Marija Laban Lazović[1] Ana Blanka[1] Tatjana Adžić-Vukičević[1,2]
Marina Đikić[3] Nikola Trboljevac[1]

RAZLIČITI OBLICI INFEKCIJE MIKOBAKTERIJAMA KOD BOLESNIKA NA ANTI-TNF TERAPIJI – PRIKAZI BOLESNIKA

Sažetak: Biološka terapija, koja uključuje antagoniste TNF alfa koristi se u lečenju autoimunih bolesti preko 20 godina. Zbog blokade T celularnog imuniteta i blokade efekta medijatora TNF-alfa bolesnici na ovoj terapiji imaju povišen rizik od razvoja infekcija bacilom tuberkuloze ili nekom od netuberkulotskih mikobakterija. I tuberkuloza i druge mikobakterioze mogu se razviti u bilo kom trenutku kod bolesnika koji su bilo kada u svom životu koristili ove lekove, čak i nakon prve injekcije. Najčešće je reč o aktivaciji latentne tuberkuloze, što se dokazuje određenim skrining testovima. IGRA testovi (QuantiFERON TB GOLD i T-SPOT.TB) su značajno senzitivniji i specifičniji u imunosuprimiranoj populaciji bolesnika u odnosu na tuberkulinski test (PPD). Postoje savremene preporuke za dijagnostiku, praćenje, hemoprofilaksu i lečenje latentne i aktivne tuberkuloze kod odraslih i dece kod kojih se planira ili je u toku primena antagonista TNF alfa. Prevencija aktivne tuberkuloze putem dijagnostike latentne i sprovođenje hemoprofilakse jesu ključna komponenta strategije Svetske zdravstvene organizacije za eradikaciju tuberkuloze (End TB Strategy).

Ključne reči: tuberkuloza, antagonisti TNF alfa, IGRA test, hemoprofilaksa

Uvod

Tumor necrosis factor-alfa (TNF-alfa), interleukin 12 (IL 12) i interferon gama (IF gamma) su najznačajniji medijatori koji učestvuju u zaštiti od intracelularnih infekcija, posebno mikobakterijama. Najvažniji među njima, TNF-alfa, ima ključnu ulogu

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

[2] Medicinski fakultet, Univerzitet Beograd

[3] Urgentni centar, Univerzitetski klinički centar Srbije

u inflamatornoj reakciji i formiranju granuloma. Više od dvadeset godina u terapiji brojnih autoimunih bolesti, pre svega reumatskog i psorijaznog artritisa, ulceroznog kolitisa i Kronove bolesti, primenjuju se biološki lekovi, među kojima i antagonisti TNF-alfa. Ova vrsta lekova najčešće se primenjuje nakon neuspeha kortikosteroidne ili druge imunosupresivne terapije. Zbog blokade T celularnog imuniteta i blokade efekta medijatora TNF-alfa bolesnici na ovoj terapiji imaju povišen rizik od razvoja infekcija bacilom tuberkuloze ili nekom od netuberkulotskih mikobakterija (1). Dužina primene antagonista TNF-alfa nije važna za nastanak infekcije. I tuberkuloza (TB) i druge mikobakterioze (NTMB) mogu se razviti u bilo kom trenutku kod bolesnika koji su bilo kada u svom životu koristili ove lekove, čak i nakon prve injekcije (2). Najčešće je reč o aktivaciji latentne tuberkuloze (LTBI), što se dokazuje određenim skrining testovima (3). Osim plućne, veoma se često viđa ekstrapulmonalna tuberkuloza u vidu tuberkuloznog limfadenitisa, pleuritisa i peritonitisa, kao i oblici milijarne tuberkuloze, posebno kod primene infliksimaba (2). Tegobe kod infekcije mikobakterijama često nisu klasične respiratorne, već opšte – zamor, preznojavanje i febrilnost, i ne smeju se povezivati sa osnovnim oboljenjem, utoliko pre što primena bioloških lekova efikasno smanjuje tegobe osnovnog oboljenja. Postoje savremene preporuke za dijagnostiku, praćenje, hemioprofilaksu i lečenje latentne i aktivne tuberkuloze kod odraslih i dece kod kojih se planira uvođenje antagonista TNF-alfa ili su već na ovoj terapiji (4).

Prikazi slučajeva

Prikazujemo slučajeve troje bolesnika lečenih u Klinici za pulmologiju KCS koji su bili na biološkoj terapiji antagonistima TNF-alfa, a kod kojih su se razvili različiti oblici infekcije mikobakterijama.

Prvi slučaj

Bolesnica T. D., 60 godina, medicinska sestra, prevedena iz Klinike za infektivne i tropske bolesti KCS gde je mesec dana hospitalno ispitivana i lečena zbog nejasnog febrilnog stanja. Reč je o bolesnici koja se od svoje 20. godine lečila zbog psorijaze i psorijaznog artritisa koji se razvio nakon primene vakcine protiv velikih boginja. Lečena je nesteroidnim antiinflamatornim lekovima do svoje 58. godine, nije prihvatala predloženu imunosupresivnu terapiju, ali jeste samoinicijativno i često koristila ampule depo-preparata kortikosteroida („Diprofos“). Zbog progresije bolova u zglobovima u daljem toku bolesti šest meseci je primala metotrexat, ali bez efekta i uz izražena neželjena dejstva u vidu oticanja potkolenica. Lek je isključen, a bolesnica je pristala na biološku terapiju antagonistima TNF-alfa (infliksimab, preparat „Remicade“). Prvu

injekciju je dobro podnela. Nakon primene druge injekcije (dve nedelje nakon prve doze) dolazi do razvoja visoke telesne temperature do 40c praćene jezom, drhtavicom i malaksalošću. Nisu bile prisutne respiratorne tegobe. U Klinici za infektivne i tropske bolesti KCS sprovedena je detaljna dijagnostika i isključeni su bakterijski i virusni uzroci povišene telesne temperature na koje se posumnjalo. Proširene imunološke analize, hormonski status štitaste žlezde i tumorski markeri bili su uredni. Na PA radiografiji grudnog koša verifikovani su fibrozno izmenjeni voluminozni hilusi, a na skeneru grudnog koša obostrane, difuzne mikronodularne milijarne promene u plućnom parenhimu. U ličnoj anamnezi navela je arterijsku hipertenziju, bila je pušač.

