

Letter to the Editor

Tiotropium use and pulmonary function in patients with constrictive bronchiolitis

Uso de tiotrópio e função pulmonar em portadores de bronquiolite constritiva

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To the Editor:

Tiotropium, a long-acting muscarinic antagonist bronchodilator with well-established use in COPD, has recognized activity in reducing lung hyperinflation, as well as in relieving dyspnea and improving exercise capacity in this population of patients.⁽¹⁾ In a recently published article,⁽²⁾ tiotropium was shown to be able to attenuate TGF- β -induced airway remodeling. In addition, the combination of albuterol and tiotropium has been shown to elicit an acute response in patients with constrictive bronchiolitis (CB) secondary to graft-versus-host disease after bone marrow transplantation, there being a significant variation in FEV₁, FVC, or both, in 7 of 17 patients tested.⁽³⁾ Therefore, smooth muscle plays a significant role in CB, and tiotropium might have an inhibitory activity on bronchoconstriction and airway remodeling.

Between January of 2004 and September of 2009, tiotropium was offered (HandiHaler, 18 μ g; once a day for 30 days) to 11 consecutive patients with CB. The diagnosis of these patients is described below. Simple spirometric tests were performed before and after tiotropium use, in accordance with the Brazilian guidelines for pulmonary function testing,⁽⁴⁾ and 6 patients underwent pre-treatment plethysmography.

Eight patients were female, with the mean age at diagnosis being 49 ± 11.6 years and the mean age at initiation of tiotropium therapy being 54.9 ± 11.0 years. Six patients had a history of smoking, but only 2 had a history of greater than 5 pack-years.

Nine patients had a history of significant exposure (mold, metallurgical material, birds, herbicides, paints, seeds, and plaster). Three patients had a collagen disease (rheumatoid arthritis, in 1; Sjögren's syndrome, in 1; and both, in 1); for these three patients, collagen disease was considered the major etiological factor.

All patients underwent chest CT, which revealed direct signs of small airway disease (bronchial wall thickening, bronchiectasis, bronchiolectasis, centrilobular micronodules or opacities with a tree-in-bud pattern) in 9 patients and an indirect sign of small airway disease (mosaic attenuation) in 2 patients.⁽⁵⁾

Seven biopsies (six surgical biopsies and one transbronchial biopsy) were performed, all of which showed the presence of CB. The 3 patients with rheumatic disease did not undergo lung biopsy because their clinical, functional, and CT findings were consistent with small airway disease, whereas 1 patient did not undergo biopsy because of his severe clinical status, but this patient had clinical, functional, and CT findings of CB.

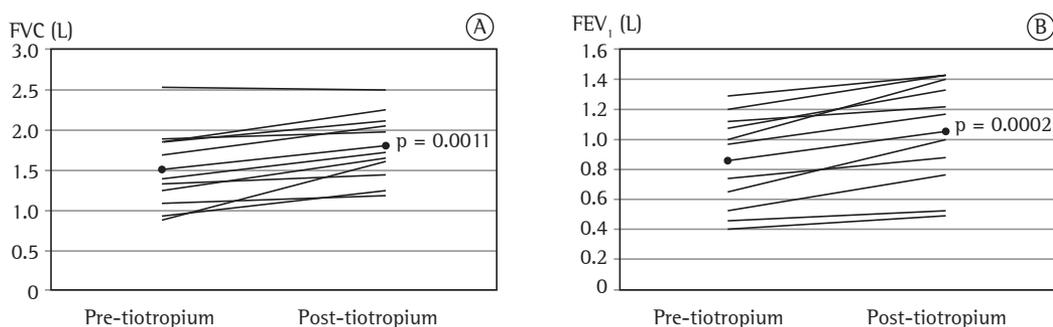
The treatments instituted before the initiation of tiotropium therapy were as follows: systemic corticosteroid therapy, in 8 patients; inhaled corticosteroid therapy, in 7; long-acting β_2 agonist therapy, in 4; methotrexate therapy, in 4; macrolide therapy, in 3; azathioprine therapy, in 2; chloroquine therapy, in 2; and cyclophosphamide therapy, in 1. Two patients had transient clinical and functional improvement, 1 of whom used methotrexate and 1 of whom used a combination of azathioprine, prednisone, and acetylcysteine.

