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TNF α Inhibitors May Improve Asthma Symptoms: A Case Series of 12 Patients with Rheumatoid Arthritis and Asthma

Matthew L. Stoll, MD, PhD^{a,b}, Daniel H. Solomon, MD, MPH^{a,c}, Kerri L. Batra, MD^{a,d}, Julia F. Simard, ScD^e, Elizabeth W. Karlson, MD^a, Paul F. Dellaripa, MD^a, Michael E. Weinblatt, MD^a, Roberta Glass, MS^a, and Nancy A. Shadick, MD, MPH^a

^a Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA 02115

^c Division of Pharmacoepidemiology, Brigham and Women's Hospital

^e Department of Epidemiology, Harvard School of Public Health, Boston MA 02115

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Introduction

Asthma is a chronic inflammatory disease that constitutes one of the leading causes of chronic obstructive pulmonary disease(1). Most patients with moderate or severe disease are treated with inhaled corticosteroids, but many patients have refractory disease(2). Treatment options for these refractory patients are limited; there are emerging data on the effectiveness of tumor necrosis factor alpha (TNF) α inhibitors(3–5), but there are no long-term studies.

In this report, we studied a large prospective RA cohort, the Brigham Rheumatoid Arthritis Sequential Study (BRASS), to identify a case series of patients with both RA and asthma, who were treated with TNF α inhibitors. We aimed to determine whether asthma symptoms correlated with TNF α inhibitor therapy.

Materials and Methods

The study population consisted of patients with RA treated at the Brigham and Women's Hospital in Boston, MA, who were enrolled in BRASS, a longitudinal cohort with 933 patients enrolled by October of 2006. The diagnosis of RA was made by the treating physician based upon the revised American College of Rheumatology criteria(6). Each patient was evaluated by a physician at baseline and every 12 months; in addition, every six months, participants completed questionnaires that included items regarding functional status, comorbid conditions, RA medicine use, non-RA medicine use, and review of symptoms, including wheezing. Eligible patients included those who reported wheezing and who also started or stopped a TNF α inhibitor after baseline, during 18 months of follow-up. Switching TNF α inhibitors was

Please address reprint requests to the corresponding author: Matthew Stoll MD, PhD: UT Southwestern Medical Center/Department of Pediatrics/5323 Harry Hines Boulevard/Dallas, TX 75390-9063. Telephone (214) 648–2386, Fax (214) 648–3557, Matthew.Stoll@UTSouthwestern.edu.

^bCurrent address: Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX 75390-9063

^dCurrent address: Division of Rheumatology, Rhode Island Hospital and the Warren Alpert Medical School of Brown University, Providence, RI 02912

not considered stopping. The decision to use TNF α inhibitors was made by the attending rheumatologist, if the patient had active disease despite treatment with one or more conventional disease-modifying anti-rheumatic drugs. In this study, patient-reported wheezing was taken as a proxy for asthma, without external validation; we excluded patients with self-reported or physician-diagnosed interstitial lung disease or emphysema. The IRB that approved of the BRASS study also approved all aspects of the current study.

Results

There were 933 patients in the BRASS cohort; 123 (13%) reported wheezing. Among these patients, 19 (15.4%) initiated or discontinued TNF α inhibitor therapy during the first 18 months of the study. Two of these 19 were enrolled in a double-blinded study involving abatacept, two had interstitial lung disease, one had emphysema, and data were incomplete on two. These seven patients were excluded from the study, leaving 12. Of these 12, 9 (75%) were female. Their median age at enrollment was 58 years, and the median disease duration was 12 years. Seven (58%) were RF-positive. Six reported prior history of smoking, but only one patient (# 2) reported smoking at baseline. This patient's smoking status did not change during the study.

