CHEST

Official publication of the American College of Chest Physicians

Asthma Unmasked With Tumor Necrosis Factor- α-Blocking Drugs

Laurent Guilleminault, Philippe Carré, Frédérique Beau-Salinas, Camille Taillé, Philippe Dieudé, Bruno Crestani, Patrice Diot and Sylvain Marchand-Adam

Chest 2011;140;1068-1071
DOI 10.1378/chest.10-2350

ISSN:0012-3692

recently described chromosomal abnormalities in proliferative pulmonary lesions in a patient with germline *BMPR2* mutation, which might represent genetic events possibly responsible for cell overgrowth. Nemenoff and colleagues[6] demonstrated that mice with a *Pten* depletion in smooth muscle cells exhibited PASMC hyperplasia, right ventricular hypertrophy, pulmonary vascular remodeling, and histopathology consistent with PAH. Moreover, the normal function of PTEN is to inhibit platelet-derived growth factor receptor (PDGFR) signaling. PDGFR activates the RAS/mitogen activated protein kinase signaling pathway implicated in cell overgrowth and apoptosis. Interestingly, it has been shown that PDGFR was overexpressed in small pulmonary arteries of patients with PAH,[7] and its activation promoted the proliferation and the migration of PASMCs.[3] Thus, we can hypothesize that mutations in the *PTEN* gene may play a role in the development of PAH in the present case by promoting the activation of the PDGFR.

In the present case, the association of PAH with Cowden syndrome could be fortuitous, and PAH could be only due to anorexigen exposure. Our patient was exposed to a 1-year dexfenfluramine intake 20 years before the onset of the first PAH symptoms. The anorexigen exposure, particularly to fenfluramine derivatives taken for >3 months, is known to be a definite risk factor for PAH.[8] Although the majority of dexfenfluramine-associated PAH occurred within the year following the drug exposure, several cases of PAH have been described many years later, but in these cases the implication of anorexigen exposure for the development of PAH is impossible to demonstrate.[8] The rare occurrence of PAH after anorexigen exposure, the delay between anorexigen intake and the onset of first PAH symptoms, the low prevalence of Cowden syndrome (one in 200,000), and the role of *PTEN* in cell functions and vascular remodeling in experimental models suggest a potential link between Cowden syndrome and PAH.

In conclusion, to our knowledge, this is the first reported case of PAH in a patient with Cowden syndrome. However, the *PTEN* mutation alone is likely insufficient to lead to PAH; it can be hypothesized that *PTEN* mutations may be a predisposing factor for the development of PAH, and anorexigen exposure may be a potential trigger.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Drs Simonneau, Humbert, and Sitbon have received consulting and lecture fees from Actelion, Bayer, GlaxoSmithKline, Eli Lilly and Co, and Pfizer, Inc. Drs Natali, Girerd, Montani, and Soubrier have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Galiè N, Hoeper MM, Humbert M, et al; Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34(6):1219-1263.
2. Eng C. PTEN: one gene, many syndromes. *Hum Mutat*. 2003;22(3):183-198.
3. Yin Y, Shen WH. PTEN: a new guardian of the genome. *Oncogene*. 2008;27(41):5443-5453.
4. Rai PR, Cool CD, King JA, et al. The cancer paradigm of severe pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008;178(6):558-564.
5. Aldred MA, Comhair SA, Varella-Garcia M, et al. Somatic chromosome abnormalities in the lungs of patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;182(9):1153-1160.
6. Nemenoff RA, Simpson PA, Furgeson SB, et al. Targeted deletion of PTEN in smooth muscle cells results in vascular remodeling and recruitment of progenitor cells through induction of stromal cell-derived factor-1alpha. *Circ Res*. 2008;102(9):1036-1045.
7. Perros F, Montani D, Dorfmüller P, et al. Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008; 178(1):81-88.
8. Souza R, Humbert M, Sztrymf B, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J*. 2008;31(2):343-348.

Asthma Unmasked With Tumor Necrosis Factor-α-Blocking Drugs

Laurent Guilleminault, MD; Philippe Carré, MD; Frédérique Beau-Salinas, MD; Camille Taillé, MD, PhD; Philippe Dieudé, MD; Bruno Crestani, MD, PhD; Patrice Diot, MD, PhD; and Sylvain Marchand-Adam, MD, PhD

