ORIGINAL RESEARCH

Anti-TNF therapy in Jordan: a focus on severe infections and tuberculosis

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Background: A high rate of infection has been reported in patients receiving treatment with anti-tumor necrosis factor (anti-TNF). This study describes the rate of and risk factors for serious infections in patients receiving anti-TNF agents in Jordan.

Methods: This retrospective observational study was conducted at a large tertiary referral center in the north of Jordan. Between January 2006 and January 2012, 199 patients who received an anti-TNF agent (infliximab, adalimumab, or etanercept) were included. Patients received the anti-TNF treatment for rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, or other conditions. A serious infection was defined as any bacterial, viral, or fungal infection that required hospitalization, administration of appropriate intravenous antimicrobial therapy, and temporary withholding of anti-TNF treatment.

Results: The mean duration of anti-TNF treatment was 26.2 months. Steroids were used in 29.1% of patients, while 54.8% were given additional immunosuppressant therapy (methotrexate or azathioprine). Only one anti-TNF agent was given in 70.4% of patients, while 29.6% received different anti-TNF agents for the duration of treatment. Serious infections were documented in 39 patients (19.6%), including respiratory tract infections (41%), urinary tract infections (30.8%), and skin infections (20.5%), and extrapulmonary tuberculosis in three patients (7.7%). Exposure to more than one anti-TNF agent was the only factor associated with a significant increase in the rate of infection (relative risk 1.9, 95% confidence interval 1.06–4.0, P=0.03).

Conclusion: Serious infections, including tuberculosis, were a common problem in patients receiving anti-TNF agents, and exposure to more than one anti-TNF agent increased the risk of serious infection.

Keywords: anti-tumor necrosis factor therapy, biologics, developing world, extra-pulmonary tuberculosis, immune mediated diseases

Introduction

Since its introduction in 1998, anti-tumor necrosis factor (anti-TNF) has markedly changed the treatment and outcome of many inflammatory diseases.[1] The efficacy and safety of these agents has been reviewed extensively in the literature.[2–4] Early randomized clinical trials showed an increased risk of serious infection that was confirmed to be even higher in later daily practice studies.[5,6] However, these studies have had inconsistent results with regard to the safety profile. Some reports have shown an increase in the overall serious infection rate,[7,8] while others reported no significant increase in serious infections.[9–11] The increased risk of developing tuberculosis has been of special concern due to the important biological role of TNF in formation of granuloma and containment of the disease.[12] The increased rate of tuberculosis has been attributed in some reports to be due to inadequate screening for latent tuberculosis

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before initiation of treatment,[13,14] while other reports found a consistent increase in new cases despite adequate preventive measures.[15,16]

Most of the data regarding the safety of anti-TNF agents with regard to infection have been reported from western populations that are believed to have a lower background rate of infections in general and of tuberculosis in particular as compared with developing countries.[17–19] Jordan is a developing country located in the Middle East with an estimated population of 6 million. The three anti-TNF agents currently licensed for use in patients with immune-mediated diseases in Jordan are infliximab, etanercept, and adalimumab. These agents have been shown to be effective in treating immune-mediated diseases.[20]

This study describes a large tertiary center experience in the north of Jordan regarding the development of serious infections, including tuberculosis, in association with use of these three anti-TNF agents.

Materials and methods

This retrospective observational study was conducted at King Abdullah University Hospital, Irbid, Jordan. King Abdullah University Hospital is a large referral center for the north of Jordan. All patients who received one month or more of anti-TNF treatment from January 2006 to January 2012 were identified through the hospital electronic pharmacy records.

Collected data included patient demographics, underlying disease for which the anti-TNF was prescribed, and the presence of any comorbidity like diabetes mellitus, hypertension, renal failure, bronchial asthma, or malignancy. Also, the type of anti-TNF agent used, duration of anti-TNF treatment, and concomitant immunosuppressant medications used (prednisolone ≥5 mg per day, methotrexate, or azathioprine) were collected. A serious infection was defined as any bacterial, viral, or fungal infection that required hospitalization, administration of appropriate intravenous antimicrobial therapy, and temporary withholding of anti-TNF treatment.

