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MAJOR ARTICLE

Association of Tumor Necrosis Factor α Inhibitor Use with Diagnostic Features and Mortality of Tuberculosis in the United States, 2010–2017

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Background. An elevated risk of tuberculosis (TB) disease in persons who have received tumor necrosis factor alpha inhibitor medications (TNF-α inhibitors) has been reported for nearly two decades, but clinical diagnostic features and outcomes of TB in this population remain poorly described.

Methods. We analyzed national surveillance data for TB cases among persons aged 15 years and older reported in the United States during 2010–2017 and associated mortality data reported through 2019 to describe the clinical characteristics of those receiving TNF-α inhibitors.

Results. Of 70 129 TB cases analyzed, 504 (0.7%) of the patients had TNF-α inhibitor use reported at TB diagnosis. Patients with TNF-α inhibitor use at TB diagnosis were more likely than TB patients not receiving TNF-α inhibitors to have TB diagnosed in extrapulmonary sites in conjunction with pulmonary sites (28.8% vs 10.0%, $P < .001$). Patients receiving TNF-α inhibitors were less likely to have acid-fast bacilli noted on sputum smear microscopy (25.6% vs 39.1%, $P = .04$), and more likely to have drug-resistant disease (13.5% vs 10.0%, $P < .001$). TB-attributed deaths did not significantly differ between patients receiving and not receiving TNF-α inhibitors (adjusted odds ratio, 1.46 [95% confidence interval, .95–2.26]).

Conclusions. Clinicians evaluating TNF-α inhibitor–treated patients should have a high index of suspicion for TB and be aware that extrapulmonary or sputum smear–negative TB disease is more common in these patients. No significantly diminished survival of TB patients treated with TNF-α inhibitor therapy before TB diagnosis was noted.

Keywords. biologic; immunocompromised host; mycobacterial disease; tuberculosis; TNF-α inhibitor.

The risk of tuberculosis (TB) disease among persons with exposure to TB or with latent TB infection (LTBI) increases with use of tumor necrosis factor alpha (TNF-α) inhibitors, a class of medications that is widely used in treatment of autoimmune conditions such as rheumatoid arthritis, psoriasis, Crohn disease, and ulcerative colitis. TNF-α is an essential component of host response to mycobacterial diseases, including TB, and is required for regulation of cellular immunity and formation of granulomas [1–3]. Of the TNF-α inhibitors approved for use in the United States (US) during the period covered by this analysis (ie, infliximab, adalimumab, golimumab, etanercept, and certolizumab pegol), infliximab and adalimumab are most associated with increased risk of LTBI progression to TB disease [4, 5], but all classes of TNF-α inhibitors can increase TB risk [1, 5, 6].

Elevated TB incidence in association with use of TNF-α inhibitors has been reported previously [7, 8]. However, the clinical presentation of TB in this context is not well-characterized, and most cohort data come from Asia [9–11], where baseline TB incidence is significantly higher than in the US. In a 2001 US report describing 70 incident cases of TB among patients receiving infliximab, >50% of cases were extrapulmonary, nearly 25% were disseminated, and >15% of patients died [12]. In contrast, a retrospective cohort study using Kaiser Health System data from 2000 to 2008 in the US found that among 16 TB cases in patients using TNF-α inhibitors, 11 (69%) had pulmonary disease only [13]. Although clinical outcomes of TB disease in patients receiving TNF-α inhibitors are not well-described, published data suggest that TB-associated death may be associated with use of immunosuppressive medication [14].

The purpose of this analysis is to describe clinical characteristics of US TB patients who were receiving TNF-α inhibitors at the time of their TB diagnosis, and to assess the relationship

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between use of TNF-α inhibitors and TB-related death. Because of the body of published data, we hypothesized that use of TNF-α inhibitors would be associated with extrapulmonary disease in conjunction with pulmonary disease [15], as compared to pulmonary-only disease, and with increased mortality among TB patients [16].

