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Successful management of refractory cough with the leukotriene receptor antagonist zafirlukast in a dog with chronic bronchitis: a case report

I.H. Yoon, H.J. Han, J.H. Kim*

Veterinary Medical Teaching Hospital, Konkuk University, Seoul, Republic of Korea

*Corresponding author: junghyun@konkuk.ac.kr

ABSTRACT: A 7-year-old spayed female Pomeranian dog was evaluated for a 6-month history of intractable coughing and dyspnoea. The cough was unresponsive to antibiotics and a bronchodilator medication prescribed by the previous animal hospital. No abnormalities were identified on the blood work, echocardiography and radiography. However, computed tomography revealed mild bronchiectasia. Based on the history, physical examination and non-specific diagnostic imaging findings, the dog was diagnosed with chronic bronchitis. The cough failed to resolve, despite an attempt to manage it with prednisolone, theophylline, codeine and N-acetylcysteine. With the owner's consent, we stopped all previous medications and finally tried the leukotriene receptor antagonist zafirlukast. The cough progressively improved and had mostly resolved four weeks after starting the administration of zafirlukast. The dog remained in complete remission without recurrence for seven months. This case report is the first to describe the successful long-term management of chronic cough with zafirlukast in a dog.

Keywords: anti-inflammatory medicine; bronchiectasia; canine, glucocorticoid-intolerant, non-asthmatic bronchitis

Chronic bronchitis is one of the most common causes of chronic cough in dogs and is characterised by a chronic cough lasting for more than two months (Brownlie 1990; Rozanski 2014). Chronic bronchitis can be induced by infection, allergy, a foreign body or by idiopathic causes (Brownlie 1990). Once these factors insult the bronchial walls, they can induce inflammation and subsequently irreversible structural changes of the airway (Reinero 2011). For a fundamental treatment of chronic bronchitis, it is important to give priority to blunting airway inflammation; in addition, altering the environment (e.g., limiting exposure to inhaled irritants and aero-allergens) and weight control are important for long-term treatment (Rozanski 2014). Therefore, after ruling out infectious bronchitis, the mainstay therapy for canine chronic bronchitis is glucocorticoids, because these drugs effectively suppress the inflammatory response (Rozanski 2014). With regard to alternative anti-inflammatory medicines, many studies in human medicine have recently demonstrated that leukotriene antagonists are capable of reducing airway inflammation (Calhoun et al. 1998; Ramsay et al. 2009).

Leukotrienes constitute a group of inflammatory mediators. Therefore, leukotriene antagonists such as zafirlukast are effective in human patients with chronic cough associated with asthma or nonasthmatic bronchitis (Drazen et al. 1999; Jeffery 2001; Cai et al. 2012). However, no study exists on the administration of zafirlukast for chronic cough in dogs with chronic bronchitis. This paper is the first known report describing a successful clinical outcome following zafirlukast therapy for refractory chronic cough associated with chronic bronchitis in a dog.

Case description

A 7-year-old spayed female Pomeranian dog was evaluated for a 6-month history of intractable cough-

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ing and dyspnoea. At the time of presentation, the dog was being medically managed with antibiotics and a bronchodilator. However, the dog was becoming less responsive to these medications, and the cough had progressively worsened. The patient had been regularly administered broad-spectrum anthelminthic and heartworm prevention medications. Therefore, it was unlikely that the cough was caused by parasites or heartworm disease.

On physical examination, the dog was mildly overweight (body condition score, 6/9) and had a harsh cough with serous nasal discharge. The patient had a normal respiratory rate (30 breaths/min) and body temperature (38.9 °C). However, tachycardia was observed (heart rate, 180 beats/min). There was no remarkable finding with cardiac auscultation. Blood pressure, which was measured by an automated oscillometric method, showed normotension (systolic blood pressure, 140 mm Hg). Blood work, which included complete blood counts, serum chemistry, electrolyte levels and D-dimer concentration, did not reveal any abnormal findings, except for mild hyperglycaemia (6.99 mmol/l; reference range 3.89–6.55 mmol/l), which might have been associated with