Pri prijemu u Kliniku za pulmologiju KCS bolesnica izrazito bleda, febrilna, 38,8c, lako dispnoična, acijanotična, hemodinamski stabilna, racilne osteomuskularne građe, sa urednim fizikalnim nalazom nad srcem i plućima. Pregledom dominiraju uvećana, meka supraklavikularna limfna žlezda desno, sa eritemom na koži iznad, kožne psorijatične promene i ulnarne devijacije prstiju šaka i stopala. U laboratorijskim analizama verifikuje se izražen zapaljenski sindrom (SE 100, CRP 100) i mikrocitna anemija (HGB 81, MCV 75, Fe 3), a u gasnim analizama – hipoksija (PO2 8,5 Kpa). U sputumu i bronhoaspiratu nisu uočeni acidoalkoholo-rezistentni bacili (ARB), a Levenštajn kulture (LOW K) sputuma, aspirata, krvi i urina ostale su negativne. Urinokulture, hemokulture, bakteriološke kulture sputuma i bronhoaspirata bile su sterilne, a proširene virusološke analize (uključujući HIV) negativne. Tuberkulinski kožni test (PPD) bio je izrazito buran, pozitivan. Ultrazvukom abdomena konstatovana je hepatosplenomegalija. Biopsijom supraklavikularne limfne žlezde dobijen je patohistološki nalaz granulomatoznog limfadenitisa, ***Lymphadenitis granulomatosa vs Tuberculosis caseoproductiva***. Bronhoskopski nalaz odgovarao je inflamaciji, a patohistološki nalaz transbronhijalne biopsije bio je nespecifičan (”bronchitis chronica“). Po pristizanju patohistološkog nalaza biopsije žlezde, ali i zbog radiografskog nalaza milijarne TB, uvedena je četvorna antituberkulotska terapija (H-Isoniazid 300mg, R-Rifampicin 600mg, Z-Pyrazinamid 1200mg i E-Etambutol 1200mg). Bolesnica je terapiju dobro podnosila uz uredne laboratorijske analize, brzu korekciju zapaljenskog sindroma i anemije i kliničko poboljšanje. Ambulantno lečenje nastavljeno je u Gradskom zavodu za bolesti pluća u Beogradu, sa preporukom za ukupno trajanje terapije od šest meseci, prema režimu za vanplućnu i milijarnu tuberkulozu (dva meseca HRZE, četiri meseca HR). Lečenje je sprovedeno uz velike napore patronažne službe, s obzirom na to da bolesnica nije bila raspoložena za redovne kontrole, nije se javljala na telefonske pozive i nije bila redovno dostupna patronažnoj službi. Nakon nešto više od 7 meseci od početka antituberkulotske terapije lečenje je zvanično završeno kompletnom radiografskom regresijom i potpunim povlačenjem uvećane supraklavikularne limfne žlezde, a bolesnica je odjavljena kao izlečena. Nisu poznati podaci o daljem tretmanu psorijaze i psorijaznog artritisa.

Drugi slučaj

Bolesnica A. S., 43 godine, prvi put je hospitalizovana u Klinici za pulmologiju KCS kada je, pod sumnjom na milijarnu tuberkulozu, prevedena iz Klinike za gastroenterohepatologiju KCS, gde je lečena zbog Kronove bolesti unazad tri godine. Dijagnoza Kronove bolesti postavljena je biopsijom tankog creva, kada je tokom rutinske holecistektomije verifikovan konglomerat uvećanih limfnih žlezda na nivou terminalnog ileuma i postojanje entero-enteralne fistule. Učinjena je resekcija terminalnog ileuma sa formiranjem ileocekalne anastomoze. Lečenje Kronove bolesti započeto je mesalazinom i holestiraminom, sa efektom kratkotrajne remisije bolesti. U daljem toku lečenje je nastavljeno kortikosteroidima i imunosupresivima, ali su se, i pored primenjene terapije, znaci bolesti održavali na anastomozi. Klinički su dominirale naizmenične dijareje i subokluzivne smetnje. Nastavak tretmana podrazumevao je biološku terapiju antigonistima TNF-alfa (infliksimab, preparat "Remicade"). Prve dve injekcije bolesnica je dobro podnela i gastrointestinalne tegobe bile su značajno umanjene. Međutim, nakon treće injekcije (6 nedelja nakon prve terapije) došlo je do pojave visoke telesne temperature do 40c, jeze, drhtavice, preznojavanja i izražene malaksalosti. Bolesnica nije imala respiratorne tegobe. Kolonoskopijom i ezofagogastroduodenoskopijom isključena je reaktivacija Kronove bolesti. Ultrazvuk abdomena bio je uredan. Na radiografiji grudnog koša, koja je na ranijim pregledima bila uredna, verifikovane su obostrane difuzne mikronodularne milijarne senke. Skenerom grudnog koša potvrđene su milijarne parenhimske plućne promene, hilara i medijastinalna limfadenopatija i desnostrani pleuralni izliv. Najveći konglomerat limfnih žlezda bio je subkarinealno – 33x30mm. U ličnoj anamnezi bolesnica je negirala hronične bolesti, izuzev depresivnog sindroma, i bila je pušač.

Pri prijemu u Kliniku za pulmologiju KCS bolesnica febrilna 38,5c, bleda, eupnoična u miru, acijanotična, bez periferne limfadenopatije, izrazito depresivnog raspoloženja. Fizikalni nalaz nad srcem i plućima bio je uredan. U laboratorijskim analizama verifikovani su povišeni parametri zapaljenja (CRP 168, SE 64) i blaga mikrocitna anemija (Hgb 102, MCV 80). Nije bilo poremećaja gasne ramene u arterijskoj krvi. U sputumu i bronhoaspiratu nisu viđeni acidoalkoholo-rezistentni bacili, a Levenštajn kulture sputuma bronhoaspirata, urina i krvi ostale su negativne. Virusološke i proširene imunološke analize, kao i hormonski status štitaste žlezde bili su uredni. Bronhoskopski je verifikovana proširena centralna karina, te je učinjena transkarinealna biopsija. Patohistološki nalaz bio je nespecifičan ("bronchitis chronica"). Na osnovu faktora rizika, kliničke slike, radiografskog i CT nalaza odlučeno je da se, pod sumnjom na milijarnu tuberkulozu, započne četvorna antituberkulotska terapija (H – Isoniazid 300mg, R-Rifampicin 600mg, Z-Pyrazinamid 1200mg, E-Etambutol 1200mg). Bolesnica je terapiju dobro podnosila. Na prvoj kontroli posle dva meseca, nakon inicijalne faze lečenja, konstatuje se značajna regresija parenhimskih