METHODS

Design and Patient Population

TB is a nationally notifiable condition; verified cases of TB are reported to the Centers for Disease Control and Prevention's (CDC) National Tuberculosis Surveillance System (NTSS) [16]. We analyzed data for all patients with TB aged 15 years and older, reported to NTSS from the 50 states and District of Columbia during 2010–2017, and any associated mortality data on these patients reported through 2019. Data in the NTSS during this period were collected via the Report of Verified Case of Tuberculosis (RVCT) (office of management and budget number 0920-0026), which includes information on patient demographics, TB risk factors, diagnostics, initial drug regimen, and death before or during receipt of TB treatment. The RVCT form was updated in 2009 to include additional risk factors, new drug treatments, and additional diagnostic tests; thus, only reported cases after 2009 were included in this analysis. NTSS data are protected under an Assurance of Confidentiality provided under the authority granted to CDC by Sections 306 and 308(d) of the Public Health Service Act (42 US Code [U.S.C.] 242k and 242m[d]), which prevents disclosure of any information that could be used to identify patients directly or indirectly. This project was determined not to be human subjects research by CDC and did not require approval by an institutional review board because data were collected and analyzed as part of routine public health surveillance.

Exposure and Outcomes

The primary exposure studied was use of TNF-α inhibitor therapy at the time of TB diagnosis. This was documented as a checkbox completed by TB program staff on the RVCT for each TB case under "additional TB risk factors". Covariates of interest assessed at the time of TB diagnosis included age at diagnosis, sex, race/ethnicity, birth outside the US, diabetes, end-stage renal disease (ESRD), human immunodeficiency virus (HIV) infection, excess alcohol use in the past year, drug use (injecting or noninjecting) in the past year, homelessness in the past year, private provider outpatient care, residence in a long-term care institution at the time of diagnosis, residence in a correctional facility at the time of diagnosis, employment status, presence of smear positivity (for both pulmonary disease and extrapulmonary disease), site of TB disease, and presence of first-line drug resistance. Since cavitary pulmonary disease and miliary TB were highly correlated with site of disease, these variables were excluded from logistic regression models. Covariates were chosen based on clinical relevance or previous association with TB-related morbidity or mortality [14].

The primary outcome of this analysis was TB-associated death, before starting TB treatment or during TB treatment. TB-associated death was defined by an RVCT response of (1) "status at TB diagnosis" reported as "dead" with "was TB a cause of death" reported as "yes"; or (2) "reason therapy stopped or never started" reported as "died" and "cause of death" reported as "related to TB disease" or "related to TB therapy." The outcome of death was considered complete for patients reported no later than 2010–2017 since jurisdictions have up to 2 years to submit the follow-up RVCT form (https://www.cdc.gov/tb/statistics/reports/2019/outcomes.htm).

Statistical Analysis

We described baseline characteristics of all patients and of patients with TB-associated deaths, stratified by receipt of TNF-α inhibitors. Both χ^2 tests or Fisher exact tests (when the expected cell size was <5) were used to examine whether unadjusted associations existed between TNF-α inhibitor use and all demographic and clinical risk factors, after exclusion of missing data. We used multiple imputation to impute missing values for the following variables: age at diagnosis, sex, race/ethnicity, birth outside the US, HIV infection, excess alcohol use in the past year, drug use in the past year, homelessness in the past year, employment status, and residence in a correctional facility at the time of diagnosis. The above variables were assumed to be missing at random [17] and the fully conditional specification technique [3] was employed to impute missing values. Five imputed datasets were generated, and point estimates were averaged and standard errors were derived following Rubin's rules [17]. Multiple imputation was only used to input values for missing variables considered to be missing at random. For variables not suspected to be missing at random, including outpatient provider type or smear results, the values for these variables were retained as "missing" in multivariable analyses. Odds ratios and associated 95% confidence intervals (CIs) were calculated to assess unadjusted associations between TNF-α inhibitor use and death. Statistically significant variables at the α level of .05, or those considered clinically relevant, along with TNF-α inhibitor status, were entered into a multivariable model. Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) and associated 95% CIs of factors associated with TB-related death. All statistical analyses were performed using R statistical software [18].

