Marija Laban[1], Maja Omčikus[1,2], Marina Đikić[3],
Filip Marković[1], Sead Dalifi[1]

LATENTNA TUBERKULOZA – NAJČEŠĆE DILEME ILI KO JE TRAŽIO QUANTIFERON?

Sažetak: Usled sve šire upotrebe imunosupresivne, posebno biološke terapije i epidemije HIV-a, a usled aktivacije latentne tuberkuloze (LTBI), ova, pomalo zaboravljena bolest u zapadnom svetu postaje poslednjih godina veoma aktuelna. Postoji veliki broj kategorija bolesnika koje treba testirati na latentnu tuberkulozu, PPD ili IGRA testovima. Tumačenje ovih testova je veoma delikatno jer se na osnovu njega donosi odluka o sprovođenju terapije latentne tuberkuloze, odnosno hemioprofilaksi. Poslednje dve godine, u toku pandemije kovid-19, ogroman procenat pacijenata primao je visoke doze kortikosteroidne i druge imunosupresivne terapije, te je neophodno u narednom periodu razmišljati i o potencijalnim rizicima koje bi ovi bolesnici mogli imati, u smislu obolevanja od tuberkuloze i potencijalno sprovesti testiranje na LTBI.

Uvod

Mycobacterium tuberculosis (MTB) je uzročnik tuberkuloze (TB) koji preživljava jedino kod čoveka kao domaćina. Gotovo trećina svetske populacije zaražena je bacilom tuberkuloze. Od TB u svetu godišnje oboli oko 10, a umre oko 2 miliona ljudi. Smatra se da je od TB do sada umrlo više ljudi nego od bilo koje druge infektivne bolesti. Tuberkuloza je najčešći uzrok smrti mladih između 15–49 godina u svetu. Otkrićem antituberkulotika sredinom prošlog veka tuberkuloza postaje izlečiva bolest (1). Danas u Evropi zemlje bivšeg SSSR-a imaju najvišu incidencu TB (100/100.000) usled rasplamsavanja epidemije HIV-a. Zbog opšte zdravstvene opasnosti, posebno u siromašnim i zemljama u razvoju, Svetska zdravstvena organizacija je predložila strategiju DOTS (Directly Observed Treatment Short Course), koja podrazumeva lečenje TB prema kratkotrajnom režimu (6 meseci) i pod stalnim nadzorom uzimanja

[1] Marija Laban Lazović, Klinika za pulmologiju, Univerzitetski klinički centar Srbije, e mail: marija.labanlazovic@gmail.com

[2] Medicinski fakultet, Univerzitet u Beogradu

[3] Urgentni centar, Univerzitetski klinički centar Srbije, Beograd

lekova (2). DOTS strategiju Svetska banka je proglasila najisplativijom investicijom u oblasti zdravstva do sada. Veoma ozbiljan problem u sprečavanju širenja i lečenju TB jeste pojava bacila rezistentnog na lekove. MDR TB (multi-drug resistant TB) je najteža forma tuberkuloze koja se teško i dugotrajno leči, a najčešće je posledica neodgovarajuće primene osnovnih antituberkulotskih lekova. Usled sve šire upotrebe imunosupresivne, posebno biološke terapije i epidemije HIV-a dolazi do aktivacije latentne tuberkuloze (LTBI) i ova, pomalo zaboravljena bolest u zapadnom svetu postaje poslednjih godina ponovo veoma aktuelna.