plućnih promena, a do kraja šestomesečnog antituberkulotskog tretmana i potpuna regresija svih promena. Produžena faza lečenja trajala je standardno četiri meseca uz primenu dva leka (H 300mg, R 600mg), nakon čega je šestomesečno lečenje tuberkuloze proglašeno završenim i bolesnica je odjavljena. Inače, paralelno sa terapijom tuberkuloze bolesnica je koristila imunosupresivnu terapiju (azatioprin) prema savetu gastroenterologa. Međutim, samo mesec dana po završetku antituberkulotske terapije ponovo se javljaju opšte tegobe, među kojima dominira visoka febrilnost. Učinjena je evaluacija osnovne bolesti creva i isključena je reaktivacija. Na skeneru grudnog koša i abdomena verifikuju se *de novo* medijastinalna limfadenopatija, uvećana supraklavikularna limfna žlezda sa desne strane i splenomegalija, što je konstatovano i fizikalnim pregledom. Lečenje Kronove bolesti nastavljeno je ponovnom primenom mesalazina, a azatioprin je isključen. Učinjena je biopsija supraklavikularne limfne žlezde. Patohistološki nalaz potvrdio je granulomatozni specifični limfadenitis (***Lymhadenitis granulomatosa vs Tuberculosis fibrocaseosa***). U laboratorijskim analizama registrovan je manji porast parametara zapaljenja, a na radiografiji grudnog koša proširena senka gornjeg medijastinuma na račun medijastinalne limfadenopatije, bez parenhimskih promena u plućima. Nakon detaljnog hematološkog ispitivanja nije bilo elemenata za limfoproliferativno oboljenje. Nije ponavljano bronhološko ispitivanje. Dobijeno je i drugo mišljenje patologa vezano za preparat sa operacije creva, čime je definitivno potvrđena Kronova bolest i isključena tuberkuloza creva. Započeta je antituberkulostatska terapija prema režimu ponovnog lečenja (H 300mg, R 600mg, E 1200mg, Z 1200mg i S-Streptomycin 1g (im)). Paralelno je primenjivana terapija mesalazinom. Ambulantno lečenje tuberkuloze nastavljeno je preko Gradskog zavoda za bolesti pluća prema režimu 2 meseca HRZES, 1 mesec HRZE, 5 meseci HRE. Kliničko stanje bolesnice bilo je sve vreme dobro, bez respiratornih i gastrointestinalnih tegoba i bez limfadenopatije. Lečenje tuberkuloze uspešno je završeno nakon osam meseci. Bolesnica je odjavljena, nakon čega je obavila još nekoliko rutinskih pulmoloških kontrola na kojima nisu verifikovane nove plućne promene, a kontrolne Levenštajn kulture bile su negativne.

Treći slučaj

Bolesnik K. D., 60 godina, 15 godina lečen zbog seropozitivnog reumatskog artritisa (RA) kortikosteroidima i metotrexatom, poslednje dve godine lečenja na biološkoj terapiji lekom iz grupe antagonista TNF-alfa (etanercept, preparat „Enbrel“). Bolovao je i od hronične opstrukcijske bolesti pluća. Pulmološko ispitivanje započeto je zbog prolongiranog kašlja, gušenja, noćnog preznojavanja i bolova u rukama i ramenima. Obostrano u regiji spoljašnje strane nadlaktica i ramena (regija m. deltoideusa) godinu dana su perzistirale čvrste lividne egzulcerisane tumefakcije koje nisu zarastale i pored intenzivne antibiotske terapije primenjivane ambulantno i u bolničkim

uslovima. Uzrok kožnih promena nije utvrđen uprkos ponavljanom bakteriološkom i mikološkom ispitivanju. Biopsija promena nije rađena. Na PA radiografiji grudnog koša verifikovan je sistem svetlina u donjem desnom plućnom polju, a na skeneru grudnog koša, sa posebnim osvrtom na kosti ramena, opisane su fibronodularne i kavitarne promene u donjim režnjevima oba pluća, kao i mekotkivne tumefakcije lateralno od oba humerusa uz eroziju glavica i efuzija oba ramena zgloba. Ambulantno ostavljeni sputumi bili su direktno negativni na acidoalkoholo-rezistentne bacile, a iz samo jedne Levenštajn kulture sputuma identifikovan je Mycobacterium xenopi. Bolesnik je hospitalizovan u Klinici za pulmologiju KCS zbog respiratornih tegoba, pogoršanja reumatološke bolesti i nalaza kulture sputuma.

Pri prijemu bolesnik veoma teško samostalno pokretan zbog reumatskog artritisa, afebrilan, dispnoičan, cijanotičan, bled, hemodinamski stabilan. Nad plućima auskultacijski registrovani inspirijumski pukoti nad bazama pluća, nad srcem je nalaz bio uredan. Verifikovani izraženi deformiteti po tipu ulnarenih devijacija na svim ekstremitetima, a u deltoidnim regijama egzulceisane tumefakcije promera do 10x10cm, iz kojih je secernirao serohemoragični sadržaj. Laboratorijske analize pokazale su ubrzanu SE (86) i blagu normocitnu anemiju (HGB 100, MCV 82), svi ostali parametri, uključujući i CRP, bili su u referentnom opsegu. Virusološke analize, uključujući HIV, bile su negativne. Od osam sputuma ostavljenih za analizu u Klinici za pulmologiju, u šest je kulturom i identifikacijom dokazan Mycobacterium xenopi u broju od preko 200 kolonija po sputumu. U tri sputuma direktno su dokazani ARB. Bris rane i kultura sadržaja tumefakcija bakteriološki i mikološki bili su sterilni. Levenštajn kulture sadržaja tumefakcija ostale su negativne nakon osam nedelja. Incizijom promene u regiji desnog m. deltoideusa dobijen je patohistološki nalaz kazeozne nekroze.

U skladu sa preporukama Američkog torakalnog društva (ATS), lečenje je započeto sa dva antituberkulotika (rifampicin, etambutol) i makrolidom (klaritromicin). S obzirom na to da je M. xenopi ambulantno identifikovan samo u jednoj Levenštajn kulturi sputuma, a zbog mogućnosti da je na osnovu pozitivnih direktnih mikroskopija mogla biti reč i o infekciji uzrokovanoj bacilom tuberkuloze, do pristizanja Levenštajn kultura sputuma ostavljenih tokom hospitalizacije, u terapiju su uvedeni i izonijazid i pirazinamid. Plan je podrazumevao korekciju terapije po pristizanju identifikacije uzročnika. Bolesnik je sve vreme imao izražene bolove u ekstremitetima i kičmi, te su tokom hospitalizacije, u dogovoru sa reumatologom, primenjivani i parenteralni kortikosteroidi i analgetici. Bolesnik je otpušten na kućno lečenje, a mesec i po dana od započinjanja terapije mikobakterioze,došlo je do izraženog kliničkog pogoršanja praćenog gušenjem. Bolesnik je istog dana ponovo primljen u Kliniku za pulmologiju, gde je nakon nekoliko sati preminuo. Nalaz kliničke obdukcije pokazao je da je uzrok smrti specifično oboljenje pluća – apscedirajuća granulomatozna pneumonija, dok je nalaz na srcu ukazao na granulomatozni miokarditis. U dodatnom komentaru

obducenta navodi se da je reč o diseminovanoj formi infekcije mikobakterijom M. xenopi, što je prvi potvrđeni slučaj letalnog ishoda od diseminovane mikobakterioze u našoj zemlji.