We report five cases of asthma unmasked by anti-tumor necrosis factor (TNF)-α-blocking drugs. Asthma symptoms appeared within an average of 4 months (range 1-24 months) after starting the anti-TNF-α treatment for inflammatory disease. The patients did not appear to be predisposed to asthma except for one patient who had asthma during childhood. Four patients stopped anti-TNF-α-blocking drugs with an improvement of symptoms within 1 to 5 months. In the patient with a history of childhood asthma, respiratory symptoms recurred when another anti-TNF-α therapy was started. Asthma control was achieved with inhaled steroids, allowing anti-TNF-α treatment to continue. The biotherapy was maintained for the fifth patient in association with inhaled steroids. The pathophysiologic mechanisms are unknown but are probably more complex than the T helper 1/T helper 2 imbalance suggested in the literature, and further studies are required. ***CHEST 2011; 140(4):1068–1071***

Abbreviations: BHR = bronchial hyperresponsiveness; Th = T helper; TNF = tumor necrosis factor

Case Reports

Tumor necrosis factor (TNF)-α has been implicated in asthmatic airway inflammation, which makes this cytokine a potential therapeutic target for treating some

subjects with asthma.[1] We report the cases of five patients, three men and two women, who developed intermittent (three patients) or persistent (two patients) asthma after starting anti-TNF-α treatment of inflammatory diseases (three rheumatoid arthritis, one Crohn's disease, and one ankylosing spondylarthritis). All patients gave their written informed consent for inclusion in this report.

The characteristics of patients are summarized in Table 1. Mean age was 35 years (range 19-66 years). One patient (patient 1) was a former smoker (20 pack-years). TNF-α-blocking drugs were infliximab in patients 3, 4, and 5, and etanercept and adalimumab in patients 1 and 2, respectively. Patient 3 received infliximab and then adalimumab. Anti-TNF-α treatment was used in combination with methotrexate in patient 2 and azathioprine in patient 3. Patients 1 and 5 received prednisone 10 mg/d associated with methotrexate and azathioprine, respectively, as part of the treatment of the inflammatory disease.

Wheezing and dyspnea appeared within an average of 4 months (range 1-24 months) after beginning the anti-TNF-α treatment. None of the patients presented with acute severe asthma. None of them had blood eosinophilia or rhinosinusitis during anti-TNF-α treatment. Patients 2 and 4 reported a past history of familial atopy. Patients 3 and 5 had a personal atopy with sensitization to airborne allergen. Lung function tests, performed after the onset of the respiratory symptoms, were normal in patients 1, 2, and 5 (with intermittent asthma). Only patient 2 was tested for bronchial hyperresponsiveness (BHR), and the test was positive with a provocative dose causing a 20% reduction in FEV_1 in 1 s of 173 μg. Lung function tests revealed airway obstruction in patients 3 and 4 with persistent asthma (FEV_1 80% predicted and 51% predicted, respectively). In patient 4, reversible criteria were not met (FEV_1 increased from 2,960 mL to 3,140 mL, ie, by 8%). He had never smoked, had not been exposed to any significant air pollution, and had never previously suffered from dyspnea. Patient 3 had a reversible obstruction with prebronchodilator FEV_1 of 2,660 mL and postbronchodilator FEV_1 of 3,180 mL (19.5% increase). This patient reported having asthma when she was a child, but she had been asymptomatic for >5 years. This patient tested positive to dust and cat hair on a prick test, but she did not have a cat at home. Patient 5 had positive prick-test reactions to dust mites, cockroaches, and wormwood. Prick tests using anti-TNF-α were negative in four patients (patients 1, 2, 3, and 5). Total serum IgE levels, assayed before starting asthma treatment, were within the normal range in all patients (3-40 IU/mL). High-resolution CT scan of the lung was normal in all patients.

Respiratory treatment involved inhaled steroids in cases 1, 2, and 4 and an association of inhaled steroid and long-acting β_2-agonist in cases 3 and 5. Steroid dosage for asthma control ranged from 500 μg/d to 2,000 μg/d of beclomethasone equivalent. The anti-TNF-α treatment was stopped in patients 1, 2, 3, and 5 because of the emergence of asthma symptoms. The symptoms disappeared within 1 to 5 months. In patient 4 with persistent asthma (FEV_1 51%), inhaled corticosteroid treatment was initiated and anti-TNF-α treatment was maintained with improvement of asthma symptoms. Patient 3 initially stopped treatment with infliximab, but the inflammatory disease relapsed. Adalimumab was introduced 6 months after stopping infliximab. After three infusions, dyspnea and wheeze occurred. Spirometry demonstrated a nonreversible bronchial obstruction (an FEV_1 increase of 190 mL, ie, 7%). As anti-TNF-α was considered mandatory to treat the inflammatory bowel disease, the patient remained on biotherapy associated with inhaled steroids, which controlled the asthma symptoms.

The clinical and pulmonary function test follow-up of these patients ranged from 3 to 5 years after the asthma diagnosis. As there were no relapses of respiratory symptoms during this period, the follow-up did not include any further CT scans.