PPD/IGRA testovi

U cilju potvrde latentne tuberkuloze (LTBI) koriste se i tuberkulinski test (PPD) i specifični imuno- testovi – tzv. IGRA testovi (*Interferon-Gamma Release Assays, Quantiferon*) (3). PPD je jedan od retkih *in vivo* testova koji je stvoren u 19. veku i još uvek je u aktivnoj upotrebi. Predstavlja reakciju kasnog tipa preosetljivosti na koži. Interpretaciju rezultata PPD testa prate brojne kontroverze. Na rezultat testa mogu uticati stanje stresa, alergije, druge infekcije, bolesti limfnih organa, primena kortikosteroida i drugih imunosupresiva i skorašnja infekcija MTB. Rezultat testa tumači se prema veličini induracije na mestu aplikacije tuberkulina 72 h od injekcije, ne posmatra se veličina eritema. Osnovna mana PPD testova je česta pojava lažno negativnih (HIV/AIDS status, primena imunosupresivnih lekova, malnutricija, bolesti limfnih organa) i lažno pozitivnih nalaza (BCG vakcinacija, netuberkulotske mikobakterioze (NTMB)), kao i subjektivnost testa. Do 2001, kada je odobrena upotreba Quantiferona, PPD je bio jedini test za detekciju latentne tuberkuloze. IGRA testovi su zasnovani na imunoenzimskoj ELISA metodi koja detektuje otpuštanje interferona gama (IF gamma) iz T limfocita u svežoj heparinizovanoj krvi senzibilisanih osoba (4). Postoje dve generacije IGRA testova: ”Quantiferon TB Gold“ i ”T- SPOT.TB“. Quantiferon TB Gold, koji je u upotrebi u našoj zemlji, meri stvaranje IF gamma nakon inkubacije ispitivanog uzorka krvi (16–24h) sa kompleksom specifičnih antigena M. tuberculosis ELISA tehnikom. Njime se mere ćelijski posredovane imunološke reakcije na antigene koji simuliraju mikobakterijske proteine. Zbog svoje specifičnosti IGRA test je pouzdaniji pokazatelj prisustva latentne tuberkulozne infekcije od tuberkulinskog kožnog testa. Pozitivan IGRA test nije sam po sebi dokaz aktivne tuberkuloze, a latentna tuberkuloza kao forma infekcije može u tom obliku perzistirati čitavog života. Samo se 10% osoba inficiranih MBT u toku života razboli, od čega polovina u prve dve godine nakon infekcije. Oko 90% zaraženih osoba ostaje u fazi latentne infekcije.

IGRA ili Quantiferon test je savremena dijagnostička metoda, sa senzitivnošću i specifičnošću od 98%, po mnogim kriterijumima preciznija od tuberkulinskog testa. Pouzdan je i kod vakcinisanih BCG vakcinom i kod imunokompromitovanih.

Quantiferon test, kao ni PPD, ne može razlikovati aktivnu od latentne TB. Negativni Quantiferon test ne isključuje aktivnu TB, skoro ¼ bolesnika sa aktivnom TB ima negativni IGRA test. Razlike PPD i IGRA testa su u načinu izvođenja (PPD *in vivo,* IGRA *in vitro*), objektivnosti tumačenja (PPD subjektivan), brzini dobijanja rezultata (PPD 72h, IGRA 24h) i broju poseta lekaru (za PPD test – dve, za IGRA test – jedna poseta lekaru). SZO ne preporučuje sprovođenje IGRA testa nakon PPD, ukoliko je PPD pozitivan u zemljama sa niskom i umerenom incidencom TB. Pozitivni IGRA test može, mada retko, označavati i infekciju netuberkulotskim mikobakterijama.

U dijagnozi latentne tuberkuloze u našoj zemlji koristi se Quantiferon TB Gold zbog velikog procenta besežirane populacije, iako smernice nalažu da se oba testa mogu koristiti sa istim nivoom pouzdanosti. Ukoliko je nalaz IGRA testa neodređen, a to je najčešće kod imunosuprimiranih ili imunokompromitovanih pacijenata, nema svrhe ponavljati ga. U tom slučaju se LTBI može dokazati samo PPD-om. Quantiferon može biti lažno pozitivan ukoliko se učini tri dana posle PPD-a, te i o tome treba voditi računa.

