamma release assays), have a higher specificity versus Mantoux test and do not depend on previous BCG vaccination or on allergic reactions that may occur with skin tests (Mantoux test and Diaskintest) [31].

In 2015, Sun H., Hsueh P., and Liu W. have tested 608 HIV-infected patients using the T-SPOT.TB assay in order to determine its predictive value [33]. 534 of the patients (87.8%) with negative test results did not develop tuberculosis within 2.5 years after testing. In 10 patients (1.6%) with inconclusive T-SPOT.TB results, also no tuberculosis was detected in the following 2.5 years. Of the 64 patients (10.5%) with positive results, one patient developed tuberculosis in the following 2.5 years. Thus, authors showed that a negative T-SPOT.TB result has a high diagnostic value in excluding tuberculosis.

In 2016, Huo and Peng [34] have conducted a meta-analysis to compare the efficacy of QantiFERON-TB Gold and T-SPOT.TB assays in detecting active tuberculosis infection. The HIV-infected subjects included in their analysis had mean CD4+ cell counts of 400 cells per mm^3. Nine cohorts from countries with a high prevalence of tuberculosis in HIV-infected subjects (over 40 cases per 100,000 population) and two cohorts from countries with a low prevalence of tuberculosis in HIV patients (less than 40 cases per 100,000 population) were analyzed. Huo and Peng established that QantiFERON-TB assay has a sensitivity of 69% and a specificity of 76%, whereas T-SPOT.TB assay has a sensitivity of 89% and a specificity of 87%. I.e. T-SPOT.TB was found to be more accurate than QantiFERON-TB Gold.

In 2016, Ayubi et al. [35] have conducted a meta-analysis to compare the efficacy of QuantiFERON versus tuberculin skin test in detecting latent tuberculosis in HIV patients. The analysis included 20 studies where HIV patients had high CD4+ cell counts. The authors found that the QuantiFERON assay has a higher sensitivity versus the tuberculin skin test. However, with the decrease of CD4+ cell counts below 200 cells/μL the rate of negative QuantiFERON results increased, which means that its sensitivity reduced.

In 2016, Kussen et al. [36] have conducted a study in Brazil to compare the efficacy of the QuantiFERON assay

versus tuberculin skin test in diagnosing latent tuberculosis in HIV patients. A total of 154 subjects were tested, of which 9% did not return to confirm the diagnosis. In 115 subjects, both tests showed negative results, 12 subjects had a negative tuberculin skin test result and a positive QuantiFERON result, and 4 subjects had a positive tuberculin skin test result and a negative QuantiFERON result. A total of 13 patients were diagnosed with latent tuberculosis infection and were treated with isoniazid for 6 months. The QuantiFERON assay was found to confirm 8% more cases versus tuberculin skin test and had a sensitivity of 69% and a specificity of 90%. With that said, tuberculin skin test yielded positive results in patients with CD4+ cell counts over 300 cells/mm^3, whereas a positive diagnosis with the QuantiFERON assay was obtained with CD4+ cell counts below 300 cells/mm^3. However, authors concluded that the QuantiFERON assay should be used in combination with tuberculin skin testing rather than alone.

In 2011, A. Cattamanchi et al. [37] have conducted a systematic review and meta-analysis to assess the efficacy of IGRAs for the detection of tuberculosis in HIV-infected subjects who could benefit from treatment for latent tuberculosis. The search identified 37 studies which included 5736 HIV-infected individuals. Data analysis showed that HIV-infected subjects with positive IGRA results had a higher risk of active tuberculosis. In HIV-infected subjects with active tuberculosis, T-SPOT.TB showed a higher sensitivity versus QFT-GIT. Also, T-SPOT.TB proved to be less affected by immunosuppression versus QFT-GIT and tuberculin skin test.

P. Madukar, G. Sotgiu [38] concluded that both tuberculin skin test and IGRAs have a lower sensitivity in immunocompromised patients, especially those with severe immunodeficiency, and cannot predict the progression of infection to active tuberculosis. As with tuberculin skin testing, a positive IGRA result does not always mean that active tuberculosis will eventually develop.

In HIV patients, the more severe the immunodeficiency, the higher the risk of generalized tuberculosis [39]. Tuberculosis is reported in 30-70% of HIV patients with blood CD4+ cell counts below 200 per 1 mm^3 [22, 32].

