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The Rates of Serious Infections in HIV-infected Patients Who Received Tumor Necrosis Factor (TNF)-α Inhibitor Therapy for Concomitant Autoimmune Diseases

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Abstract

Objectives—To estimate the incidence of serious infections in patients with HIV infection and autoimmune disease who were treated with tumor necrosis factor (TNF) -α inhibitor therapy, and to compare these rates among stratified viral load levels.

Methods—Using a unified search strategy, four centers identified HIV-infected patients exposed to TNF-α inhibitors. Patient characteristics and infection data were assessed via chart review in all patients who were ≥18 years old and received TNF-α inhibitor therapy after HIV diagnosis between January 1999 and March 2015.

Results—Twenty-three patients with 26 uses of TNF-α inhibitor therapy provided 86.7 person-years of follow-up. Two (8.7%) experienced at least 1 serious infection episode, an overall incidence rate of 2.55 per 100 patient-years (95% CI 0.28–9.23). The incidence rate per 100 patient-years was 3.28 (95% CI 0.04–18.26) among patients with viral load > 500 copies/mL at therapy initiation and 2.09 (0.03–11.65) among patients with viral load ≤ 500 copies/mL.

Conclusion—This study suggests that TNF-α inhibitors may have a comparable rate of serious infections to the range of those observed in registry databases when used in patients with HIV infection under active care.

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INTRODUCTION

Management of patients with HIV infection with concomitant chronic autoimmune diseases is complex and potentially problematic. Drugs commonly used to treat inflammatory diseases, especially biologic therapies, have known suppressive effects on integrated host defense mechanisms and thus must be employed with great caution in an already immunosuppressed population. The incidence and prevalence of severe autoimmune diseases in HIV infection has fortunately declined with the advent of combination antiretroviral therapy (cART) [1], but occasional cases of severe inflammatory diseases, especially disorders such as seronegative arthropathies are still encountered and are not always easily controlled with conventional disease modifying antirheumatic drugs (DMARDs). In these types of patients clinicians must consider additional therapies including biologic therapies.

While TNF-α inhibitors are widely used with relative safety in HIV-infected patients with a variety of immune mediated inflammatory conditions (IMIDS), their use is also well documented to be associated with numerous adverse effects, including an increased rate of serious and opportunistic infections. In particular, mycobacterial and fungal infections are of concern as they are traditionally seen with advanced HIV infection. Thus, practitioners have been hesitant to initiate TNF-α inhibitors in this setting.

Advances in care of HIV-infected individuals have transformed over the past two decades. In patients with access to and adherent to cART, life expectancy has improved dramatically [2]. In addition, the favorable treatment outcomes of both non AIDS-defining [3] and AIDS-defining malignancies [4] as well as the increasing success in solid organ transplantation [5] in these individuals demonstrate the capacity of HIV-infected patients on effective cART to tolerate robust immunosuppression. Accordingly, it is important to critically appraise the capacity of HIV-infected patients with associated autoimmune disease to tolerate immunosuppressive therapies.

To date, there are limited data including case reports and small case series supporting the safety of TNF-α inhibitors for refractory autoimmune diseases in HIV-infected individuals [6–10]. Therefore, we performed a multi-center study to further examine the rates of serious infections in HIV-infected patients treated with TNF-α inhibitors for autoimmune diseases.

PATIENTS AND METHODS

Data collection

HIV-infected patients who were exposed to TNF-α inhibitors between January 1999 and March 2015 from 4 centers (Cleveland Clinic, Johns Hopkins Hospital, University of Miami Health System and Brigham and Women's Hospital) were identified by using a unified search strategy of each center's electronic medical records. Only patients who received TNF-α inhibitors after HIV diagnosis, documented by EIA/Western blot or HIV-1 RNA, were included. Patient demographics, comorbidities, HIV data, immunosuppressive therapy (conventional therapy and corticosteroid), TNF-α inhibitor therapy (type, duration and adverse events) and infectious events were obtained. HIV infection data included HIV status,

duration, absolute CD4-cell counts and HIV viral loads before TNF-α inhibitor initiation or the closest values if the former was not available, and cART. Serious infections were defined as infections requiring hospitalization and/or intravenous antibiotics.

Statistical analysis

Categorical variables were described by frequency with percentage and continuous variables by median with range. For each patient, the person-time of observation was calculated from the therapy start date until death, stop date, or the end of the study interval. Serious infection rates per 100 patient-years were compared between patients with viral loads ≤ 500 and > 500 copies/mL using Chi-square and Fisher exact test. *P* values of < 0.05 were considered statistically significant. Statistical analysis was performed using STATA version 14 statistical software (StataCorp, College Station, Texas).