Aktivna i latentna tuberkuloza

Između aktivne i latentne tuberkuloze postoje bitne razlike. Aktivna TB podrazumeva razmnožavanje bacila tuberkuloze i razvoj aktivne zarazne bolesti, bolesnik ima simptome, patološki radiografski nalaz i pozitivnu mikroskopiju, MGIT i/ili Levenštajn kulturu ili patohistološki nalaz tkiva. Latentna tuberkuloza (LTBI) označava stanje nakon infekcije MBT, gde bacil tuberkuloze miruje i ne razmnožava se. Osoba koja ima LTBI je zaražena, ali ima kompetentan imunski sistem koji sprečava razvoj bolesti, nema simptome, ne postoje radiografske promene u plućima, a uzročnik se ne može dokazati metodom mikobakteriološke kultivacije ili biopsijom. Osoba sa LTBI ne može inficirati druge osobe. Još uvek nije poznato od čega zavisi trajanje latentnog oblika infekcije, kao ni na koji način MTB godinama u inficiranoj osobi živi pritajen i neaktivan. Ipak, uzročnik se iz stanja mirovanja može aktivirati, te osobe sa LTBI imaju povišen rizik od razvoja aktivne postprimarne TB. Aktivacija latentne TB zavisi od virulencije uzročnika, ali mnogo više od stanja domaćina i njegovog imunološkog sistema. Bolesti i stanja kod kojih je olakšan proces aktivacije LTBI su stanja sniženog imuniteta, HIV/ AIDS, primena imunosupresivne terapije (npr. kortikosteroida u dozi od 15mg/dan duže od dve do četiri nedelje), stanja nakon transplantacija organa, maligniteti, bubrežna insuficijencija, posebno bolesnici na hemodijalizi, diabetes mellitus, neuhranjene osobe, kontakti sa osobom koja ima aktivnu TB. Bolesnici koji godinama koriste kortikosteroidnu terapiju, metotreksat, azatioprin, antimalarike, endoksan, ciklosporin, sulfasalazin već samom svojom bolešću su imunokompromitovani. Latentna tuberkuloza je teška za detekciju kod imunosuprimiranih bolesnika (5).

Biološka terapija

Savremena biološka terapija, koja je poslednjih godina standard i prva linija lečenja za mnoge bolesti, kao što su reumatski artritis, ankilozirajući spondilitis, ulcerozni kolitis, Kronova bolest, sistemske bolesti, predstavlja poseban faktor rizika za razvoj aktivne tuberkuloze, najpre putem aktivacije latentne. Zbog toga ovi bolesnici moraju biti redovno evaluirani u smislu procene rizika za LTBI, uz sprovođenje određenih dijagnostičkih metoda i testova u određenim vremenskim intervalima (Rtg snimak pluća, PPD ili IGRA test).

Duže od 15 godina, koliko se primenjuju, jedan od najznačajnijih faktora koji dovodi do reaktivacije latentne tuberkuloze jeste primena lekova iz grupe inhibitora TNF alfa. Inhibitori TNF alfa su vrsta imunomodulatornih bioloških lekova koji se primenjuju kod određenih zapaljenskih i autoimunih bolesti, kao što su reumatski artritis, ankilozirajući spondilitis, psorijaza i inflamatorne bolesti creva. Imunomodularni biološki lekovi imaju sposobnost da menjaju imuni odgovor, a jedno od glavnih neželjenih dejstava njihove primene je povećana sklonost ka infekcijama – pre svega tuberkulozi.

Ovu grupu lekova čine:

1. anti-TNF lekovi (etanercept, infliksimab, adalimumab, certozilumab),
2. antagonisti IL 1 receptora (anakinra),
3. antagonisti IL 6 receptora (tocilizumab),
4. blokatori CD 20 (rituximab),
5. blokatori kostimulatornih signala (abatacept).

Od svih ovih lekova za razvoj aktivne i reaktivaciju LTBI najveći rizik predstavlja upotreba anti-TNF terapije, u okviru koje razlikujemo dve podgrupe lekova:

1. monoklonska antitela koja se vezuju za TNF –„MABOVI“ (infliksimab, adalimumab),
2. fuzioni proteini – „CEPTOVI“ (etanercept).