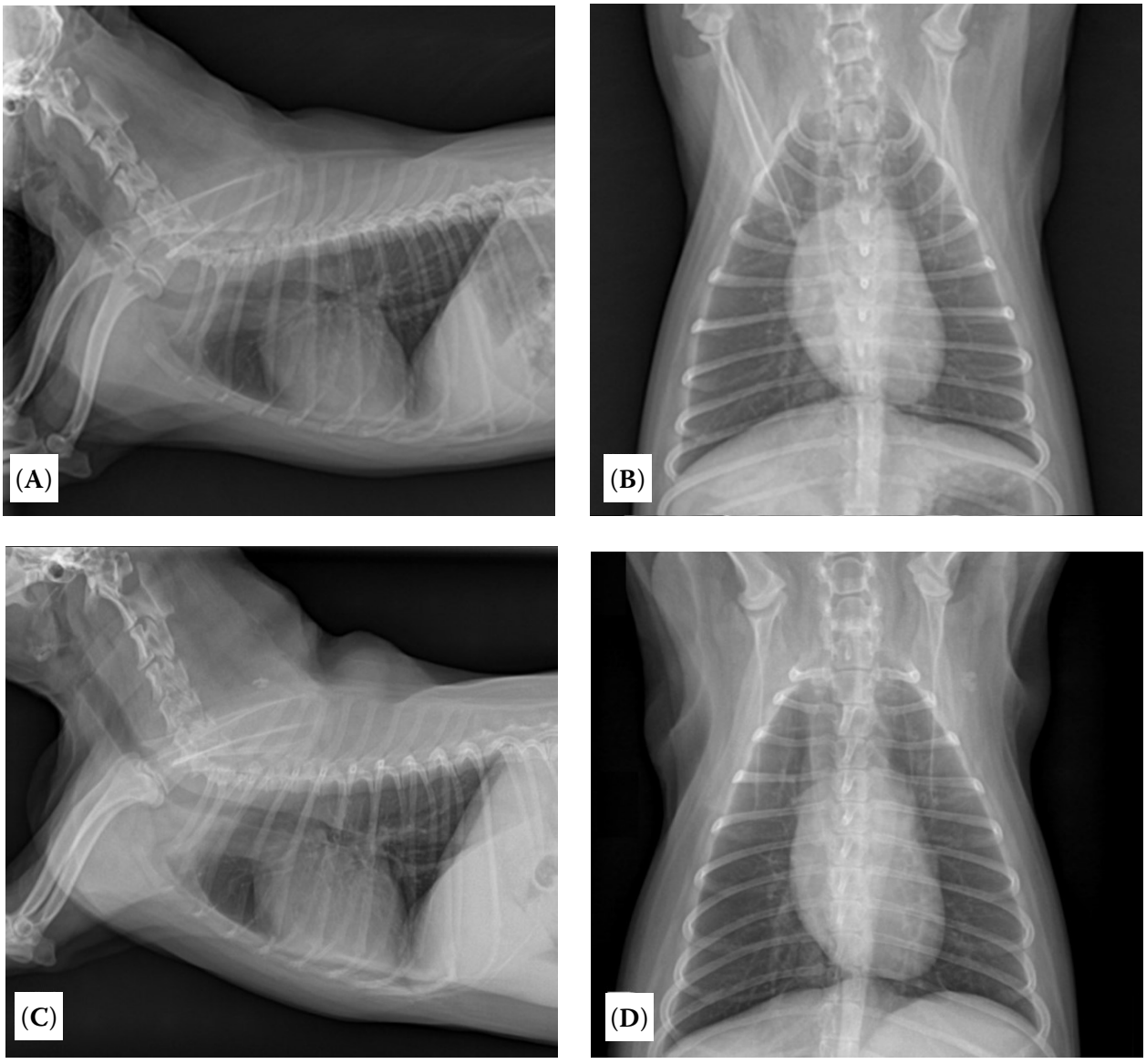

Figure 1. Thoracic radiography in a dog with chronic cough before (**A**, **B**) and after (**C**, **D**) zafirlukast therapy. At presentation, no remarkable findings are observed in the overall lung field in the right lateral view (**A**) and in the ventrodorsal view (**B**). Ten weeks after initiating zafirlukast therapy, no remarkable changes compared to the first medical examination were observed in the right lateral view (**C**) and ventrodorsal view (**D**)

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stress. Radiography showed no remarkable findings in the overall lung field and a cardiac size within the normal range (vertebral heart score, 10.2; reference range 8.5–10.5) (Figures 1A and 1B). To exclude other potential causes of coughing, the dog underwent computed tomography, which also showed no remarkable findings, except for mild bronchiectasia (Figure 2). Based on the history, physical examination and diagnostic imaging findings, the dog was diagnosed with chronic bronchitis. Bronchoalveolar lavage (BAL) fluid analysis and culture were recommended for identification of causes of infection or allergy; however, the owner refused further examinations.