Lung function tests, performed on average 3 years after stopping anti-TNF-α treatment, showed normal FEV_1 and FEV_1/FVC in patients 1, 2, and 5. BHR was screened in two patients. Patient 1 had no BHR after stopping anti-TNF-α, but these data were not available during anti-TNF-α treatment. BHR persisted in patient 2 with q provocative dose causing a 20% reduction in FEV_1 in 1 s at 300 μg (compared with 173 μg during anti-TNF-α treatment). During anti-TNF-α treatment, airway obstruction persisted in patients 3 and 5, with FEV_1/FVC of 65% and 66% and FEV_1 of 76% and 51%, respectively. Reversibility criteria were not met for either patient.

The diagnosis of asthma was made on the basis of recurrent wheezing, breathlessness, and coughing, in accordance with the definition of the American Thoracic Society.[2] Only one patient had a history of smoking, and none of the patients had any other detectable underlying respiratory disease.

Discussion

The causality of anti-TNF-α in respiratory symptoms can be evaluated on the basis of the classic pharmacologic imputability criteria using the model suggested by Edwards and Aronson.[3] Asthma symptoms appeared after

Manuscript received September 10, 2010; revision accepted February 9, 2011.
Affiliations: From the Service de pneumologie et exploration fonctionnelle respiratoire (Drs Guilleminault, Carré, Diot, and Marchand-Adam), Hôpital Bretonneau, and the Department of Clinical Pharmacology/Regional Centre of Pharmacovigilance (Dr Beau-Salinas), CHRU Tours, Tours; Unité INSERM U618, Faculté de médecine (Drs Guilleminault, Diot, and Marchand-Adam), Université François Rabelais, Tours; the Service de Pneumologie (Drs Taillé and Crestani), and the Service de rhumatologie (Dr Dieudé), APHP, Hôpital Bichat-Claude-Bernard, Paris; and Unité INSERM U700, Faculté de X. Bichat (Drs Taillé and Crestani), Université René Descartes, Paris, France.
Correspondence to: Laurent Guilleminault, MD, CHRU Tours, Hôpital Bretonneau, Service de pneumologie et exploration fonctionnelle respiratoire, 2 Boulevard Tonnelle, 37032 Tours, France; e-mail: guillel@free.fr

DOI: 10.1378/chest.10-2350

Table 1—*Characteristics of Patients With Asthma Unmasked by Anti-TNF-α Treatment*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Female	Female	Male	Female
Age, y	55	66	19	35	35
Inflammatory disease	Rheumatoid arthritis	Rheumatoid arthritis	Crohn's disease	Ankylosing spondylitis	Rheumatoid arthritis
Anti-TNF-α	Etanercept	Adalimumab	Infliximab then adalimumab	Infliximab	Infliximab
Immunosuppressive treatment	Methotrexate, prednisone 10 mg/d	Methotrexate	Azathioprine	Nonsteroidal antiinflammatory	Azathioprine, prednisone 10 mg/d
Familial atopy	No	Contact dermatitis and asthma in father	No	Asthma in brothers	No
Personal atopy	No atopy symptoms, skin tests negative	No atopy symptoms, skin tests negative	Allergic rhinitis, asthma in childhood, prick test positive to dust and cat hair	NA	Prick test positive to dust mites, cockroaches, and wormwood
Anti-TNF-α prick test	Negative	Negative	Negative	NA	Negative
IgE, IU/mL	NA	10	NA	3	40
Lung function	FEV_1/FVC 77% FEV_1 116%	FEV_1/FVC 72% FEV_1 112% BHR	FEV_1/FVC 68% FEV_1 80% Reversible	FEV_1/FVC 66% FEV_1 51% Not reversible	FEV_1/FVC 75% FEV_1 74%
Kco, mmol/min/kPa/L	93	91	NA	NA	82
Time to asthma onset	2 y	3 mo	4 mo and after each infusion	2 y	1 mo
Asthma treatment	Fluticasone 500 μg/d	Beclomethasone 500 μg/d	Fluticasone 1,000 μg/d and salmeterol	Fluticasone 1,000 μg/d	Fluticasone 1,000 μg/d and salmeterol
Anti-TNF-α stopped	Yes	Yes	No	No	Yes
Clinical evolution	Respiratory symptoms disappeared	Respiratory symptoms disappeared	Improvement after stopping Infliximab, relapse under adalimumab	Clinical symptoms decreased after receiving inhaled corticosteroids	Respiratory symptoms disappeared
Lung function evolution	FEV_1/FVC 73% FEV_1 117% No BHR	FEV_1/FVC 70% FEV_1 107% BHR	FEV_1/FVC 65% Not reversible FEV_1 76% under adalimumab	FEV_1/FVC 66% Not reversible FEV_1 51% under infliximab	FEV_1/FVC 81% FEV_1 98%