Data on use of inhaled corticosteroids and reports of wheezing, as well as use of TNF α inhibitor therapy and corticosteroids for all 12 patients are shown in Figure 1. Etanercept was used by patients 1, 2, 9, 11, and 12, infliximab by patients 3, 4, and 10, and adalimumab by patients 5, 6, 7, and 8. Nine RA patients began use of a TNF α inhibitor during the study period and continued to use them at the end of the study period (Figure 1a). Eight of them (1–7, 9) reported wheezing during the six month period before or coincident with starting the TNF α inhibitor, while the other developed wheezing during the six months after initiation of TNF α inhibitor therapy; none of the nine reported wheezing at the end of the study period. Three patients discontinued a TNF α inhibitor during the study period (Figure 1b), all of whom reported wheezing following discontinuation. The TNF α inhibitor was restarted in patient 11, whose wheezing subsequently resolved.

Data on use of oral corticosteroids are also shown in Figure 1; these were prescribed by the rheumatologist to treat the patient's RA. Among the five patients who started TNF α inhibitors and also used corticosteroids (Figure 1a), the steroid dose was decreased after initiation of the TNF α inhibitor, yet wheezing improved in all of them, suggesting that the improvement in wheezing was not due to concomitant oral corticosteroid therapy. In contrast, among the three who discontinued TNF α inhibitors (Figure 1b), one had an increase in the corticosteroid dose, another had a decrease, and a third never used.

Discussion

We reviewed the records of 12 patients with RA who either started or discontinued TNF α inhibitor therapy and who also reported a history of wheezing; all of them were followed prospectively for 18 months. We found that all nine of the patients who began TNF α inhibitors and reported wheezing during the 18-month study period demonstrated resolution by the end of the follow-up period. In contrast, of the three patients who discontinued TNF α inhibitor therapy and reported wheezing during the study period, the wheezing developed in all three cases after discontinuing the medicine.

This study has important limitations. The most important is its non-randomized, observational design, and the small number of patients studied, which precludes statistical analysis or evaluation of potential confounding factors. In addition, we were unable to confirm that the etiology of the wheezing was due to asthma; however, self-reported wheezing has greater than 90% specificity for asthma (7,8). Further, most other causes of wheezing, such as chronic

infections and congestive heart failure, serve as contraindications to TNF α therapy and might be expected to worsen as a result of such therapy. Finally, pulmonary function tests were not performed in any of these patients, so we were not able to confirm improvements in wheezing. Despite these limitations, this study does have several strengths including the long duration of follow-up, detailed information on medicine use and respiratory symptoms, patient and provider lack of awareness of our hypothesis regarding TNF α inhibitors and asthma, and the consistency of our findings.

Thus, this case series adds to the growing body of literature on the potential role of TNF α inhibition in patients with asthma. Large randomized controlled studies are needed to confirm these findings.

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References

1. Silva GE, Sherrill DL, Guerra S, et al. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59–65. [PubMed: 15249443]
2. Leung DY, Spahn JD, Szefer SJ. Steroid-unresponsive asthma. *Semin Respir Crit Care Med* 2002;23:387–398. [PubMed: 16088632]
3. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor- α in asthma. *Am J Respir Crit Care Med* 2006;174:753–762. [PubMed: 16840747]
4. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012–1018. [PubMed: 16166100]
5. Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006;354:697–708. [PubMed: 16481637]
6. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–324. [PubMed: 3358796]
7. de Marco R, Cerveri I, Bugiani M, et al. An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma. *Eur Respir J* 1998;11:599–605. [PubMed: 9596109]
8. Remes ST, Pekkanen J, Remes K, et al. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002;57:120–126. [PubMed: 11828040]

Figure 1a. Patients initiating therapy with TNF α inhibitors **Figure 1b. Patients discontinuing therapy with TNF α inhibitors** **Figure 1.**

Figure 1a Patients initiating therapy with TNF α inhibitors. Changes in reported wheezing is shown (WWW), along with use of TNF α inhibitors (bar), and oral corticosteroids (dashed line.) Time since entry into the registry is shown at the bottom, and the Y-axis depicts the dose of prednisone equivalent.

Figure 1b. Patients discontinuing therapy with TNF α inhibitors. See caption of Figure 1a for details.