T-SPOT.TB assay was not found to be affected by drug therapy. In HIV-infected patients, both tests are highly accurate but the QuantiFERON assay more frequently yields false negative results when CD4+ cell counts are markedly decreased. T-SPOT.TB sensitivity is essentially independent of age, whereby the sensitivity of QuantiFERON reduces after the age of 30 years. Based on this literature review, the T-SPOT.TB assay may be recommended in the following cases: in patients taking drugs that inhibit gamma interferon production (glucocorticoids); in patients taking drugs that reduce leukocyte levels (NSAIDs: Aspirin, paracetamol, Ketorol; also cytostatic agents etc.); in children under 5 years; and in elderly subjects.

Conclusions

The search for methods to improve early diagnosis of tuberculosis remains a pressing issue. According to literature data published in the last two decades, IGRAs showed higher specificity and sensitivity versus tuberculin skin tests. The most challenging issue is early detection of tuberculosis infection in HIV-infected individuals, especially at the stage of severe immunodeficiency. In this group of patients, most promising is the use of T-SPOT.TB immunologic assay in combination with other diagnostic methods (immunologic, molecular-genetic, radiographic, morphologic).

References

1. *Cohen A., Mathiasen V.D., Schön T., Wejse C.* The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur. Respir. J. 2019 Sep 12; 54 (3): 1900655. doi: 10.1183/13993003.00655-2019. PMID: 31221810.
2. *Lai C.C., Tan C.K., Lin S.H. et al.* Diagnostic performance of whole-blood interferon-gamma assay and enzyme-linked immunospotassay for active tuberculosis. Diagn. Microbiol. Infect. Dis. 2011; 71 (2): 139–143.
3. *Higuchi K., Sekiya Y., Igari H. et al.* Comparison of specificities between two interferon-gamma release assays in Japan. Int. J. Tuberc. Lung Dis. 2012 Sep; 16 (9): 1190–1192. Epub 2012 Jun 28. PMID: 22748102. doi: 10.5588/ijtld.11.0829.
4. *Simpson T., Tomaro J., Jobb C.* Implementation of an interferon-gamma release assay to screen of tuberculosis in refugees and immigrants. J. Immigr. Minor. Health 2013; 15 (4): 686–692.
5. *Bae W., Park K.U., Song E.Y. et al.* Comparison of the Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB According to Patient Age. PLoS ONE 2016; 11 (6): e0156917. doi: 10.1371/journal.pone.0156917.
6. *Chiappini E., Accetta G., Bonsignori F. et al.* Interferon-γ release assays for the diagnosis of Mycobacterium tuberculosis infection in children: a systematic review and meta-analysis. Int. J. Immunopathol. Pharmacol. 2012; 25 (3): 557–564.
7. *Detjen A.K., Keil T., Roll S. et al.* Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. Clin. Infect. Dis. 2007 Aug 1; 45 (3): 322–328. doi: 10.1086/519266. Epub 2007 Jun 15. PMID: 17599309.
8. *Kampmann B., Whittaker E., Williams A. et al.* Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. Eur. Respir. J. 2009 Jun; 33 (6): 1374–1382. doi: 10.1183/09031936.00153408. Epub 2009 Feb 5. PMID: 19196815.
9. *Chiappini E., Bonsignori F., Mazzantini R. et al.* Interferon-gamma release assay sensitivity in children younger than 5 years is insufficient to replace the use of tuberculin skin test in western countries. Pediatr. Infect. Dis. J. 2014; 33 (12): 1291–1293. doi: 10.1097/INF.0000000000000432.
10. *Abubakar I., Drobniewski F., Southern J. et al.* Prognostic value of interferon-γ release assays and tuberculin skin test in predicting