Diskusija

Kroz tri različita primera prikazali smo komplikacije primene anti-TNF terapije u vidu ozbiljnih infekcija mikobakterijama – slučajeve pojave dve forme tuberkuloze – milijarne i TB limfadenitisa kod bolesnica na terapiji infliksimabom i slučaj diseminovane mikobakterioze sa smrtnim ishodom kod bolesnika na etanerceptu.

Infliksimab je najpotentniji antagonist TNF-alfa, sa visokim rizikom od obolevanja od tuberkuloze, najpre kao posledice postojanja latentne TB u zemljama sa visokom i umerenom prokuženošću bacilom tuberkuloze, kao što je naša (2). Antagonisti TNF-alfa su lekovi koji se primenjuju u terapiji reumatskog i psorijaznog artritisa, psorijaze, Kronove bolesti i ulceroznog kolitisa, najčešće nakon neuspeha kortikosteroidne i imunosupresivne terapije i usled rezistencije bolesti (5). Blokadom efekta medijatora TNF-alfa remeti se njegova ključna uloga u sprečavanju tuberkuloze i infekcija netuberkulotskim mikobakterijama. Efekat na simptome osnovne bolesti je značajan, ali je rizik od infekcije mikobakterijama veliki i postoji uvek, bez obzira na vreme započinjanja ili prekida primanja biološke terapije. Slično visok rizik postoji i za adalimumab. Infliksimab i adalimumab pripadaju grupi „mabova“, monoklonskih antitela koja se vezuju direktno za TNF-alfa (6). Etanercept pripada grupi „ceptova“, fuzionih proteina koji spajaju solubilni receptor za TNF i konstantni kraj IgG1 antitela. Tuberkuloza nastaje vrlo brzo od početka terapije antagonistima TNF-alfa. Kod upotrebe infliksimaba u skoro polovini slučajeva tuberkuloza se javlja u prvih 90 dana (12 nedelja) od početka njegove primene, što ukazuje da je najverovatnije reč o reaktivaciji LTBI (7). TB infekcija udružena sa primenom etanercepta nastaje ređe i kasnije u odnosu na infliksimab i adalimumab. Forme infekcije mikobakterijama su različite. Najčešća je plućna tuberkuloza, ali nisu retke ekstrapulmonalne forme, milijarna plućna ili generalizovana tuberkuloza, kao i infekcije netuberkulotskim mikobakterijama (NTMB), na koje se retko pomisli (8). Rizik prve bolesnice, osim upotrebe infliksimaba, bila je i nekontrolisana upotreba depo preparata kortikosteroida koji se i danas često primenjuju zbog brzog i dobrog efekta na smanjenje reumatskih tegoba, najčešće samoinicijativno od strane bolesnika, a bez preporuke i nadzora lekara. Kod druge bolesnice takođe je najpre reč o reaktivaciji LTBI pod terapijom infliksimabom. Kod ove bolesnice potpuno je ispoštovana dužina i način lečenja milijarne TB (2 HRZE, 4 HR – ukupno 6 meseci). Za kasniji razvoj TB limfadenitisa dodatni faktor rizika bila je primena imunosupresivne terapije istovremeno sa antituberkuloticima, što je bilo neophodno zbog aktivne Kronove bolesti. Azatioprin je, ipak, isključen čim se pojavila sumnja na recidiv TB. Treći je do sada kod nas nezabeleženi slučaj

smrtnog ishoda HIV negativnog bolesnika zbog diseminovane infekcije Mycobacterium xenopi koji je bio na terapiji etanerceptom. Kao što je već naglašeno, primena etanercepta je značajno ređe udružena sa pojavom TB u odnosu na infliksimab, a infekcije netuberkulotskim mikobakterijama, posebno u generalizovanoj formi, u praksi su retke (9). Sva tri bolesnika, inače HIV negativna, inicijalno su bila na dugotrajnoj imunosupresivnoj terapiji, a zbog rezistencije bolesti ili neželjenih efekata uvedena je anti-TNF terapija (10). Kod svih bolesnika dominirale su opšte tegobe, a infekcija nakon upotrebe antagonista TNF-alfa razvila se brzo i burno.

Zbog toga je u većini zemalja uveden skrining i terapija latentne tuberkuloze (LTBI) pre započinjanja biološke terapije, pre svega lekovima iz grupe antagonista TNF-alfa, a u cilju smanjenja incidence aktivne TB kod ovih bolesnika. Odstupanje od metoda skrininga radi otkrivanja LTBI i prevencije aktivne TB hemioprofilaksom dovodi do znatno češćeg obolevanja kod bolesnika na anti-TNF terapiji (4). Dakle, ukoliko bolesnik kome treba uvesti anti-TNF terapiju nema simptome koji bi ukazivali na aktivnu TB neophodno je skrining testovima isključiti eventualno postojanje latentne tuberkuloze. Metode za dijagnostiku LTBI su tuberkulinski kožni test (PPD) i IGRA testovi (11). IGRA testovi su oni koji se dominantno preporučuju. Samo njihovom primenom ne mogu se razdvojiti latentna i aktivna TB, ali je ovo jedini način da se izdvoje osobe koje bi imale benefit od hemioprofilakse, kada se sprovedu i druga dopunska ispitivanja. Osoba koja ima LTBI nema simptome bolesti, nije zarazna, ima urednu radiografiju grudnog koša i negativnu direktnu mikroskopiju i Levenštajn kulture, a pozitivne testove PPD i/ ili IGRA. Osoba koja ima aktivnu TB ima manifestnu bolest, izražene simptoma infekcije, zarazna je, PPD ili IGRA su najčešće pozitivni, Rtg snimak pluća je obično patološki, a direktna mikroskopija ili Levenštajn kulture su kod plućne forme obično pozitivni. Lečenje aktivne TB je obavezno. Hemioprofilaksa podrazumeva upotrebu jednog antituberkulotika (Isonijazid 300mg 6–9 meseci), dok drugi režim podrazumeva istovremenu upotrebu dva antituberkulotika (Isoniazid 300 mg, Rifampicin 600mg 3 meseca, što je ređe u upotrebi jer se teže podnosi, ili Rifampicin 600mg 4 meseca).