All patients were screened for tuberculosis by standard tuberculin skin testing before initiation of anti-TNF treatment and yearly for the duration of therapy. Tuberculin skin testing ≥5 mm was considered positive. Patients with a positive tuberculin skin test and a normal chest radiograph received isoniazid for 9 months. Duration of treatment was defined as the time from initiation of anti-TNF therapy until discontinuation of data collection. Data were collected from the hospital medical records and by directly contacting patients.

Both descriptive and inferential techniques were used in the statistical analysis. In the descriptive statistics, means and standard deviations of age in years at initiation of anti-TNF and duration of treatment with an anti-TNF were computed. Frequencies and percentages were used to describe categorical patient characteristics. Cross-tabulation summaries of agent versus infection and agent versus patient characteristics are given. In the inferential statistics, relative risk and its confidence interval for patients who were exposed to more than one anti-TNF associated with infection were computed. The formulae for computing the relative risk and confidence interval are given in the Results section. Test of association using Pearson's chi-square test of independence was also used in the analysis. Statistical Package for Social Sciences version 17 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. The study was approved by the institutional review board of Jordan University of Science and Technology and King Abdullah University Hospital in the north of Jordan.

Results

In total, 199 patients were included in the study. The mean age at initiation of anti-TNF therapy was 39.2 (6–75) years, and 50.8% of patients were males.

Rheumatoid arthritis was the underlying disease in 85 patients (42.7%), ankylosing spondylitis in 47 (23.6%), inflammatory bowel disease in 28 (14.1%), psoriasis and psoriatic arthritis in 21 (10.6%), juvenile idiopathic arthritis in eight (4%), Behçet's disease in eight (4%), and idiopathic uveitis in two (1%). The mean duration of treatment with anti-TNF agents was 26.2 (range, 1–91) months. Steroids were used in 54 patients (27.1%). The mean dose of oral prednisolone was 8.1 (range, 5–40) mg/day. Other immunosuppressants (methotrexate or azathioprine) were used in 109 patients (54.8%). Only a single anti-TNF agent was used in 140 patients (70.4%) throughout the duration of treatment, while 59 patients (29.6%) switched to another agent during the treatment period. A summary of patient characteristics according to agent used is provided in Table 1.

Serious infections were documented in 36 patients (18.1%). Respiratory tract infections were the most commonly encountered, with a total of 16 episodes (41%), followed by urinary tract infections (12 episodes, 30.8%) and skin infections (eight episodes, 20.5%, Table 2). Three patients (7.7%) developed active extrapulmonary tuberculosis despite a negative tuberculin skin test prior to initiation of anti-TNF therapy (Table 3).

Of the 36 patients who had serious infection, seven (19.4%) required admission to intensive care for septic shock and hypoxia. One patient with rheumatoid arthritis on

Table 1 Patient characteristics according to anti-TNF agent used

Type of anti-TNF	Patients (n)	Age, years (mean ± SD)	Duration of treatment, months (mean ± SD)	Patients on steroids[a] (n)	Oral steroid dose (mg/day) (mean ± SD)	Nonbiological immunosuppressants	Serious infection
All	199	39.2±14.5	26.2±17.4	54 (27.1%)	8.1±6.4	109 (54.8%)	36 (18.1%)
Infliximab	53 (26.7%)	38.2±14.2	22.7±18.8	15 (27.8%)	6.8±2.4	25 (47.2%)	11 (20.8%)
Adalimumab	61 (30.7%)	41.6±13.4	19.1±9.9	18 (33.3%)	8.6±7.2	43 (70.5%)	7 (11.5%)
Etanercept	26 (13.1%)	42±13.2	25.5±15.3	8 (14.8%)	6.6±2.3	14 (53.8%)	2 (7.8%)
Multiple agents[b]	59 (29.6%)	36.4±13.4	36.9±18.2	13 (24.1%)	9.6±9.5	27 (45.7%)	16 (27.1%)

Notes: [a]Steroids, oral prednisolone; [b]exposure to more than one anti-TNF agent.
Abbreviations: TNF, tumor necrosis factor; SD, standard deviation.

adalimumab required mechanical ventilation post coronary artery bypass surgery and eventually died from pneumonia and septic shock. Two patients were receiving infliximab for Crohn's disease and died from septic shock.