the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. Lancet Infect. Dis. 2018; 18 (10): 1077–1087.
11. *Santin M., Munoz L., Rigau D.* Interferon-c Release Assays for the Diagnosis of Tuberculosis and Tuberculosis Infection in HIV-Infected Adults: A Systematic Review and Meta-Analysis. PLoS ONE 2012; 7 (3): e32482. doi: 10.1371/journal.pone.0032482.
12. *Chee C.B., Gan S.H., Khinmar K.W. et al.* Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. J. Clin. Microbiol. 2008 Jun; 46 (6): 1935–1940. doi: 10.1128/JCM.02403-07. Epub 2008 Apr 9. PMID: 18400912; PMCID: PMC2446854.
13. *Sester M., Sotgiu G., Lange C. et al.* Interferon-γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. Eur. Respir. J. 2011 Jan; 37 (1): 100–111. doi: 10.1183/09031936.00114810. Epub 2010 Sep 16. Erratum in: Eur. Respir. J. 2012 Mar; 39 (3): 793. PMID: 20847080.
14. *Diel R., Goletti D., Ferrara G. et al.* Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur. Respir. J. 2011 Jan; 37 (1): 88–99. Epub 2010 Oct 28. Erratum in: Eur. Respir. J. 2012 Mar; 39 (3): 793. PMID: 21030451. doi: 10.1183/09031936.00115110.
15. *Lai C.C., Tan C.K., Lin S.H. et al.* Diagnostic performance of whole-blood interferon-γ assay and enzyme-linked immunospot assay for active tuberculosis'. Diagn. Microbiol. Infect. Dis. 2011 Oct; 71 (2): 139–143. doi: 10.1016/j.diagmicrobio.2011.05.013. Epub 2011 Aug 15. PMID: 21840675.
16. *Ling D., Pai M., Davids V., Brunet L. et al.* Are interferon-γ release assays useful for diagnosing active tuberculosis in a high-burden setting? European Respiratory Journal 2011; 38: 649–656; doi: 10.1183/09031936.00181610.
17. *Kobashi Y. et al.* Clinical evaluation of interferon-gamma release assay (IGRA) in patients with nontuberculous mycobacterial disease. European Respiratory Journal 2012 Sep; 40 (Suppl. 56): P2715.
18. *Luo Y., Tan Y., Yu J. et al.* The Performance of Pleural Fluid T-SPOT.TB Assay for Diagnosing Tuberculous Pleurisy in China: A Two-Center Prospective Cohort Study. Front Cell Infect. Microbiol. 2019; 9: 10. Published 2019 Jan 30. doi: 10.3389/fcimb.2019.00010.
19. *Бородулин Б.Е., Бородулина Е.А., Куликова И.И. и др.* Туберкулез у ВИЧ-инфицированных в крупном промышленном центре. Пульмонология 2007; (2): 56–59 [*Borodulin B.E., Borodulina E.A., Kulikova I.I. i dr.* Tuberculosis in HIV-infected people in a large industrial center. Pul'monologiya 2007; (2): 56–59 (In Russ.)].
20. *Бородулина Э.В., Бородулина Е.А., Гладунова Е.П., Вдоушкина Е.С.* Медико-социальная характеристика впервые выявленных пациентов с туберкулезом. Медицинский альянс 2018; (3): 41–46 [*Borodulina E.V., Borodulina E.A., Gladunova E.P., Vdoushkina E.S.* Medical and social characteristics of newly diagnosed patients with tuberculosis. Meditsinskii al'yans 2018; (3): 41–46 (In Russ.)].
21. *Мохрякова Т.Е., Синицын М.В.* Туберкулез у больных с ВИЧ-инфекцией: Брошюра ГБУЗ «Московский городской научно-практический центр борьбы с туберкулезом Департамента здравоохранения города Москвы. Тверь: Триада 2016 [*Mokhryakova T.E., Sinitsyn M.V.* Tuberculosis in patients with HIV infection: Brochure of the Moscow City Scientific and Practical Center for Tuberculosis Control of the Moscow City Health Department. Tver': Triada 2016 (In Russ.)].
22. *Зимина В.Н., Васильева И.А., Кравченко А.В. и др.* Диагностика туберкулеза у больных с ВИЧ-инфекцией. Туберкулез и болезни легких 2014; (10): 3–10 [*Zimina V.N., Vasil'eva I.A., Kravchenko A.V. i dr.* Diagnosis of tuberculosis in patients with HIV infection. Tuberkulez i bolezni legkikh 2014; (10): 3–10 (In Russ.)].
23. *Зимина В.Н., Белобородова Е.Н.* Проба Манту, Диаскинтест, T-spot.TB или квантифероновый тест — какой выбрать для диагностики латентной инфекции?: Курс фтизиатрии В.Н. Зиминой. Медицинский институт РУДН, coinfection.net. 2018 [*Zimina V.N., Beloborodova E.N.* Mantoux test, Diaskintest, T-spot.TB or quantiferon test — which one to choose for diagnosing a latent infection?: Kurs ftiziatrii V.N. Ziminoi. Meditsinskii institut RUDN, coinfection.net (In Russ.)].
24. *Бородулина Е.А.* Скрининг туберкулезной инфекции. Современные рекомендации. Аллергология и иммунология в педиатрии 2017; 2 (49): 29–33 [*Borodulina E.A.* Screening for tuberculosis infection. Modern recommendations. Allergologiya i immunologiya v pediatrii 2017; 2 (49): 29–33 (In Russ.)].
25. *Аксенова В.А., Барышникова Л.А., Клевно Н.И., Кудлай Д.А.* Скрининг детей и подростков на туберкулезную инфекцию в России — прошлое, настоящее, будущее. Туберкулез и болезни легких 2019; 97 (9): 59–67 [*Aksenova V.A., Baryshnikova L.A., Klevno N.I., Kudlay D.A.* Screening children and adolescents for tuberculosis infection in Russia — past, present, future. Tuberkulez i bolezni legkikh 2019; 97 (9): 59–67 (In Russ.)].
26. *Аксенова В.А., Леви Д.Т., Александрова Н.В. и др.* Туберкулез у детей: современные методы профилактики и ранней диагностики. Доктор.Ру 2017; 15 (144): 9–15 [*Aksenova V.A., Levi D.T., Aleksandrova N.V. i dr.* Tuberculosis in children: modern methods of prevention and early diagnosis. Doktor.Ru 2017; 15 (144): 9–15 (In Russ.)].
27. *Кудлай Д.А.* Биомаркеры и иммунологические тесты. Экспериментально-клинические параллели латентной туберкулезной инфекции. Туберкулез и болезни легких 2020; 98 (8): 63–74 [*Kudlay D.A.* Biomarkers and immunological tests. Experimental and clinical parallels of latent tuberculosis infection. Tuberkulez i bolezni legkikh 2020; 98 (8): 63–74 (In Russ.)]. doi: 10.21292/2075-1230-2020-98-8-63-74.
28. *Кудлай Д.А., Старшинова А.А., Довгалюк И.Ф.* Аллерген туберкулезный рекомбинантный: 10-летний опыт применения теста у детей и подростков в Российской Федерации (данные метаанализа). Педиатрия им. Г.Н. Сперанского 2020; 99 (3): 121–129 [*Kudlay D.A., Starshinova A.A., Dovgalyuk I.F.* Recombinant tuberculous allergen: 10-year experience of using the test in children and adolescents in the Russian Federation (meta-analysis data). Pediatriya im. G.N. Speranskogo 2020; 99 (3): 121–129 (In Russ.)].
29. *Старшинова А.А., Кудлай Д.А., Довгалюк И.Ф. и др.* Эффективность применения новых методов иммунодиагностики туберкулезной инфекции в Российской Федерации. Педиатрия 2019; 98 (4): 229–235 [*Starshinova A.A., Kudlay D.A., Dovgalyuk I.F. i dr.* The effectiveness of new methods of immunodiagnostics of tuberculosis infection in the Russian Federation. Pediatriya 2019; 98 (4): 229–235 (In Russ.)]. doi: 10.24110/0031-403X-2019-98-4-229–235.
30. *Слогоцкая Л.В., Синицын М.В., Кудлай Д.А.* Возможности иммунологических тестов в диагностике латентной туберкулезной инфекции и туберкулеза. Туберкулез и болезни легких 2019; 97 (11): 46–59 [*Slogotskaya L.V., Sinitsyn M.V., Kudlay D.A.* Possibilities of immunological tests in the diagnosis of latent tuberculosis infection and tuberculosis. Tuberkulez i bolezni legkikh 2019; 97 (11): 46–59 (In Russ.)]. doi: 10.21292/2075-1230-2019-97-11-46-58.
31. *Slogotskaya L.V., Litvinov V., Kudlay D.A. et al.* New skin test with recombinant protein CFP10-ESAT6 in patients (children and adults) with tuberculosis, non-tuberculosis disease and latent TB infection. European Respiratory Journal 2012; 40 (S56): 416.
32. *Каминский Г.Д., Кудлай Д.А., Панова А.Е. и др.* Тактика врача при выявлении, диагностике и профилактике сочетанной