Nijedan od naša tri pacijenta nije inicijalno imao skrining za LTBI, niti je primao hemioprofilaksu. U vreme kada su započinjali biološku terapiju skrining na LTBI nije bio obavezan kao što je danas. Nesprovođenje hemioprofilakse je osnovni razlog razvoja aktivne TB infekcije kod svih bolesnika. Uvođenjem Smernica za dijagnostiku latentne tuberkuloze, koje je izdala Klinika za pulmologiju KCS i Respiratorno udruženje Srbije obnovljenim 2016. i ažuriranim 2019, ujednačeni su standardi i u pravcu skrininga aktivne i latentne TB pre početka anti-TNF terapije (4). Osim anamneze, fizikalnog pregleda i radiografije grudnog koša, ispitivanja uzoraka na ARB i Levenštajn kulture, neophodni su skrining testovi – tuberkulinski kožni test PPD i/ ili IGRA testovi (QuantiFERON TB GOLD i T-SPOT.TB) koji su značajno senzitivniji i specifičniji u imunosuprimiranoj populaciji bolesnika u odnosu na PPD.

Ključna pitanja u anamnezi tiču se prethodnog lečenja aktivne ili LTBI, postojanja simptoma za aktivnu TB i BCG vakcinacije. Kod bolesnika koji su ranije adekvatno lečeni zbog aktivne TB ne primenjuje se hemioprofilaksa, izuzev ako ne postoji jasan podatak o veoma verovatnoj reinfekciji (4). Anti-TNF terapija može se započeti 4 nedelje nakon hemioprofilakse. Biološka terapija i hemioprofilaksa se u daljem toku primenjuju paralelno. Preporuka je da se pulmološka evaluacija i radiografije grudnog koša kod bolesnika na anti-TNF terapiji sprovode na tri meseca upravo zbog moguće pojave aktivne tuberkuloze. Razvoj TB tokom primene anti-TNF terapije ne može se u potpunosti sprečiti i pored primene hemioprofilakse čija je efikasnost 60–90%. U tom slučaju lečenje aktivne tuberkuloze u punom režimu je obavezno, kao što je obavezno i trenutno obustavljanje anti-TNF terapije. Ukoliko je anti-TNF terapija neophodna, ona se može nastaviti nakon završetka inicijalne faze lečenja TB i to samo ako nije reč o milijarnoj TB. Ipak, najbolje bi bilo antagonIst TNF-alfa zameniti biološkim lekom drugog mehanizma dejstva, kao što su tocilizumab ili rituximab.

Zaključak

Anti-TNF terapija je značajan faktor rizika za nastanak teških, diseminovanih i ekstrapulmonalnih formi tuberkuloze i mikobakterioza. Na TB i mikobakterioze uvek se mora posumnjati kod prolongiranih opštih ili respiratornih tegoba bolesnika na anti-TNF terapiji. Uz poštovanje smernica za skrining i lečenje latentne i aktivne tuberkuloze smanjuje se učestalost obolevanja bolesnika na imunosupresivnoj terapiji, a posebno antagonistima TNF-alfa. IGRA testovi (QuantiFERON i T-SPOT.TB) značajno su senzitivniji i specifičniji u populaciji imunosuprimiranih bolesnika, u odnosu na tuberkulinski test. Izvođenje ovih testova jedini je način da se identifikuju one osobe koje bi imale benefit hemioprofilakse u populaciji asimptomatskih bolesnika pre početka, pre svega, anti-TNF terapije (12). Kod postojanja aktivne TB anti-TNF terapija je kontraindikovana, a kod potvrđene LTBI sprovodi se hemioprofilaksa. Prevencija aktivne tuberkuloze putem otkrivanja LTBI i primene hemioprofilakse je ključna komponenta strategije Svetske zdravstvene organizacije za eliminaciju TB (End TB Strategy).

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Marija Laban Lazović[1] Ana Blanka[1] Tatjana Adžić-Vukičević[1,2]
Marina Đikić[3] Nikola Trboljevac[1]

DIFFERENT FORMS OF MYCOBACTERIAL INFECTIONS IN PATIENTS RECEIVING ANTI-TNF THERAPY – CASE REPORTS

Abstract: Biological agents, including TNF-alpha antagonists, have been used in treatment of autoimmune diseases for over 20 years. Due to impaired T-cell immunity and blocked effects of TNF-alpha mediator, patients receiving this therapy have increased risk of developing tuberculosis or other non-tuberculous mycobacterial infections. Both tuberculosis and other mycobacterial infections may occur anytime in patients who have ever used these medicines, even after the first injection. Most often we see activation of latent tuberculosis confirmed by screening tests. IGRA tests (QuantiFERON and T-SPOT.TB) are significantly more sensitive and specific for testing population of immunosuppressed patients, in comparison to tuberculosis skin test. There are contemporary recommendations for diagnosing, monitoring, chemoprophylaxis and treatment of latent and active tuberculosis in adults and children in case of planning administration of TNF-alpha antagonists or in cases when these drugs have already been used. Prevention of active tuberculosis via diagnosing LTBI and use of chemoprophylaxis is the crucial component of the strategy of World Health Organization for elimination of TB (End TB Strategy).

Key words: tuberculosis, TNF-alpha antagonists, IGRA test, chemoprophylaxis

Introduction

Tumor necrosis factor- alpha (TNF- alpha), interleukin 12 (IL 12) and interferon gamma (IF gamma) are the most significant mediators taking part in protection from

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

[2] Faculty of Medicine, University of Belgrade

[3] Emergency Center, University Clinical Center of Serbia

intracellular infections, particularly mycobacterial infections. The most important among them is TNF-alpha, playing crucial role in the inflammatory response and granuloma formation. Biological agents, including TNF-alpha antagonists, have been used in treatment of autoimmune diseases, above all for treatment of rheumatoid and psoriatic arthritis, ulcerative colitis and Crohn`s disease, for over 20 years. This kind of agents is mostly used after the failure of corticosteroids or other immunosuppressant drugs. Due to impaired T-cell immunity and blocked effects of TNF-alpha mediator, patients receiving this therapy have increased risk of developing tuberculosis or other non-tuberculous mycobacterial infections (1). Duration of anti-TNF-alpha therapy is of no relevance for developing infections. Both tuberculosis (TB) and other mycobacterial infections (NTMB) may occur anytime in patients who have ever used these medicines, even after the first injection (2). Most often we see activation of latent tuberculosis (LTBI), confirmed by screening tests (3). Beside pulmonary, very often we see extrapulmonary tuberculosis in form of tuberculous lymphadenitis, pleuritis and peritonitis, as well as forms of miliary tuberculosis, particularly with use of infliximab (2). Mycobacterial infections often do not cause expected respiratory problems, but generalized difficulties such as fatigue, sweating and fever, and must not be related to the primary disease, especially because biological agents efficiently alleviate symptoms of primary disease. There are contemporary recommendations for diagnosing, monitoring, chemoprophylaxis and treatment of latent and active tuberculosis in adults and children in case of planning administration of TNF-alpha antagonists or in cases when these drugs have already been used (4).