MABOVI izazivaju znatno veću učestalost razvoja tuberkuloze od CEPTOVA. Tuberkuloza nastaje veoma brzo nakon upotrebe anti-TNF terapije i to, pre svega, kod upotrebe MABOVA (imfliksimab, adalimumab), u odnosu na CEPTOVE (etanercept). U slučaju infliximaba TB nastaje oko 90 dana nakon započinjanja upotrebe biološkog leka, što govori da je, najpre, reč o aktivaciji LTBI, a veliki broj osoba kod kojih se ovaj proces dešava je već ranije lečen od tuberkuloze (6). Zbog toga svi pacijenti pre započinjanja anti-TNF terapije moraju biti pažljivo sagledani da bi se sprečila reaktivacija latentne ili razvoj tuberkuloze primenom hemoprofilakse. Ukratko, bolesnici sa autoimunim ili hroničnim zapaljenskim bolestima koji se moraju lečiti biološkim lekovima, a pre svega antagonistima TNF alfa, imaju povišen rizik od TB i to uglavnom mehanizmom reaktivacije latentne TB infekcije (7). Rituximab, kao blokator CD20 receptora, ima značajno niži potencijal za razvoj LTBI u odnosu na druge vrste biološke terapije (8).

Koga treba testirati na LTBI?

Na LTBI treba testirati osobe u bliskom kontaktu sa aktivnom TB, povremenom kontaktu sa visokozaraznom TB, zdravstvene radnike sa rizikom, HIV pozitivne, obolele od AIDS-a, osobe koje imaju patološki nalaz na radiografiji grudnog koša sa apikalnim fibronodularnim promenama tipičnim za bolovale od TB ili silikoze, bolesnike na terapiji inhibitorima TNF alfa ili dugotrajnoj kortikosteroidnoj terapiji (duže od dve do četiri nedelje u dozi od 15 mg/dan), osobe na hemodijalizi (9,10,11). Rutinsko sistematsko testiranje na LTBI kod osoba sa DM, alkoholičara, pušača i pothranjenih se ne preporučuje (3).

Kod bolesnika koji su već lečeni kompletnim režimom zbog aktivne TB nije neophodno primenjivati hemoprofilaksu, osim kada postoji jasan podatak o mogućoj reinfekciji – bliski pouzdan kontakt sa osobom koja je direktno pozitivna i/ili ima aktivnu plućnu TB (12). Ukoliko postoji radiografija grudnog koša sa tipičnim sekvelama ranije lečenog specifičnog procesa u gornjim plućnim poljima neophodno je testiranje na aktivnu TB, najpre mikobakteriološkim metodama kultivacije. Tek nakon odluke pulmologa o isključivanju aktivne tuberkuloze započinje se hemioprofilaksa. Ukoliko na radiografiji grudnog koša postoje fibrozne promene koje mogu ukazivati da postoji spontano izlečeni specifični proces, što se najčešće registruje u gornjim plućnim poljima i plućnim vrhovima indikovano je primeniti terapiju za LTBI. Prisustvo malih kalcifikata u plućnom parenhimu ne zahteva hemoprofilaksu. Ove preporuke odnose se na one kod kojih je u planu primena biološke terapije, a ne na pacijente imunokompromitovane iz drugih razloga (hemoterapijom, diabetes mellitusom, dužom primenom kortikosteroida).

Hemioprofilaksa

Režim hemioprofilakse najčešće podrazumeva šest ili, ređe, devet meseci primene izonijazida. Drugi mogući režim podrazumeva hemioprofilaksu sa dva leka – izonijazid i rifampicin u trajanju od 3 meseca, što se nešto teže podnosi, ali sa dobrim odgovorom. Ista hemioprofilaksa odnosi se i na HIV + pacijente. Neke od poslednjih studija donose zaključke da je i tretman koji podrazumeva četiri meseca primene samo rifampicina podjednako efikasan, bezbedan i jeftiniji od tromesečne kombinacije rifampicin – izonijazid, te da se može primenjivati kao adekvatna, jeftinija i jednostavnija terapija (13). Nakon hemioprofilakse ne preporučuje se kontrola Quantiferona, tj. ne proverava se „da li je LTBI izlečena".