RESULTS

In total, 70 129 TB cases were included in these analyses. Unadjusted results for TB patients by TNF-α inhibitor therapy status are presented in Table 1; missing data are shown in

Table 1. Characteristics of Patients With Tuberculosis by Tumor Necrosis Factor Alpha Inhibitor Therapy Status, United States, 2010–2017 (N = 70 129)[a]

	TNF-α Inhibitor (n = 504)		No TNF-α Inhibitor (n = 69 625)		
Characteristic	No.	(%)	No.	(%)	*P* Value
Age at diagnosis, y					<.001
15–24	21	(4.2)	7786	(11.2)	
25–44	130	(25.8)	23 832	(34.2)	
45–64	207	(41.1)	22 866	(32.8)	
≥65	146	(29.0)	15 134	(21.7)	
Sex					<.001
Female	269	(53.4)	26 981	(38.8)	
Male	235	(46.6)	42 637	(61.2)	
Race					<.001
Asian	206	(41.0)	23 164	(33.3)	
Black	50	(9.9)	15 212	(21.9)	
Hispanic	106	(21.1)	19 649	(28.3)	
Other[b]	9	(1.8)	1784	(2.6)	
White	132	(26.2)	9655	(13.9)	
Place of birth					.30
Non–US born	335	(66.5)	47 807	(68.7)	
US born	169	(33.5)	21 778	(31.3)	
Diabetes					.04
Not reported	434	(86.1)	57 496	(82.6)	
Reported	70	(13.9)	12 129	(17.4)	
End-stage renal disease					.97
Not reported	494	(98)	68 157	(97.9)	
Reported	10	(2)	1468	(2.1)	
HIV status					<.001
HIV negative	426	(99.3)	56 951	(93.4)	
HIV positive	3	(0.7)	4010	(6.6)	
Excess alcohol use past year					<.001
No	488	(97.6)	60 962	(88.7)	
Yes	12	(2.4)	7826	(11.3)	
Drug use past year[c]					<.001
No	493	(98.0)	63 690	(92.6)	
Yes	10	(2.0)	5104	(7.4)	
Homelessness past year[d]					<.001
No	503	(99.8)	65 317	(94.4)	
Yes	1	(0.2)	3851	(5.6)	
Private outpatient provider					<.001
No	311	(61.7)	53 857	(77.5)	
Yes	193	(38.3)	15 661	(22.5)	
Resident long-term care facility[e]					.84
No	496	(98.6)	68 367	(98.4)	
Yes	7	(1.4)	1117	(1.6)	
Resident of corrections facility[f]					<.001
No	501	(99.6)	66 517	(95.8)	
Yes	2	(0.4)	2908	(4.2)	
Employment status					.002
Employed	250	(49.9)	29 100	(42.9)	
Not employed	251	(50.1)	38 676	(57.1)	
Initial sputum smear result					.04
Negative	291	(57.7)	33 970	(48.8)	
Positive	129	(25.6)	27 215	(39.1)	
Not done	84	(16.7)	8403	(12.1)	
Initial smear result, any[g]					.34
Negative	227	(45.0)	31 708	(45.5)	
Positive	271	(53.8)	36 451	(52.4)	
Not done	6	(1.2)	1454	(2.1)	

Table 1. Continued

Characteristic	TNF-α Inhibitor (n = 504)		No TNF-α Inhibitor (n = 69 625)		*P* Value
	No.	(%)	No.	(%)	
Site of TB disease					<.001
Both	145	(28.8)	6949	(10.0)	
Extrapulmonary	140	(27.8)	14 387	(20.7)	
Pulmonary	219	(43.5)	48 261	(69.3)	
Drug resistance[h]					<.001
No	333	(66.1)	47 199	(67.8)	
Yes	68	(13.5)	6941	(10.0)	
Not done	89	(17.7)	13 018	(18.7)	

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; TNF-α, tumor necrosis factor alpha; US, United States.

[a]Includes all TB cases age 15 years or older diagnosed in the US between 2010 and 2017. Percentages may not sum to 100% due to rounding. Missing data for each variable are presented in Supplementary Table 1; column totals for each variable may not sum to total due to missing data. Percentages and *P* values were calculated excluding missing data.

[b]This category includes persons of American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander races, as well as persons of multiple races.

[c]Injection or noninjection drug use within 12 months prior to TB diagnosis.

[d]Homeless within 12 months prior to TB diagnosis.

[e]Resident of long-term institution at time of diagnosis.