инфекции ВИЧ и туберкулез. Практическое руководство/ под ред. И.А. Васильевой. М., 2020; 152 [*Kaminskii G.D., Kudlay D.A., Panova A.E. i dr.* Doctor's tactics in the detection, diagnosis and prevention of co-infection with HIV and tuberculosis. Practical guide / pod redaktsiei I.A. Vasil'evoi. M. 2020; 152 (In Russ.)].
33. *Sun H.Y., Hsueh P.R., Liu W.C. et al.* Risk of Active Tuberculosis in HIV-Infected Patients in Taiwan with Free Access to HIV Care anda Positive T-Spot. TBTest. PLoSOne 2015; 10 (5): e0125260.
34. *Huo Z., Peng L.* Accuracy of the interferon-γ release assay for the diagnosis of active tuberculosis among HIV-seropositive individuals: a systematic review and meta-analysis. BMC Infectious Diseases 2016; 16: 350.
35. *Ayubi E. et al*. The clinical usefulness of tuberculin skin test versus interferon-gamma release assays for diagnosis of latent tuberculosis in HIV patients: a meta-analysis. PLOS ONE 2016; 11 (9).
36. *Kussen G.M.B. et al*. Interferon-gamma release assay versus tuberculin skin test for latent tuberculosis infection among HIV patients in Brazil. J. Infect. Dis. 2016; 20 (1): 69–75.
37. *Cattamanchi A., Smith R., Steingart K.R. et al.* Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. Journal of Acquired Immune Deficiency Syndromes 1999; 56 (3): 230–238. doi: 10.1097/QAI.0b013e31820b07ab.
38. *Madukar P., Sotgiu G.* Diagnostics for latent TB infection: incremental, not transformative progress. European Respiratory Journal 2016 Mar; 47 (3): 704–706. doi: 10.1183/13993003.01910-2015.
39. *Latorre I., Martínez-Lacasa X., Font R. et al.* IFN-γ response on T-cell based assays in HIV-infected patients for detection of tuberculosis infection. BMC Infect. Dis. 2010; 10: 348. Published 2010 Dec 10. doi: 10.1186/1471-2334-10-348.