Pacijenti na biološkoj terapiji moraju da budu redovno kontrolisani na tuberkulozu, u intervalima od 6 meseci, dok bolesnike na anti-TNF terapiji treba kontrolisati na tri meseca (3). Biološka terapija može se uvesti već nakon mesec dana od započinjanja hemioprofilakse i u daljem toku obe terapije primenjuju se paralelno. U slučaju da kod

pacijenta dođe do razvoja TB dok je na biološkoj terapiji, ona se odmah isključuje i rade se testovi rezistencije na MTB. Po završetku lečenja TB ili LTBI biološki lek bi trebalo zameniti. Ako je tuberkuloza aktivna, a biološki lek se mora što pre započeti, uvodi se neposredno po završetku inicijalne faze lečenja. Kod 10–15% pacijenata sa pozitivnim Quantiferon testom naknadnim ispitivanjima bude potvrđena aktivna tuberkuloza. Aktivna tuberkuloza se, posebno kod visokorizičnih grupa i pacijenata na biološkoj terapiji, može razviti i nakon kompletno sprovedene hemioprofilakse.

Zaključak

Prevencija aktivne TB putem prepoznavanja LTBI i hemioprofilakse je osnovna komponenta strategije Svetske zdravstvene organizacije za eliminaciju tuberkuloze (2). Masovna populaciona ispitivanja na LTBI nisu moguća iz ekonomskih i tehničkih razloga, ali je značaj otkrivanja LTBI u rizičnim grupama izuzetno veliki. U današnjim okolnostima smatra se da je rizik od obolevanja od aktivne TB smanjen upravo zahvaljujući otkrivanju i lečenju latentne tuberkuloze. U budućim godinama pokazaće se da li je na procenat LTBI ili aktivne TB uticala neracionalna upotreba kortikosteroida i drugih imunosupresiva, kao i ostalih lekova primenjivanih tokom pandemije kovid-19 i da li će detekcija LTBI i hemioprofilaksa u tim kategorijama biti neophodna.

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Marija Laban[1], Maja Omčikus[1,2], Marina Đikić[3],
Filip Marković[1], Sead Dalifi[1]

LATENT TUBERCULOSIS – MOST COMMON DILEMMAS OR WHO ASKED FOR QUANTIFERON?

Abstract: Due to the increasing use of immunosuppressants, particularly biological therapy, as well as HIV epidemics, latent tuberculosis (LTBI) is being activated, and this disease, which had been rather forgotten in the Western world, is becoming a topical issue in the recent years. Numerous categories of patients should be tested for latent tuberculosis, using PPD or IGRA tests. Interpreting test results is a very touchy issue, since it is the way to determine therapy of latent TB, that is, to decide on chemoprophylaxis. For the last two years, during the Covid-19 pandemics, large percentage of patients received high doses of corticosteroid and other types of immunosuppressant therapies, and it is therefore necessary to consider the potential risks for these patients, in terms of contracting tuberculosis and perhaps testing them for LTBI.