[f]Resident of correctional facility at time of diagnosis.

[g]Initial smear result for any available specimen with reported acid-fast bacilli studies, including sputum, body fluid, or tissue.

[h]Presence of resistance to isoniazid, rifampin, pyrazinamide, and/or ethambutol among culture-positive cases with drug susceptibility results.

Supplementary Table 1. Of the TB cases, 504 (0.7%) had TNF-α inhibitor use reported at time of TB diagnosis. Compared to patients not receiving TNF-α inhibitors, those receiving TNF-α inhibitors differed significantly in terms of race ($P < .001$) and age distribution ($P < .001$), and included higher proportions of Asian (41.0% vs 33.3%) and non-Hispanic White patients (26.2% vs 13.9%), patients aged 45–64 years (41.1% vs 32.8%) or ≥65 years (29.0% vs 21.7%), and women (53.4% vs 38.8%, $P < .001$). The proportion of patients born outside the US was similar in the 2 groups (66.5% vs 68.7%, $P = .3$). Compared to those not receiving TNF-α inhibitors, a higher percentage of TB patients receiving TNF-α inhibitors received outpatient TB care from a private healthcare provider (38.3% vs 22.5%, $P < .001$). Other reported sources of outpatient TB care included the public health department, Indian Health Service or tribal health department, hospital only, and correctional or institutional providers. A lower percentage of patients receiving TNF-α inhibitors were non-Hispanic Black (9.9% vs 21.9%) or Hispanic (21.1% vs 28.3%), reported HIV infection (0.7% vs 6.6%, $P < .001$), reported homelessness in the year preceding diagnosis (0.2% vs 5.6%, $P < .001$), or were unemployed (50.1% vs 57.1%, $P = .002$).

In unadjusted analyses (Table 1), site of TB disease varied significantly based on TNF-α inhibitor receipt ($P < .001$), with a greater percentage of patients who received TNF-α inhibitors manifesting disease in both pulmonary and extrapulmonary sites (28.8% vs 10.0%) or extrapulmonary only sites (27.8% vs 20.7%) compared with patients with only pulmonary disease. Patients receiving TNF-α inhibitors were less likely to have acid-fast bacilli (AFB) noted on sputum smear microscopy (25.6% vs 39.1%, $P = .04$). Among TNF-α inhibitor users with sputum specimens collected and examined, more than half were AFB sputum smear negative (291/420 [69.3%]). TB patients with TNF-α inhibitor use were more likely to be diagnosed with drug-resistant disease than patients without reported TNF-α inhibitor use (13.5% vs 10.0%, $P < .001$).

Characteristics of TB patients who had TB-associated deaths are presented in Table 2. After adjustment for confounders, TNF-α inhibitor use was not statistically associated with TB-related death (aOR, 1.46 [95% CI, .95–2.26]). To explore the potential moderating effect of site of TB disease in the relationship between TNF-α inhibitor use and death, an interaction term was estimated, but was not statistically significant and was excluded from the final multivariable model. A small sample size limited our ability to compare characteristics of patients with TB-associated death, based on TNF-α inhibitor use (Table 3).

DISCUSSION

This analysis indicates that over an 8-year period in the US, few TB cases were reported as recipients of TNF-α inhibitor medications, but patients receiving TNF-α inhibitors at diagnosis and had different clinical characteristics from those of the general population of TB patients, with no significantly increased odds of TB-related death among TB patients using TNF-α inhibitors.

We found that more patients receiving TNF-α inhibitors were diagnosed with disseminated TB disease involving both pulmonary and extrapulmonary sites of disease than patients not receiving TNF-α inhibitors. This finding is consistent with most published data [12, 15, 19–23], with the exception of a small (N = 16) US-based cohort study that found most were diagnosed with only pulmonary disease [13]. Our analysis also found that patients with pulmonary TB disease receiving TNF-α inhibitors were more often diagnosed with AFB sputum smear

Table 2. Univariate and Multivariate Analyses of Characteristics Associated With Tuberculosis-Associated Death Among Patients With Tuberculosis, United States, 2010–2017 (n = 69 730)[a]