Presentation of cases

We will present the cases of three patients treated at the Clinic for Pulmonology of the Clinical Center of Serbia, who received biological therapy of TNF-alpha antagonists and developed different forms of mycobacterial infections.

Case 1

Female, T. D., 60 years old, a nurse, transferred from the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, where she was examined and treated for a month because of fever of unknown origin. After the vaccine against smallpox, at the age of 20, she developed psoriasis and psoriatic arthritis and ever since received different therapies. Until the age of 58 she was refusing suggested immunosuppressant therapy and was treated with non-steroid anti-inflammatory drugs, but did use, frequently and on her own, corticosteroid depot ampoules ”Diprofos“). Due to progressive joint pain, she received metotrexat for 6 months, but with no effect

and with pronounced side effect of lower legs swelling. Therefore, this treatment has stopped and she agreed to receive biological therapy of TNF-alpha antagonists (infliximab – ”Remicade“). First injection she tolerated well. After the second one (two weeks after the first dose), she developed high fever, up to 40°C, with chills, shivering and malaise. There were no respiratory symptoms. Detailed diagnostics were completed at the Clinic for Infectious and Tropical Diseases CCS, which excluded suspected bacterial and viral causes of fever. Additional immunological analyses, thyroid tests and tumor markers showed no irregularities. PA radiography verified fibrous changes of voluminous hilums, and thoracic CT showed bilateral, diffuse, micronodular miliar changes of the lung parenchyma. The anamnesis of this patient included arterial hypertension and smoking.

When admitted to the Clinic for Pulmonology of the Clinical Center of Serbia, she was very pale, with temperature of 38,8°C, mild dyspnea, without cyanosis, hemodynamically stable, of gracile osteomuscular constitution, with regular physical findings of heart and lungs. Examination revealed enlarged, soft supraclavicular lymph node on the right, and skin erythema above psoriatic changes and ulnar deviations of hands and feet. Laboratory findings verified severe inflammatory syndrome (SE 100, CRP 100) and microcytic anemia (HGB 81, MCV 75, Fe 3), while gas analysis showed hypoxia (PO2 8,5 Kpa). Acido-alcohol resistant bacillus (ARB) was not found in sputum and bronchial aspirate, and Loewenstein cultures (LOW K) of sputum, aspirate, blood and urine remained negative. Urine culture, blood culture and sputum and bronchial aspirate bacteriological cultures were sterile, and broader virological tests (including HIV) were negative. Tuberculosis skin test (PPD) triggered pronounced positive reaction. Abdominal ultrasound showed hepatosplenomegaly. Biopsy of supraclavicular lymph node led to pathohystological finding of granulomatous lymphadenitis ***Lymphadenitis granulomatosa vs. Tuberculosis caseoproductiva***. Bronchoscopic finding indicated inflammation, while pathohystological finding of transbronchial biopsy was non-specific (”bronchitis chronica“). After pathohystological finding in the biopsied lymph node, but also due to radiographic finding of miliary RB, anti-TB therapy was introduced (H- Isoniazid 300mg, R-Rifampicin 600mg, Z- Pyrazinamid 1200mg and E- Etambutol 1200mg). Patient tolerated this therapy well, with good laboratory findings, fast improvement of inflammatory syndrome, anemia and clinical improvement as well. Outpatient treatment was continued at the City Institute for Pulmonary Diseases in Belgrade, with the recommendation of administering therapy for 6 months, according to the protocol for extrapulmonary and miliary tuberculosis (two months of HRZE, four months HR). Treatment was completed with special efforts of home-care personnel, since the patient was in no mood for regular check-ups, nor did she respond to phone calls and attempts of home-care service to reach her. A bit over 7 months after the beginning of anti-TB therapy, treatment was officially over, with the complete radiographic regression and reduction of the previously enlarged

supraclavicular lymph node, and the patient was discharged as cured. We have no knowledge on further treatment of psoriasis and psoriatic arthritis.

Case 2

Patient A. S., age 43, admitted to the Clinic for Pulmonology of the Clinical Center of Serbia for the first time when she was transferred, due to suspected miliary tuberculosis, from the Clinic for Gastroenterology and Hepatology of the Clinical Center of Serbia, where she was treated for 3 years already for Crohn`s disease. Diagnosis of Crohn`s disease was reached by small intestine biopsy, when during routine cholecystectomy a conglomerate of enlarged lymph nodes was found at the level of terminal ileum, as well as entero-enteral fistula. Resection of terminal ileum was performed, with ileocecal anastomosis. Treatment of Crohn`s disease began with mesalazine and colestyramin, leading to short-term remission of the disease. In further treatment were used corticosteroids and immunosuppressant's, but despite the therapy, symptoms of the disease persisted on anostomosis. Prevailing clinical features were alternating diarrhea and suboclusive disorders. Next step in treatment was biological therapy of TNF-alpha antagonists (infliximab – "Remicade"). Patient tolerated initial two injections well, and gastrointestinal discomfort was significantly reduced. But after the third injection (6 weeks after the first), she developed fever up to 40°C, with chills, shivering, sweating and extreme malaise. There were no respiratory difficulties. Colonoscopy and esophagogastroduodenoscopy eliminated reactivation of Crohn`s disease. Abdominal ultrasound was regular. Chest radiography, which showed no changes before, verified bilateral diffuse micronodular miliary shadows. Thoracic CT confirmed miliary changes of lung parenchyma, hilar and mediastinal lymphadenopathy, and pleural effusion on the right side. The largest lymph node conglomerate was subcarinal – 33x30 mm. In her anamnesis the patient denied having any chronic disease, except for depressive syndrome, and stated she used to smoke.