RESULTS

Patient characteristics are demonstrated in Table 1. Of 23 patients, there were 18 men (78.3%). The median age at TNF-α inhibitor initiation was 47 years (20–66 years). Most patients (7/23; 30.4%) had psoriatic arthritis; 4(17.4%) had rheumatoid arthritis; 3 (13%) had psoriasis; 2 (8.7%) each had ankylosing spondylitis, inflammatory arthritis and ulcerative colitis; and 1 (4.3%) each had reactive arthritis, Sjogren's with neuropathy, or undifferentiated spondyloarthropathy. Few patients had other comorbidities: 3 had cirrhosis; 2 had diabetes; 2 had COPD; 1 had chronic kidney disease; and 1 had both cirrhosis and diabetes. Nine (39.1%) took prednisone while treated with TNF-α inhibitors with median prednisone dose of 15 mg (2.5–60 mg). Seven patients (30.4%) were on conventional immunosuppressive therapies; 6 on methotrexate and 1 on mercaptopurine. Almost every patient was treated with cART (22/23, 95.7%). The only patient who was not on cART experienced severe psoriatic arthritis despite being on methotrexate. He did not have infections; however, the follow-up data was only 0.5 month. Of 26 uses of TNF-α inhibitors, most (16/26) were Etanercept, 6 were Adalimumab, and 4 were Infliximab. The median duration was 39.5 months (0.5–105 months).

These individuals provided 86.7 person-years of follow-up. The median CD4- cell count and viral load at therapy initiation were 541.5 cell/mm^3 (1–1100) and undetectable (50% were undetectable), respectively. Two (8.7%) experienced 1 serious infection episode, providing an overall infection rate of 2.3 per 100 patient-years (95% CI 0.26–8.33). The patient from Johns Hopkins Hospital developed *Streptococcus pyogenes* pneumonia complicated by empyema and bacteremia while on etanercept monotherapy. He was admitted for 25 days and TNF-α inhibitor was stopped. The other patient from Brigham and Women's Hospital was on sulfazalazine 1000 mg twice daily, prednisone 2.5 mg daily, and etanercept when he had Methicillin sensitive *Staphylococcus aureus* chest tube infection after being admitted for pleural effusion of unknown etiology. He was admitted for 14 days, and TNF-α inhibitor was also discontinued. At the time of the infection, viral loads were < 50 copies/mL, and CD4-cell counts were > 200 cell/mm^3. Interestingly, CD4-cell counts increased and viral loads were stable during the infectious episodes. There were no opportunistic infections.

The rates of serious infections were not significantly different between patients with viral load > 500 copies/mL at therapy initiation and patients with viral load ≤ 500 copies/mL (3.28, 95% CI 0.04–18.26; vs 2.09, 95% CI 0.03–11.65, $p = 0.7788$) (Table 2).

DISCUSSION

In this study, we described the rates of serious infections in HIV-infected patients receiving TNF-α inhibitors for autoimmune disease. We found that the cumulative incidence of serious infections was 8.69% (2/23) with an incidence rate of 2.3 per 100 patient-years (95% CI 0.26–8.33). The incidence rates in patients with viral load > 500 copies/mL at therapy initiation was slightly higher than those with viral load ≤ 500 copies/mL; however, they were not significantly different. Our results are generally within the range reported by Curtis et al [11] in the rheumatoid arthritis uninfected by HIV (1.9–6.6 per 100 patient-years). These data suggest that TNF-α inhibitors have a comparable rate of serious infections to those observed in rheumatoid arthritis registries, when used in patients with HIV infection under active care. The largest case series of 8 patients published in the literature [7] had a higher infection rate (1/8, 12.5%) than we see in our series, but it is difficult to interpret given the small sample size. A recent review of 27 published cases [10] found that infections were experienced in 4 patients (15%). However, the infection rate in person-years was not reported and there were many lost follow-up data.

Tuberculosis and fungal infections, which are opportunistic infections seen at increased rates in both TNF-α inhibitors users and untreated HIV infection were not observed in our study, although a case of pulmonary and nodal tuberculosis has been reported in the literature [8]. Patients who developed serious infections have been reported with the use of etanercept [6, 9], where etanercept was discontinued due to frequent polymicrobial infections and septic shock after influenza vaccination. One patient in the series of Cepada et al [7] developed a facial abscess while on infliximab. In our analysis, we did not make comparisons between the different drugs within the TNF-α inhibitor class because the number of cases was too small.