Introduction

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (MTB), which survives only in human hosts. Annually around 10 million people get TB, and approximately 2 million die. It is believed that TB has killed more people than any other infectious disease. Tuberculosis is the world's most common cause of death among young persons aged 15–49. Discovery of anti-TB drugs in the mid-twentieth century made TB a curable disease (1**)**. The highest incidence of TB in contemporary Europe is in former USSR countries (100/100.000), because of the progression of HIV epidemics. Since it is a general health hazard, World Health Organization recommended, especially in poor and developing countries, DOTS (Directly Observed Treatment Short Course) strategy, i.e. short regimen (6 months) TB treatment under direct observation of taking medicines **(**2). World Bank has declared DOTS strategy the most cost-effective health

[1] Marija Laban, Clinic for Pulmonology, University Clinical Center of Serbia, Belgrade, e mail: marija.labanlazovic@gmail.com

[2] Faculty of Medicine, University of Belgrade

[3] Emergency Center, University Clinical Center of Serbia, Belgrade

investment ever. A very serious threat to prevention of spreading and treatment of TB is posed by occurrence of a drug resistant bacillus. MDR TB (multi-drug resistant TB) is the most severe form of tuberculosis, difficult to treat and requiring long lasting therapy, and most often is the consequence of inadequate use of basic anti-TB drugs. Due to increasing and more and more widespread use of immunosuppressants, particularly biological therapy, and HIV epidemics, latent tuberculosis (LTBI), this rather forgotten disease in the Western world, has been reactivated in the recent years.

PPD/ IGRA Tests

Both PPD tuberculosis test and specific immune-tests – so called IGRA tests (*Interferon-Gamma Release Assays, Quantiferon*) are used to confirm latent tuberculosis (LTBI) (3). PPD is one of the few *in vivo* tests created in XIX century that has been actively used ever since. It represents a reaction of late skin hypersensitivity. Interpretation of PPD test results is very controversial. Results can be affected by stress, anergy, other infections, lymph node diseases, use of corticosteroids and other immunosuppressants, as well as recent MTB infection. Test results are interpreted depending on induration at the site of tuberculin application 72 hours after injection, not by the size of erythema. Main flaws of PPD tests are that they often have false negative (due to HIV/AIDS status, use of immunosuppressants, malnutrition, lymphatic organ diseases) and false positive results (BCG vaccination, non-tuberculous mycobacterioses (NTMB)), as well as test subjectivity. Until 2001, when the use of Quantiferon was approved, PPD was the only test for detection of latent tuberculosis. IGRA tests are based on enzyme-linked immunosorbent assay, ELISA, which detects release of interferon gamma (IF gamma) from T lymphocytes in fresh, heparinized blood of sensitized persons (4). There are two generations of IGRA tests: "Quantiferon TB Gold" and "T- SPOT.TB". Quantiferon TB Gold, used in our country, measures release of IF gamma after incubation of examined blood specimen (16–24h) with complex of specific M. tuberculosis antigens using ELISA technique. It measures cell mediated immunological responses to antigens which simulate mycobacterial proteins. Due to its specificity, IGRA test is more reliable indicator of latent TB infection than tuberculosis skin test. Positive IGRA test does not itself prove the presence of active tuberculosis, and latent tuberculosis as a form of infection can persist as latent whole life long. Only 10% of persons infected with MBT get sick in some point of their lives, and half of them within the first two years of getting infected. Approximately 90% of infected persons remain in the stage of latent infection.

IGRA or Quantiferon test is a contemporary diagnostic method, with sensitivity and specificity of 98%, more precise than tuberculosis test by many criteria. It is reliable for BCG vaccinated and immunocompromised persons. Neither Quantiferon nor PPD test can distinguish active from latent TB. Negative Quantiferon test does not

exclude active TB, and almost fourth of patients with active TB have negative IGRA test results. PPD and IGRA tests differ in the way they are performed (PPD *in vivo*, IGRA *in vitro*), objectivity of interpretation (PPD is subjective), speed of obtaining results (PPD takes 72 hours, while IGRA takes 24 hours), and number of visits to doctors (for PPD test a patient has to see the doctor twice, and for IGRA once). WHO does not recommend IGRA test after PPD in case of positive PPD results in patients in countries with low and moderate TB incidence. Positive IGRA test results may, although rarely, indicate infection of non-tuberculous mycobacteria.