She was admitted to the Clinic for Pulmonology of the Clinical Center of Serbia with fever of 38.5°C, pale, eupneic at rest, non-cyanotic, with no peripheral lymphadenopathy, and in very depressed mood. Physical findings of heart and lungs were regular. Laboratory findings verified inflammation (CRP 168, SE 64) and mild microcytic anemia (Hgb 102, MCV 80). There were no gas exchange disorders in arterial blood. No acido-alcohol-resistant bacilli were found in sputum and bronchial aspirate, and Loewenstein cultures of sputum, bronchial aspirate, urine and blood were negative. Virological and further immunological analyses, as well as hormonal thyroid analyses were normal. Bronchoscopy verified widening of the main carina and transcarinal biopsy was performed. Pathohystological finding was non-specific ("bronchitis chronica"). Based on the risk factors, clinical picture, radiographic and CT findings, it was decided, due to suspected miliary TB, to begin quadruplet anti-TB

treatment (H – Isoniazid 300mg, R- Rifampicin 600mg, Z- Pyrazinamide 1200mg, E- Ethambutol 1200mg). The therapy was tolerated well. At the first check-up, two months after the therapy started, there was a significant regression of changes of lung parenchyma, and at the end of six-month anti-TB treatment complete regression of all changes was achieved. The continuation phase of treatment lasted for four months, as recommended, and included two drugs (H 300mg, R 600mg). Then this six month treatment was declared completed and patient was discharged. Along with anti-TB therapy, the patient used immunosuppresants (azathioprine) as recommended by gastroenterologist. But only a month after completing anti-TB treatment, general symptoms recurred. Dominant symptom was high temperature. Primary gastrointestinal disease was evaluated and possibility of reactivation was excluded. Thoracic and abdominal CT verified *de novo* lympadenopathy, enlarged supraclavicular lymph node on the right and splenomegaly, which was registered by the physical exam as well. Treatment of Crohn`s disease was continued with mesalazine, again, and without azatioprin. Biopsy of the supraclavicular lymph node was performed. Pathohystological finding confirmed granulomatous specific lymphadenitis ***(Lymhadenitis granulomatosa vs. Tuberculosis fibrocaseosa*)**. Laboratory analyses registered mildly elevated inflammation parameters, and chest radiography showed wider upper mediastinal shadow due to mediastinal lymphadenopathy, with no changes in lung parenchyma. After detailed hematologic examination, nothing pointed toward lymphoproliferative diseases. Bronchologic examination was not repeated. Second opinion of the pathologist was obtained, related to biopsy from intestinal surgery, and it confirmed the diagnosis of Crohn`s disease and excluded intestinal tuberculosis. Anti-TB treatment in accordance to the retreatment regimen was initiated (H 300mg, R 600mg, E 1200mg, Z 1200mg, S- Streptomycin 1g (im)). Along with it the patient received mesazaline. Outpatient treatment of tuberculosis was continued, in accordance with the regimen: two months of HRZES, one month of HRZE, 5months of HRE. Clinical status of the patient was good all along, with no respiratory and no gastrointestinal difficulties, and with no lymphadenopathy. Treatment of tuberculosis lasted for 8 months and was successfully completed. Patient was discharged, had several routine pulmonary check-ups later on, without findings of new pulmonary changes, and follow-up Loewenstein cultures were negative.

Case 3

Patient K. D., aged 60, treated for 15 years for seropositive rheumatoid arthritis (RA) with corticosteroids and metotrexate, and for the last two years receiving biological drug from the group of TNF-alpha antagonists (etanercept – ”Enbrel“). Also suffering from chronic obstructive lung disease. Pulmonary examinations started because of persistent cough, night sweats and painful arms and shoulders. On outer

side of both upper arms and, also bilaterally, in the shoulder region (m. deltoideus), for a whole year he had persistent solid livid exulcerated tumefactions which could not heal despite intense antibiotic therapy he received both outpatient and in hospital. The cause of skin changes was not determined despite repeated bacteriological and mycological analyses. Biopsy was not performed. PA chest radiography verified lighter parts of lower part of the right lung, and thoracic CT, particularly focused on shoulder bones, showed fibronodular and cavitary changes of the lower lobes of both lungs, as well as soft-tissue tumefactions laterally to both humeruses, with erosion of humeral heads and effusion of both shoulder joints. Sputums obtained via outpatient procedures were directly negative for acido-alcohol-resistant bacilli, and only in one Loewenstein culture was identified Mycobacterium xenopi. Due to respiratory difficulties, worsened rheumatological disease and sputum finding, the patient was admitted to the Clinic for Pulmonology, Clinical Center of Serbia.

He was admitted as hardly mobile on his own, due to rheumatoid arthritis, with no fever, dyspneic, cyanotic, pale, hemodynamically stable. Lung auscultation registered inspiratory crackles over lung bases, while heart findings were normal. Severe deformities like ulnar deviations were verified on all extremities, and in deltoid regions were found exulcerated tumefactions up do 10x10cm, with serohemorrhagic secretions. Laboratory analyses found higher SE (86) and mild normocytic anemia (HGB 100, MCV 82), while all other parameters, including CRP, were within referent ranges. Virological analyses, including HIV test, were negative. Out of eight sputums left to be analyzed at the Clinic for Pulmonology, in six was identified Mycobacterium xenopi (over 200 colonies per sputum). In three sputums ARB were directly verified. Wound swab and culture of tumefactions` content were bacteriologically and mycologicaly sterile. Loewenstein cultures of content of tumefactions remained negative after eight weeks. Incision of the change in the region of right deltoid muscle led to pathohystological finding of caseous necrosis.

In accordance with the ATS (American Thoracic Society) guidelines, the treatment began with two anti-TB drugs (rifampicin, ethambutol) and a macrolid (clarithromycin). Since M. xenopi was verified only in one Loewenstein sputum culture taken through outpatient procedure, and because of the possibility that direct positive microscopies reveal infection caused by TB bacillus, while waiting for the results of Loewenstein cultures obtained in hospital, izoniazid and pyrazinamide were also included. The plan was to correct the therapy after identification of the cause. Patient had severe pains in extremities and spine all the time so, in consultations with rheumatologist, he also received parenteral corticosteroids and painkillers. He was discharged, to continue therapy at home, but month and a half after initiation of anti-mycobacterial treatment, his state severely deteriorated, including suffocations. He was instantly readmitted, the same day, to the Clinic for Pulmonology CCS, where he died several hours later. Findings of clinical autopsy determined that cause of death

was a specific disease - granulomatous pneumonia with abscesses, while findings on his heart indicated granulomatous myocarditis. Pathologist noted it was a disseminated form of M. xenopi mycobacterial infection, and that was the first confirmed case of lethal outcome of disseminated mycobacteriosis in our country.

Discussion

Three different cases presented complications of anti-TNF treatment such as severe mycobacterial infections – cases of two forms of TB – miliary and TB lymphadenitis in patients treated with infliximab and a case of disseminated mycobacteriosis with lethal outcome in patient receiving etanercept.