Patients who were exposed to more than one anti-TNF agent had a higher risk of serious infection than those who received a single anti-TNF, ie, 16/59 (27.1%) versus 20/140 (14.3%), respectively, with a relative risk of 1.9 (95% confidence interval 1.06–4.0, P=0.03). This association remained significant after adjusting for potential confounding factors such as age, sex, steroid use, primary diagnosis, comorbidities, and use of another immunosuppressant.

Discussion

This is the first study from Jordan to report the risk of infection in patients with immune-mediated diseases requiring treatment with anti-TNF agents. The rate of infection, including tuberculosis, was much higher than what has been reported in western countries. Anti-TNF agent switchers had a higher risk of infection.

Anti-TNF agents have been shown to be effective in treating immune-mediated diseases.[21] One proposed mechanism is neutralization of soluble TNF or blocking TNF receptors from binding to their ligands. A complement-mediated effect may be as important as the anti-TNF effect on intracellular signaling, resulting in apoptosis and suppression of cytokine production.[22] Studies have suggested that TNF signaling

in tuberculosis is required for macrophage survival, and lack of this signal causes increased macrophage death and necrosis, leading to disease reactivation. This loss of TNF signaling confers a bacterial growth advantage, both within the macrophage and in the extracellular space after death of the macrophage.[23] It is generally known that patients with chronic inflammatory disease have an increased risk of infection for several disease-related reasons.[24,25]

In our study, almost one in five patients receiving anti-TNF treatment developed a serious infection. Exposure to more than one anti-TNF agent during therapy doubles the risk of developing a serious infection. How much of this percentage is excess risk attributable to anti-TNF therapy is not known due to lack of a control group. It is difficult to assemble an adequate cohort of controls because patients requiring anti-TNF treatment usually have more severe disease which, in itself, leads to a higher background risk of infection regardless of the treatment received.[26,27] We attempted to identify the factors associated with development of infection in exposed patients. The only variable that appeared to have a significant association with development of a serious infection was exposure to more than one anti-TNF agent.

To the authors' knowledge, this study is the first to report the risk of infection in patients receiving anti-TNF treatment in Jordan. There are no published data from the Middle East that describe the rate of infection in patients taking anti-TNF agents

Table 2 Patient characteristics according to type of infection

	Extrapulmonary tuberculosis	Respiratory infections	Urinary tract infections	Skin and soft tissue infections
Patients (n)	3	16	12	8
Mean age (years)	41.0	35.2	29.8	38.1
Mean duration of anti-TNF therapy (months)	29.7	34.7	25.1	38.3
Oral prednisolone use (n)	2 (66.7%)	7 (43.8%)	4 (33.3%)	3 (37.5%)
Other immunosuppressants (n)	1 (33.3%)	10 (62.5%)	9 (75%)	6 (75%)

Abbreviation: TNF, tumor necrosis factor.

Table 3 Characteristics of patients who developed active tuberculosis

	Age, (years)	Sex	Diagnosis	Site of infection	Anti-TNF agent	Months of anti-TNF treatment	Steroids	Other immunosuppressants
Patient 1	42	Female	RA	Peritoneal	Adalimumab	33	Yes	Methotrexate
Patient 2	28	Female	RA	Peritoneal	Adalimumab + etanercept	50	No	None
Patient 3	53	Male	IBD	Miliary	Infliximab	6	Yes	None