We analyzed 22 simple spirometric tests (2 per patient; Table 1). The median duration of tiotropium therapy was 21 days (interquartile range, 17.5-42.0), with a minimum of 14 days. The FVC and FEV₁ values before and after tiotropium use are shown in Figure 1. Six patients underwent plethysmography at baseline, and all had normal or increased TLC and increased RV, suggesting air trapping, consistent with the clinical diagnosis of CB. After the initiation of tiotropium therapy, FEV₁ increased from 870 ± 310 mL to $1,060 \pm 350$ mL ($18.7 \pm 9.2\%$; $p = 0.0002$) and FVC increased from $1,520 \pm 500$ mL to $1,800 \pm 420$

Table 1 – FVC and FEV₁ before and after the initiation of tiotropium therapy in the patients studied and percent change.^a

Patient	Pre-therapy FEV ₁ , L	Post-therapy FEV ₁ , L	Δ, %	Pre-therapy FVC, L	Post-therapy FVC, L	Δ, %
1	0.99 (39)	1.41 (56)	30	1.69 (57)	2.06 (70)	18
2	1.09 (55)	1.35 (68)	19	1.39 (56)	1.72 (70)	19
3	0.46 (22)	0.51 (24)	10	1.10 (42)	1.18 (45)	7
4	1.13 (46)	1.22 (50)	7	2.53 (88)	2.51 (88)	-1
5	0.54 (17)	0.77 (23)	30	0.89 (22)	1.61 (40)	45
6	0.98 (27)	1.19 (37)	18	1.85 (42)	2.25 (57)	18
7	1.21 (63)	1.43 (74)	15	1.85 (79)	2.11 (89)	12
8	0.75 (39)	0.88 (46)	15	1.33 (58)	1.45 (63)	8
9	1.29 (60)	1.42 (66)	9	1.88 (72)	1.98 (76)	5
10	0.42 (13)	0.51 (16)	18	0.92 (24)	1.24 (33)	26
11	0.66 (26)	1.02 (37)	35	1.24 (41)	1.64 (51)	24
Mean	0.87 (37)	1.06* (45)	19	1.52 (53)	1.80** (62)	17

^aValues expressed as n (%). *p = 0.0002. **p = 0.0011.

**Figure 1** – Variation in FEV₁ (in A) and in FVC (in B) before and after tiotropium use. The darker lines represent the mean values.

mL ($16.5 \pm 12.6\%$; $p = 0.0011$), whereas the FEV₁/FVC showed no significant change (from 0.57 ± 0.11 to 0.58 ± 0.12 ; $p = 0.46$). Figure 1 shows the change in FVC and FEV₁ for each patient, as well as the mean values for the group.

The mean functional gain was 280 mL or 16.5% for FVC and 190 mL or 18.7% for FEV₁, values that are similar to those reported in patients with COPD.⁽¹⁾ Only 2 of the 11 patients did not show improvement of greater than 100 mL in FEV₁, FVC, or both, and it was impossible to predict the presence of response solely on the basis of clinical characteristics.

Our findings show that patients with CB have prolonged functional improvement with the use of a drug with a recognized anticholinergic effect, suggesting that acetylcholine plays a role in the pathophysiology of CB through bronchial smooth muscle contraction. To our knowledge, this is the first case series showing spirometric

improvement with tiotropium use in patients with CB of different etiologies, which justifies the need for larger and longer studies to evaluate the impact of tiotropium bromide use on the progression of CB.^(3,6)

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