Characteristic	OR	(95% CI)	*P* Value	aOR	(95% CI)	*P* Value
TNF-α inhibitor therapy						
No	Ref	…		…	…	
Yes	1.54	(1.02–2.32)	.04	1.46	(.95–2.26)	.09
Age at diagnosis, y						
15–24	Ref	…		…	…	
25–44	2.56	(1.79–3.78)	<.01	2.26	(1.78–3.80)	<.01
45–64	7.83	(5.46–11.24)	<.01	6.23	(4.32–8.99)	<.01
≥65	22.18	(15.51–31.71)	<.01	16.14	(11.23–23.22)	<.01
Sex						
Female	Ref	…		…	…	
Male	1.28	(1.17–1.40)	<.01	1.11	(1.00–1.22)	.04
Race/ethnicity						
White	Ref	…		…	…	
Black	0.70	(.61–.80)	<.01	0.95	(.82–1.10)	.48
Asian	0.65	(.57–.74)	<.01	1.13	(.96–1.34)	.15
Hispanic	0.65	(.57–.74)	<.01	1.20	(1.03–1.41)	.02
Other[b]	1.27	(1.01–1.59)	.04	1.56	(1.23–1.99)	<.01
Place of birth						
US-born	Ref	…		…	…	
Non–US born	0.58	(.53–.63)	<.01	0.71	(.61–.82)	<.01
Diabetes						
Not reported	Ref	…		…	…	
Reported	1.89	(1.72–2.08)	<.01	1.10	(.99–1.22)	.08
End-stage renal disease						
Not reported	Ref	…		…	…	
Reported	5.81	(4.99–6.77)	<.01	3.55	(3.00–4.20)	<.01
HIV status						
Negative	Ref	…		…	…	
Positive	1.64	(1.41–1.92)	<.01	2.37	(1.97–2.85)	<.01
Excess alcohol use past year						
No	Ref	…		…	…	
Yes	1.54	(1.37–1.73)	<.01	1.47	(1.27–1.69)	<.01
Drug use past year[c]						
No	Ref	…		…	…	
Yes	0.87	(.73–1.03)	.11	…	…	
Homelessness past year[d]						
No	Ref	…				
Yes	1.25	(1.06–1.48)	<.01	0.92	(.76–1.11)	.38
Private outpatient provider						
No	Ref	…		…	…	
Yes	0.57	(.50–.64)	<.01	0.48	(.42–.54)	<.01
Resident of long-term care facility[e]						
No	Ref	…		…	…	
Yes	6.73	(5.70–7.94)	<.01	3.35	(2.80–4.02)	<.01
Resident of corrections facility[f]						
No	Ref	…		…	…	
Yes	0.25	(.16–.37)	<.01	0.42	(.27–.63)	<.01
Employment status						
Employed	Ref	…		…	…	
Not employed	3.90	(3.48–4.38)	<.01	1.99	(1.74–2.27)	<.01
Initial smear result, any[g]						
Negative	Ref	…		…	…	
Positive	2.17	(1.97–2.39)	<.01	1.74	(1.57–2.93)	<.01
Not done	4.85	(3.61–6.50)	<.01	4.34	(3.14–5.99)	<.01
Site of TB disease						
Pulmonary only	Ref	…		…	…	

Table 2. Continued

Characteristic	OR	(95% CI)	*P* Value	aOR	(95% CI)	*P* Value
Extrapulmonary only	0.53	(.46–.61)	<.01	0.80	(.69–.93)	<.01
Both	1.91	(1.70–2.13)	<.01	1.98	(1.76–2.24)	<.01
Drug resistance[h]						
No	Ref	…		…	…	
Yes	0.94	(.82–1.07)	.36	1.15	(1.00–1.32)	.05
Not done	0.17	(.14–.21)	<.01	0.25	(.20–.31)	<.01

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis; TNF-α, tumor necrosis factor alpha; US, United States.

[a]Includes all TB cases age 15 years or older diagnosed in the US between 2010 and 2017 with confirmed death outcomes, excluding patients with missing information on outpatient provider type or smear result.

[b]This category includes persons of American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander races, as well as persons of multiple races.

[c]Injection or noninjection drug use within 12 months prior to TB diagnosis, not included in multivariate model due to insignificance in the univariate model.