CD4-cell counts increased, and viral loads were stable in two patients who had serious infections. This finding was similar to the report of Cepada [7] in which 7 of 8 patients were observed to have stable HIV parameters. Three small trials have reported no adverse effects of TNF-α inhibitors on CD4-cell counts and viral loads in HIV-infected patients [12–14].

The limitations of our study include the small number of patients, which underscores the diminishing frequency of HIV-associated autoimmune diseases in the cART era [1]. In addition, this study did not include a control group; therefore, it is still uncertain how the rate of serious infections with the use of TNF-α inhibitors compares to a more closely matched population from the same clinics. Thirdly, due to the retrospective nature of study, the available baseline pre-TNF laboratory tests may not reflect true baseline levels of CD4-cell count and viral load precisely when TNF-α inhibitor therapies were started. Also due to electronic medical records being implemented at different centers and ability to comprehensively search, there may have been additional cases that were not detected. Another limitation is that these were academic medical centers which may have a bias

toward more severe underlying rheumatic disease and higher likelihood of initiating TNF-α inhibitors and more severe HIV infection management. Finally, given that the rates of infection we used in the comparisons are for RA only and patients in this study have a range of different conditions, the comparator estimates may not be the same in other conditions.

From a practical perspective, we believe our data are clinically useful for clinicians caring for HIV-infected patients with attendant autoimmune diseases who need remitive therapy. It is unlikely that any large trials will primarily assess safety of this class of drugs in this setting and thus the rates of infection are reassuring. In today care model we would recommend that HIV-infected patients in whom biologic therapy is contemplated meet at least the current standards of virologic control and CD4 levels required for orthotropic solid organ transplantation (>200 cells/mm^3 for kidney and >100 cells/mm^3 for liver) [21–23], which are not unreasonable and in line with our findings.

In summary, HIV-infected patients with autoimmune diseases who received TNF-α inhibitor therapy had comparable rates of serious infections to those observed in registry databases when TNF-α inhibitors were used in routine care for patients with RA. Further studies are warranted to establish the long-term safety, efficacy and more accurate virologic and immunologic effects of TNF-α inhibitors by including more patients and comparing with a control group.

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Significance and Innovations

- This is the largest study to date to examine the rates of serious infections in HIV-infected patients treated with TNF-α inhibitors for concomitant autoimmune diseases.
- We found that TNF-α inhibitors may have a comparable rate of serious infections to those observed in rheumatoid arthritis registries, when used in patients with HIV infection under active care.
- The rate of serious infections in patients with viral load > 500 copies/mL at therapy initiation was slightly higher than those with viral load ≤ 500 copies/mL; however, they were not significantly different.

Table 1

Characteristics of patients

Characteristic	Total (n=23)
Age, years, median (range)	47 (20–66)
Male, %	78.3
Comorbidities, %	
Diabetes	13
Chronic kidney disease	4.3
Chronic obstructive pulmonary disease	8.7
Cirrhosis	13
Autoimmune diseases, %	
Psoriatic arthritis	30.4
Psoriasis	13
Rheumatoid arthritis	17.4
Ankylosing Spondylitis	8.7
Inflammatory arthritis	8.7
Ulcerative colitis	8.7
Reactive arthritis	4.3
Sjogren's neuropathy	4.3
Undifferentiated spondyloarthropathy	4.3
Immunosuppression, %	
Glucocorticoids, any dose	39.1
≥ 10 mg prednisone/day	26
Conventional therapy	30.4
Methotrexate	26
6-Mercaptopurine	4.3
TNF-α inhibitor therapy, %	
Etanercept	61.5
Adalimumab	23.1
Infliximab	15.4
HIV parameters	
cART, %	95.7
CD4 nadir, cells/mm^3	210 (7–1096)
CD4 at initiation, cells/mm^3	541.5 (1–1100)
Viral load at TNF-α inhibitor initiation, copies/mL	Undetectable (Undetectable to 500,000)

TNF = tumor necrosis factor; cART = combination antiretroviral therapy.

Table 2

Rates of serious infections

Rate in patients with VL ≤ 500 copies/mL	2.09 (0.1–11.6) *
Rate in patients with VL > 500 copies/mL	3.28 (0.1–18.2) *
Overall rate	2.55 (0.2–9.2)
Rate ratio	1.56 (0.1–25.0)
Rate in Rheumatoid Arthritis registry	1.9–6.6 [17]

Values are the number of episodes per 100 patient-years (95% confidence interval) except indicated otherwise. VL = viral load.

* $P = 0.7788$ (Fisher exact test)