Abbreviations: RA, rheumatoid arthritis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

for immune-mediated disease.[28] Earlier data from Switzerland reported a rate of serious infection of 18.3% in patients with rheumatoid arthritis treated with anti-TNF agents, which is similar to what we found.[29] Lane et al, in a large retrospective study of veterans treated with anti-TNF agents, reported that 7% of their patients had at least one admission for a serious infection.[30] They also reported a higher risk of hospitalization with the use of infliximab compared with etanercept and a higher risk for hospitalization in patients taking prednisolone. In that study, infliximab was associated with a higher rate of infection compared with etanercept and adalimumab, which is in line with published international reports,[31] although the difference was not statistically significant. The most common encountered infections were those of the respiratory tract (41%), which is consistent with several earlier studies in patients treated with anti-TNF agents.[32,33] Similarly, use of steroids or other immunosuppressants has been associated with a higher rate of infection, but statistical significance could not be demonstrated likely due to the sample size.[34]

The only factor that was associated with a statistically significant increase in rate of infection was switching between multiple anti-TNF agents. In a large population-based study, Curtis et al reported a similar higher infection rate in anti-TNF switchers (seven per 100 patient-years) as compared with first-time users (4.6 per 100 patient-years).[35] Askling et al reported a similar finding, with a relative risk of infection of 2.1 for second anti-TNF users versus 1.43 for first-time users.[36] Kumar et al reported a rate of reactivation of latent tuberculosis as high as 10.6% in Indian patients treated with infliximab.[37] This comes from a population with a higher background prevalence of tuberculosis compared with the low prevalence in Jordan. In the USA, Wallis et al reported tuberculosis occurring in 144 and 35 per 100,000 of infliximab-treated and etanercept-treated patients, respectively.[38] This is similar to a report by Dixon et al in the UK.[39] In their study, 1.5% of treated patients developed extrapulmonary tuberculosis. This rate is lower than what has been reported in India but much higher than in the USA. This can be explained by the lower rate of tuberculosis in Jordan as reported by the World Health Organization (six per 100,000 population).[40]

We reported three cases of extrapulmonary tuberculosis in patients who were receiving anti-TNF therapy despite negative pretreatment screening with a tuberculin skin test. Interferon gamma release assays are thought to be superior to tuberculin skin testing in areas where Bacillus Calmette–Guerin (BCG) vaccination exposure is prevalent,[41] such as in Jordan where BCG is part of the national vaccination program. In a recent meta-analysis, tuberculin skin test positivity was influenced by BCG vaccination whereas interferon gamma release assays were not affected, and positivity of the interferon gamma release assay was associated with exposure to patients with active tuberculosis.[42,43]

Interferon gamma release assays are not widely available in Jordan, so our patients are only routinely screened by tuberculin skin testing. All three of the detected tuberculosis cases were extrapulmonary, consistent with previous reports that repeatedly estimated extrapulmonary tuberculosis to constitute more than 50% of cases of tuberculosis in patients treated with anti-TNF.[44] Two of the detected cases were peritoneal tuberculosis and the third was miliary tuberculosis. All three patients who developed tuberculosis were treated successfully with anti-tuberculous medications, and went back on a nonbiological immunosuppressant for the primary disease.

The lack of published local or regional data regarding infection in patients receiving anti-TNF therapy for immune-mediated diseases limited our ability to validate the present findings. The small sample size was a limiting factor in our study, because statistical significance could not be attained for measured frequencies. However, the similarities between the findings of this study and prior international reports do increase the reliability of our measured outcomes.

Microbiology data describing causative organisms and possibly the pattern of resistance would have enriched the results of this study. However, being a retrospective study, these data were not collected.

Conclusion

Our study is the first from Jordan to report the risk of infection in patients with immune-mediated diseases requiring treatment with anti-TNF agents. Physicians treating

immune-mediated diseases should be aware of the high risk of infection and in particular the risk of extrapulmonary tuberculosis in this patient population. In the future, a national registry should be established to help in documenting and improving outcomes of treatment for immune-mediated diseases.[45]

Disclosure

The authors report no conflicts of interest in this work.

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