Quantiferon TB Gold is used in diagnostics of latent TB in our county, due to high percent of BCG vaccinated population, even though the guidelines state that both tests can be used with the same level of reliability. If IGRA test result is inconclusive, and most commonly it is the case in immunosuppressed or immunocompromised patients, there is no point in repeated testing. In that case, LTBI can be proven only by a PPD test. It should also be taken into account that Quantiferon may give false positive results if performed three days after PPD.

Active and Latent Tuberculosis

There are essential differences between active and latent tuberculosis. Active TB involves reproduction of bacillus of tuberculosis and development of active infectious disease, symptomatic patient, pathological radiographic findings and positive microscopy, MGIT and/or Loewenstein culture or pathohystological tissue findings. Latent tuberculosis (LTBI) is a condition after MBT infection where TB bacillus is inactive and does not reproduce. A person with LTBI is infected, but has a competent immune system that prevents development of the disease, exhibiting no symptoms, with no radiographic pulmonary changes, and the cause cannot be proven by methods of mycobacterial cultivation or biopsy. A person with LBTI cannot infect others. It is still unknown what determines the duration of latent form of infection, as well as how MTB manages to persist covertly and inactively for years in an infected person. However, it can get activated, and therefore persons with LTBI have higher risk of developing active post-primary TB. Activation of latent TB does depend on virulence of its cause, but much more on the condition of host and his/her immune system. Diseases and conditions favorable to process of activation of LTBI include conditions of weakened immunity, HIV/AIDS, use of immunosuppressant therapy (e.g. corticosteroids in doses of 15 mg a day longer than two to four weeks), conditions after organ transplants, malignancies, kidney insufficiency, particularly hemodialysis patients, patients with diabetes mellitus, suffering from malnutrition, in contact with person with active TB etc. If using corticosteroids, metotrexate, azatioprin, antimalaric drugs, endoxan, cyclosporine, and sulfasalazine for years, patients are already

suffering from diseases that make them immunocompromised. Latent TB is difficult to detect in immunosuppressed patients (5).

Biological Therapy

Contemporary biological therapy, which has recently become the standard and first line treatment in many diseases, such as rheumatic arthritis, ankylosing spondylitis, ulcerous colitis, Crohn's disease, systemic diseases, represents a special risk factor for development of active tuberculosis, primarily by activating latent TB. Therefore, patients receiving biological therapy have to be regularly evaluated in terms of assessment of LTBI risk, including diagnostic methods and tests in regular time intervals (lung X-ray, PPD or IGRA test).

Ever since being used, which is for over 15 years already, drugs belonging to the group of TNF alpha inhibitors have been among most important factors contributing to reactivation of latent TB. TNF alpha inhibitors are a kind of immunomodulatory biological medicines used for certain inflammatory and autoimmune diseases, such as rheumatic arthritis, ankylosing spondylitis, psoriasis and inflammatory bowel disease. Immunomodulatory biological medicines are able to change immune response, and one of their major unwanted effects is increased susceptibility to infections – above all, to tuberculosis.

This group of medicines includes:

1. anti TNF drugs (etanercept, infliximab, adalimumab, certozilumab),
2. IL 1 receptor antagonists (anakinra),
3. IL 6 receptor antagonists (tocilizumab),
4. anti-CD 20 blocker (rituximab),
5. costimulation signal blockers (abatacept).

Out of all these drugs, the greatest risk for development of active TB and reactivation of LTBI comes from the use of anti-TNF therapy, which consists of two subcategories of medicines:

1. monoclonal TNF binding antibodies – "MABOVI" (infliximab, adalimumab),
2. fusion proteins – „CEPTOVI" (etanercept).