BHR = nonspecific bronchial hyperresponsiveness; Kco = carbon monoxide transfer coefficient; NA = not available; TNF = tumor necrosis factor.

introduction of anti-TNF-α in patients who did not appear to be predisposed to the disease. One patient had presented with asthma symptoms >5 years prior to beginning anti-TNF-α treatment. No other causes of dyspnea were found, and the hypothesis of bronchiolitis was ruled out by high-resolution thoracic CT scan, which was unremarkable. Diffusing capacity of lungs for carbon monoxide was available in three patients and was normal. No relapse of asthma occurred in the years following the diagnosis, whereas the rheumatologic and digestive inflammatory diseases persisted, ruling out the hypothesis of a link between respiratory disease and the underlying inflammatory disease.

The frequency of asthma under anti-TNF-α treatment in our patients is estimated at 0.74%, as calculated by the number of cases compared with the number of patients treated with anti-TNF-α in our hospital. This frequency is in line with data from pivotal trials of anti-TNF-α (0.3%-1.7%). However, we believe that the frequency may be underestimated because only patients followed up by pulmonologists are reported. Our observations are consistent with other anecdotal reports in the literature.[4-6]

As suggested previously, only one patient in our case series had a history of smoking, which contrasts with the previous case series published by Dubey et al.[5] In that article, only one patient was a nonsmoker and six were former or current smokers. Tobacco is a confounding factor for asthma. It is difficult to draw a conclusion from a small series of patients, but our case series does not support the hypothesis that tobacco is a risk factor for asthma in patients receiving anti-TNF-α.

The pathophysiologic mechanisms of asthma unmasked by anti-TNF-α are unknown, but several hypotheses can be put forward. Our cases make the hypothesis of an allergic reaction to anti-TNF-α unlikely. No skin or anaphylactic symptoms were observed after anti-TNF-α treatment. Bennett et al[4] suggested an involvement of T helper (Th) 1/Th2 balance in the side effects of anti-TNF-α, with a Th1 cytokine decrease, allowing Th2 to be expressed, leading to asthma symptoms. However, this mechanism is also not consistent with the low IgE rate in our patients. Immune mechanisms may be more complex than the simple Th1/Th2 balance, and two hypotheses could be considered. Th17 cells, which have been demonstrated to play a role in asthmatic airways,[7] might be involved in asthma unmasked by anti-TNF-α. TNF-α-blocking drugs might also decrease immunity, playing a role in asthma onset.[8] Anti-TNF-α, associated with methotrexate or azathioprine use, could worsen viral infection known to exacerbate asthma.[9] Indeed, the induced immunodeficiency could lead to a virus cytopathogenic effect in patients with deficient innate immunity. At the same time, release of other proinflammatory mediators secondary to TNF-α inhibition might damage respiratory epithelial cells.

To better understand the relationship between anti-TNF-α and the onset of asthma, a prospective follow-up of patients receiving this treatment, including immunologic and virologic tests, might be considered. In cases of severe asthma, anti-TNF-α withdrawal should be considered, whereas anti-TNF-α may be maintained in milder cases of asthma controlled by steroid inhalation.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Wenzel SE, Barnes PJ, Bleecker ER, et al; T03 Asthma Investigators. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med*. 2009;179(7):549-558.
2. National Heart, Lung, and Blood Institute. National Institutes of Health. Guidelines for the diagnosis and management of asthma (epr-3). National Heart, Lung, and Blood Institute. Web site. 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 28, 2007.
3. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259.
4. Bennett AN, Wong M, Zain A, Panayi G, Kirkham B. Adalimumab-induced asthma. *Rheumatology (Oxford)*. 2005;44(9):1199-1200.
5. Dubey SG, Kerrigan N, Mills K, Scott DG. Bronchospasm associated with anti-TNF treatment. *Clin Rheumatol*. 2009;28(8):989-992.
6. Janssen R, Krivokuca I, Kruize AA, Koenderman L, Lammers JW. Adalimumab-induced bronchospasm: not a class effect. *Thorax*. 2008;63(5):472-473.
7. Wang YH, Liu YJ. The IL-17 cytokine family and their role in allergic inflammation. *Curr Opin Immunol*. 2008;20(6):697-702.
8. Wallis RS. Infectious complications of tumor necrosis factor blockade. *Curr Opin Infect Dis*. 2009;22(4):403-409.
9. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol*. 2010;125(6):1178-1187.