Поступила в редакцию 26.04.2021 г.

Сведения об авторах:

Бородулина Елена Александровна — доктор медицинских наук, профессор, заведующая кафедрой фтизиатрии и пульмонологии Самарского государственного медицинского университета; 443099, Самара, Пионерская ул., д. 48; e-mail: borodulinbe@yandex.ru; ORCID 0000-0002-3063-1538; SPIN-код: 9770-5890, Author ID: 651365;
Кудлай Дмитрий Анатольевич — доктор медицинских наук, ведущий научный сотрудник лаборатории персонализированной медицины и молекулярной иммунологии Государственного научного центра «Институт иммунологии» Федерального медико-биологического агентства; 115522, Москва, Каширское шоссе, д. 24; профессор кафедры фармакологии Института фармации Первого Московского государственного медицинского университета им. И.М. Сеченова Минздрава России (Сеченовского Университета); 119991, Москва, Трубецкая ул., д. 8, стр. 2; e-mail: D624254@gmail.com; ORCID 0000-0003-1878-4467; SPIN-код: 4129-7880, Author ID: 921055;
Власова Богуслава Божидарова — студентка кафедры фтизиатрии и пульмонологии Самарского государственного медицинского университета; 443099, г. Самара, Чапаевская ул., д. 89; e-mail: boguslava.vlasova@mail.ru; ORCID 0000-0001-8618-5373;
Кузнецова Алена Николаевна — аспирант кафедры фтизиатрии и пульмонологии Самарского государственного медицинского университета; 443099, г. Самара, Пионерская ул., д. 48; e-mail: alena-suetina@mail.ru; ORCID 0000-0001-7634-0106; SPIN-код: 6331-3600, Author ID: 1037619.