MABOVI cause significantly higher incidence of TB than CEPTOVA. Tuberculosis is developed rather quickly after the use of anti-TNF therapy, before all, after the use of MABOVA (imfliximab, adalimumab), less with CEPTOVA (etanercept). In case of infliximab, TB develops around 90 days after the start of treatment, which indicates it is mostly the activation of LTBI, and many affected patients had already been treated for tuberculosis previously (6). Therefore, before starting anti-TNF therapy all patients must be carefully examined, in order to prevent reactivation of latent TB or development of TB with chemoprophylaxis. Shortly put, patients with

autoimmune or chronic inflammatory disease who must receive biological therapy, first of all TNF alpha antagonists, are at higher risk of TB, mostly through the mechanism of reactivation of latent TB infection (7). Rituximab, as blocker of CD20 receptor, has significantly lower potential for development of LTBI in comparison to other types of biological therapy (8).

Who Should Be Tested for LTBI?

We should test all persons in close contacts with active TB patients or in casual contact with highly contagious TB, health personnel at risk, HIV positive and persons with AIDS, everyone with pathological chest X-ray findings, with apical fibronodular changes typical for TB or silicosis, patients receiving TNF alpha inhibitors or long lasting corticosteroid therapies (receiving 15 or more mg a day longer than two to four weeks), and hemodialysis patients (9,10,11). Routine systematic testing for LTBI of persons with DM, alcoholics, smokers and malnourished persons is not recommended (3).

In patients who had already received complete regimen treatment due to active TB, it is not necessary to use chemoprophylaxis, except in case of clear indication of possible reinfection – through close contacts with person being directly positive and/or having active lung TB (12). If chest X-ray reveals typical sequelae of previously treated specific process in upper lungs, it is necessary to perform testing for active TB, first using mycobacterial methods of cultivation. Only after a pulmonologist excludes the possibility of active TB, chemoprophylaxis may be started with. If chest X-ray shows fibrous changes that could indicate spontaneously healed specific process, which is most commonly registered in upper lobes and apices, it is indicated to administer therapy against LTBI. Presence of small calcifications in lung parenchyma does not require chemoprophylaxis. These recommendations apply to all cases where biological therapy is planned, not to patients immunocompromised due to other causes (chemotherapy, diabetes mellitus, prolonged use of corticosteroids).

Chemoprophylaxis

Chemoprophylaxis regimen most often includes taking isoniazid for six, or less often, nine months. Another possible regimen consists of chemoprophylaxis of using two drugs – isoniazid and rifampicin for 3 months, which is harder to tolerate but provides good therapeutic response. The same chemoprophylaxis applies to HIV+ patients. Some of the recent studies conclude that even the treatment of four months of using rifampicin only is equally efficient, safe and cheaper than rifampicin-isoniazid combination for three months, so it can be used as adequate, cheaper and simpler

treatment (13). Quantiferon is not recommended after the chemoprophylaxis, i.e. there is no need to check "whether LTBI has been cured".

Patients receiving biological therapy must have regular check-ups for tuberculosis, every six months, while patients receiving anti TNF treatment should be checked every three months (3). Biological therapy may begin already a month after starting chemoprophylaxis and further on both therapies may be used parallelly. In case that a patient develops TB while on biological therapy, it should be stopped immediately and tests of resistance to MTB are to be performed. After completing TB or LTBI treatment, biological drug should be switched. If TB is active, and biological treatment is to be started with as soon as possible, it is to be introduced just after completing initial treatment phase. In 10 to 15% of patients with positive Quantiferon test results, later examinations turn out to confirm active tuberculosis. Especially in high-risk groups and patients receiving biological therapy, active tuberculosis may develop even after fully completed chemoprophylaxis.

Conclusion

Prevention of active TB through recognition of LTBI and chemoprophylaxis is the main component of World Health Organization Strategy for Elimination of Tuberculosis (2). Mass check-ups of population for LTBI are impossible due to economic and technical reasons, but it is vital to diagnose LTBI within groups at risk. Under present circumstances it is considered that risk of developing active TB has been decreased exactly because of diagnostics and treatment of latent tuberculosis. Future will show whether the percentage of LTBI or active TB will be affected by irrational use of corticosteroids and other immunosuppresants, as well as other drugs used during the Covid-19 pandemics, and whether detecting LTBI and chemoprophylaxis would be necessary among these categories of patients.

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