Infliximab is the most potent TNF-alpha antagonist, carrying high risk of tuberculosis, primarily as a consequence of latent TB in countries with high and moderate seroprevalence to tuberculosis, such as Serbia (2). Anti-TNF antagonists are used in treatment of rheumatic and psoriatic arthritis, psoriasis, Crohn`s disease and ulcerative colitis, usually after failure of treatment with corticosteroids and immunosuppressants or because of resistance to these drugs (5). Blocking the effect of TNF-alpha mediators interferes with the crucial role of preventing tuberculosis and infections with non-TB mycobacteria. Efficiency in alleviating symptoms of the primary disease is significant, but the risk of mycobacterial infection is high and always present, regardless of the moment of initiating or discontinuing biological treatment. Similarly, there is high risk when it comes to adalimumab. Infliximab and adalimumab belong to the group of ”mabs“, monoclonal antibodies that bind specifically to TNF-alpha (6). Etanercept belongs to the group of „cepts“, fusion proteins fusing soluble TNF receptor to the constant end of IgG1 antibodies. Tuberculosis develops soon after initiation of therapy with TNF-alpha antagonists. When infliximab is used, almost in half of cases TB occurs within the first 90 days (12 weeks) since the beginning of therapy, which most probably indicates the reactivation of LTBI (7). TB infection following etanercept treatment occurs less often and later on in the treatment in comparison with infliximab and adalimumab. There are different forms of possible mycobacterial infections. Usually it is lung tuberculosis, but extrapulmonary forms, miliary lung or generalized tuberculosis are also common, as well as non-tuberculous mycobacteria (NTMB) – which are rarely suspected (8). Apart from the use of infliximab, the first patient was also at risk because of uncontrolled use of depot corticosteroids which are still often used for their fast and successful alleviation of rheumatic symptoms, and are most often used by patients on their own, with no doctor`s prescription or supervision. In case of second patient it was about LTBI reactivation following infliximab treatment. Duration and protocol of treating miliary TB was fully realized according to guidelines (two months- Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (HRZE) and 4 months -Isoniazid, Rifampicin (HR)- 6 months in total). Additional risk factors

for further development of TB lymphadenitis was the use of immunosuppressant therapy along with anti-TB medication, which was necessary because of the active Crohn`s disease. But azathioprine was excluded as soon as recidivant TB was suspected. Third case, the first registered lethal outcome of disseminated Mycobacterium xenopi infection in HIV negative patient receiving etanercept treatment. As already underlined, use of etanercept carries significantly smaller risk of TB in comparison with infliximab, and non-TB mycobacteria, especially generalized infections, are rarely seen in practice (9). All three patients, otherwise HIV-negative, were initially on long-term immunosuppressive therapy, and due to disease resistance or side effects, anti-TNF therapy was introduced (10). General symptoms were prevalent in all patients, and infections after the use of TNF-alpha antagonists developed quickly and dramatically.

Therefore most countries introduced screening and treatment of latent tuberculosis (LTBI) prior to biological treatment, primarily with drugs belonging to the group of TNF-alpha antagonists, in order to reduce the incidence of active TB in these patients. Lack of screening, for the purpose of identifying LTBI and preventing active TB through chemoprophylaxis, leads to significantly higher incidence of the disease in patients receiving anti-TNF therapy (4). Accordingly, if a patient who should receive anti-TNF therapy has no symptoms indicating active TB, it is necessary to perform screening tests in order to eliminate the possibility of latent TB.

Methods to diagnose LTBI include tuberculosis skin test (PPD) and IGRA tests (11). IGRA tests are most commonly recommended. These tests alone cannot distinguish latent from active TB, but it is the only way to select persons who would benefit from chemoprophylaxis, after performing other additional examinations. A person with LTBI has no symptoms and is not contagious, her chest radiography shows no irregularities, microscopy and Loewenstein cultures are negative, but PPD and/or IGRA tests are positive. A person with active TB has manifested disease, symptoms of infections, is contagious, PPD or IGRA are usually positive, chest x-ray usually shows pathological changes, and direct microscopy or Loewenstein cultures are – in pulmonary forms – usually positive. Treating active TB is compulsory. Chemoprophylaxis includes use of one anti-TB drug (Isoniazid 300mg for 6 to 9 months), but there is also another regimen of simultaneous use of two anti-TB drugs (Isoniazid 300mg, Rifampicin 600mg, for 3 months, which is less often used because it is not tolerated so well or Rifampicin 600mg for 4 months).

None of our three patients underwent LTBI screening initially, nor did they get chemoprophylaxis. At the time their treatments were initiated, LTBI screening was not compulsory, as it is today. Lack of chemoprophylaxis is the main cause of developing active TB infection in all patients. Adoption of Guidelines for Diagnosing Latent Tuberculosis, issued by the Clinic for Pulmonology, Clinical Center of Serbia and Serbian Respiratory Society, updated in 2019, harmonized standards in sense that

screening is recommended both for active and latent TB prior to initiating anti-TNF therapy (4). Apart from anamnesis, physical examination and chest radiography, it is required to test samples to ARB and Loewenstein cultures, and to perform screening tests including tuberculosis skin test PPD and/or IGRA tests (QuantiFERON TB GOLD and T-SPOT.TB) – and latter are significantly more sensitive and specific in case of immunosuppressed patients in comparison with PPD. Crucial questions in anamnesis refer to previous treatments of active or LTBI, symptoms of active TB and BCG vaccination. In patients previously adequately treated for active TB, chemoprohylaxis is not used, except if there are clear indicators of high possibility of reinfection (4). Anti-TNF therapy can start 4 weeks after chemoprophylaxis. Further on, biological therapy and chemoprohylaxis can be used simultaneously. It is recommended for patients using anti-TNF therapy to have pulmonary evaluation and chest radiographies every 3 months, exactly because possible occurrence of active tuberculosis. Developing TB during use of anti-TNF therapy cannot be completely prevented, in spite of use of chemoprophylaxis with 60–90% efficiency. In such cases it is necessary to treat active TB with complete treatment regimen, as well as to discontinue anti-TNF therapy immediately. If anti-TNF treatment is necessary, it can be continued after completing initial phase of TB treatment, but only if it is not the miliary form of TB. But the best would be to replace TNF-alpha antagonist with biological drugs which mechanisms of action are different, such as tocilizumab or rituximab.

Conclusion

Anti-TNF therapy is an important risk factor for developing severe, disseminated and extrapulmonary forms of tuberculosis and mycobacterioses. TB and mycobacterioses must always be suspected in long lasting generalized or respiratory symptoms in patients receiving anti-TNF therapy. Following guidelines for screening and treatment of latent and active tuberculosis reduces frequency of the disease in patients using immunosuppressive therapy, and especially TNF-alpha antagonists. IGRA tests (QuantiFERON and T-SPOT.TB) are significantly more sensitive and specific for testing population of immunosuppressed patients, in comparison to tuberculosis skin test. These tests are the only way to identify patients who would have benefited from the chemoprophylaxis among patients asymptomatic before the initiation of anti-TNF therapy (12). Anti-TNF therapy is contraindicated in cases of active TB and cases of confirmed LTBI require chemoprophylaxis. Prevention of active tuberculosis via diagnosing LTBI and use of chemoprophylaxis is the crucial component of the strategy of World Health Organization for elimination of TB (End TB Strategy).

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