[d]Homeless within 12 months prior to TB diagnosis.

[e]Resident of long-term institution at time of diagnosis.

[f]Resident of correctional facility at time of diagnosis.

[g]Initial smear result for any available specimen with reported acid-fast bacilli studies, including sputum, body fluid, or tissue.

[h]Presence of resistance to isoniazid, rifampin, pyrazinamide, and/or ethambutol among culture-positive cases with drug susceptibility results; included in the multivariate model despite the fact it shows insignificance in the univariate model.

microscopy–negative disease. This could be the result of a pathophysiologic link to treatment with biologics, similar to the presentation of paucibacillary TB disease in immunosuppressed patients with HIV infection [24], who more often have extrapulmonary, smear-negative, and noncavitary disease. This finding could also be related to earlier diagnosis in patients with increased access to specialty private doctors, with TNF-α inhibitor treatment serving as a proxy for the ability to have continuity of medical care with a rheumatologist. It should be noted, however, that initial symptoms of TB disease can mimic an inflammatory disease that a treating clinician may empirically treat with local or systemic immunosuppression, leading to delayed TB diagnosis, and potentially a higher burden of disease outside the lung [12, 25, 26].

The finding of higher resistance to first-line drugs among TB patients treated with TNF-α inhibitors is interesting for clinical management considerations, but the cause of the drug resistance was uncertain, as this database for analysis did not include extensive patient history prior to TB diagnosis, such as prior LTBI treatment and adherence, or risk for contact with other patients with drug-resistant disease.

In our analysis, we did not find a significantly increased risk of TB-related mortality among TNF-α inhibitor users. Published studies comparing TB mortality in TNF-α inhibitor users vs nonusers are limited, and prospective studies are needed. In a single retrospective study of TB mortality by Beavers et al during 2005–2006, multivariable analysis demonstrated that receiving immunosuppressive medications was significantly associated with TB-related deaths; this analysis included patients receiving both prednisone and TNF-α inhibitors [14]. Similar to TB-related mortality associations in our analyses, the Beavers et al study found a TB-related mortality association with smear positivity, drug resistance, HIV, long-term care residence, and age. In a study of TB patient mortality from 2009 to 2013 by Hannah et al [27], TNF-α inhibitor use was combined with post–organ transplantation to define "any immunosuppression," which was significantly associated with an increased adjusted odds of TB-related mortality (aOR, 2.20 [95% CI, 1.71–2.83]), controlling for HIV, end-stage renal disease, multidrug-resistant TB, and increasing age. Finding similar variables significantly related to TB mortality as these other 2 studies lends confidence to our model estimates. It is worth noting that patients with reported TNF-α inhibitor use in our study varied significantly from nonusers in terms of key structural determinants of health such as race and employment, and that other unmeasured structural determinants may be acting as confounders.

The primary limitation of this analysis is its reliance on surveillance data and its possible underascertainment of TNF-α inhibitor use and TB-related mortality. Because TNF-α inhibitor therapy reported on the RVCT may underestimate or fail to capture the true number of patients who have recently received TNF-α inhibitors at the time of TB diagnosis, our analysis may not capture differences between groups and our results may be biased toward the null hypothesis. Our analyses did not capture the outcomes of death after therapy, slow response to therapy, or disability, nor are they able to describe whether patients had TNF-α inhibitors held during TB treatment, which could affect mortality. Although prior work suggests that different types of TNF-α inhibitors are associated with differential risk of TB disease [4, 28], our database did not include a population denominator of all TNF-α inhibitors in use, and also did not include data on type TNF-α inhibitor therapy or concurrent prednisone use. Prior studies have suggested a median duration of 12 weeks between start of infliximab treatment to onset of TB [12] with longer durations outside the US [29, 30]; however, our work was not able to capture duration of TNF-α inhibitor therapy prior to TB diagnosis. Future work should assess both infectious and noninfectious risks associated with individual drugs, as well as the contribution of specific inflammatory disorders, which may independently impact TB risk [6].

Table 3. Characteristics of Persons With Tuberculosis Who Were Dead at Diagnosis or Died During Treatment by Tumor Necrosis Factor Alpha Inhibitor Status, United States, 2010–2017

	TNF-α Inhibitor (n = 24)		No TNF-α Inhibitor (n = 2310)		
Characteristic	No.	(%)	No.	(%)	*P* Value[a]
Age at diagnosis, y					.41[b]
15–24	1	(4.2)	33	(1.4)	
25–44	2	(8.3)	261	(11.3)	
45–64	6	(25.0)	739	(32.0)	
≥65	15	(62.5)	1277	(55.3)	
Sex					.02
Female	14	(58.3)	762	(33)	
Male	10	(41.7)	1548	(67)	
Race/ethnicity					.01[b]
Asian	8	(33.3)	683	(29.6)	
Black	0	(0)	493	(21.4)	
Hispanic	6	(25.0)	584	(25.3)	
Other[c]	0	(0)	99	(4.3)	
White	10	(41.7)	441	(19.1)	
Place of birth					.63
Non–US born	15	(62.5)	1278	(55.3)	
US born	9	(37.5)	1024	(44.3)	
Diabetes					.33
No	20	(83.3)	1672	(72.4)	
Yes	4	(16.7)	638	(27.6)	
ESRD					.72[b]
No	23	(95.8)	2089	(90.54)	
Yes	1	(4.2)	221	(9.6)	
HIV status					.40[b]
Negative	14	(58.3)	1270	(55.0)	
Positive	0	(0)	177	(7.7)	
Homeless past year[d]					.41[b]
No	24	(100)	2115	(91.6)	
Yes	0	(0)	161	(7.0)	
Private outpatient provider					
No	15	(62.5)	1990	(86.1)	<.01
Yes	9	(37.5)	316	(13.7)	
Employment status					1.00[b]
Employed	4	(16.7)	371	(16.1)	
Not employed	19	(79.2)	1839	(79.6)	
Initial smear result, any[e]					1.00[b]
Negative	7	(29.2)	642	(27.8)	
Not done	0	(0)	84	(3.6)	
Positive	17	(70.8)	1583	(68.5)	
Site of TB disease					<.01[b]
Both	10	(41.7)	427	(18.5)	
Extrapulmonary only	4	(16.7)	247	(10.7)	
Pulmonary only	10	(41.7)	1636	(70.8)	
Drug resistance[f]					.41[b]
No	20	(83.3)	1826	(79.0)	
Yes	2	(8.3)	255	(11.0)	
Not done	2	(8.3)	89	(3.9)	

Column totals for each variable may not sum to total due to missing data.

Abbreviations: ESRD, end-stage renal disease; HIV, human immunodeficiency virus; TB, tuberculosis; TNF-α, tumor necrosis factor alpha; US, United States.

[a] *P* values calculated without missing values.

[b] Fisher exact test.

[c] This category includes persons of American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander races, as well as persons of multiple races.

[d] Homeless within 12 months prior to TB diagnosis.

[e] Initial smear result for any available specimen with reported acid-fast bacilli studies, including sputum, body fluid, or tissue.

[f] Presence of resistance to isoniazid, rifampin, pyrazinamide, and/or ethambutol among culture-positive cases with drug susceptibility results.

TNF-α inhibitors were initially approved for use in treatment of rheumatoid arthritis, but in the decades since their initial approval, their use has expanded dramatically and continues to grow. Inevitably, clinicians communicating with patients on these therapies will be faced with questions about TB risk, diagnosis, and clinical outcomes. TB prevention through testing for and treatment of latent TB infection is recommended for persons with immunocompromising diseases and before administration of immunosuppressive medications [31].

While this study did not demonstrate a statistically significant association between TNF-α inhibitor use and mortality, clinicians evaluating TNF-α inhibitor–treated patients with extrapulmonary manifestations should have a high index of suspicion for TB and consider additional tests before ruling out TB. The lack of a definitive diagnostic test for LTBI represents an urgent research gap that impacts many TB patients [32]; an improved diagnostic test for LTBI with predictive value for progression to TB disease would be particularly helpful for patients embarking on TNF-α inhibitor therapy. Additionally, as use of both TNF-α inhibitor and other biologic therapy increases, improved TB surveillance efforts that capture type and duration of immune-modulating therapy are urgently needed.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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