As previous medications such as antibiotics and a bronchodilator ineffectively controlled the refractory cough, we administered for five weeks prednisolone at 0.5 mg/kg *per os* (PO) twice daily (BID) (Solondo; Yuhan Co., Ltd., Seoul, Republic of Korea), chlorpheniramine (0.3 mg/kg PO BID; Peniramin; Yuhan Co., Ltd.), theophylline (10 mg/kg PO BID; Theolan-B SR Cap; Alvogen, Seoul, Republic of Korea), codeine (0.5 mg/kg PO BID; Codening Tab; Chong Kun Dang Pharmaceutical Corp., Ltd., Seoul, Republic of Korea) and N-acetylcysteine (20 mg/kg PO BID; Moktin Cap; Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea). However, the cough was not resolved and the dog began exhibiting corticosteroid-associated polyuria, polydipsia and polyphagia. Serum chemistry analysis revealed elevation in the activity of alanine transaminase (177 U/l; reference range 19–70 U/l). At this time and with the owner's consent, we gradually reduced the dose of prednisolone and stopped all other medications. We then tried the orally active leukotriene receptor antagonist zafirlukast (5 mg/kg PO BID; Accolate; AstraZeneca US, Wilmington, USA). With the administration of zafirlukast, the frequency and duration of the cough progressively improved, and by four weeks, the cough was mostly resolved. On thoracic radiography 10 weeks after the start of zafirlukast treatment, the bronchointerstitial pattern had mildly improved compared to the previous radiography examination at the first presentation (Figures 1C and 1D). For seven months, the dog remained in complete remission. During that time, the dog did not experience any adverse effects, and biochemistry analysis revealed normal results for the hepatic and renal panels.

DISCUSSION AND CONCLUSIONS

The radiographic signs of canine chronic bronchitis are thickening of the bronchial walls and an increased number of visible bronchial walls; however, not all patients have these radiographic changes (Padrid 1992). Some authors consider radiography to be relatively non-specific for chronic bronchitis (Mantis et al. 1998). In the present study, thoracic radiography revealed no remarkable findings on pre- and post-treatment, although the clinical symptoms improved after zafirlukast therapy. However, radiography is helpful in excluding other causes of coughing such as congestive heart failure, pulmonary neoplasia, pulmonary oedema and pneumonia in patients suspected of having chronic bronchitis (McKiernan 2000). With regard to other imaging techniques, echocardiography in dogs with canine chronic bronchitis can reveal right heart enlargement

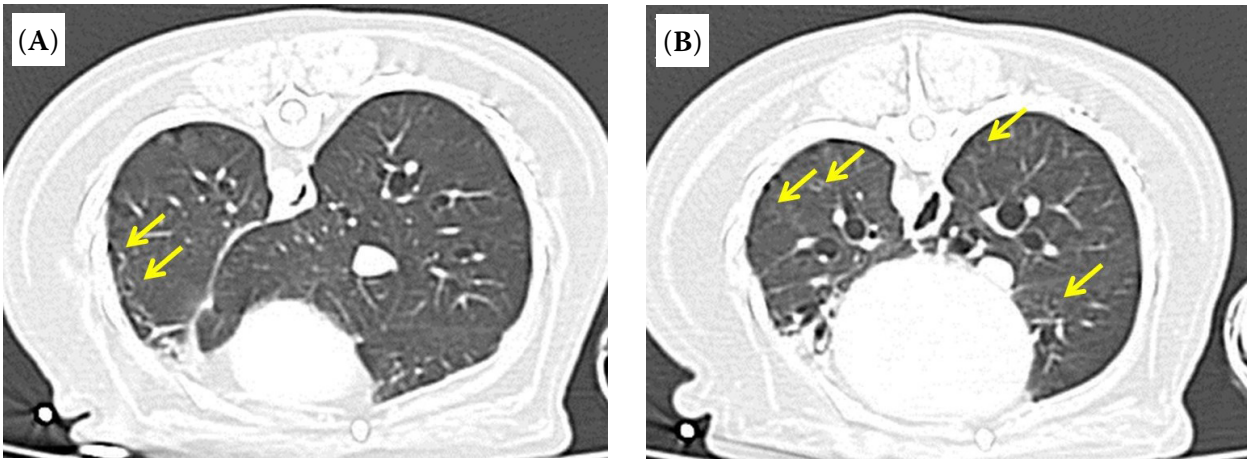

Figure 2. Computed tomography image of a dog with chronic cough. The bronchioles (arrows) are mildly dilated, which is consistent with bronchiectasia

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and cor pulmonale caused by secondary pulmonary hypertension (Rozanski 2014). However, the patient in this report did not show any other cardiac abnormalities in thoracic radiography and echocardiography. Computed tomography can reveal more details of the airway, compared to routine thoracic radiographs (Rozanski 2014). In this patient, computed tomography showed mild bronchiectasia but no other remarkable findings. Furthermore, BAL fluid analysis and culture can be used to identify the specific causes of canine chronic bronchitis, although these techniques generally are not required for diagnosing chronic bronchitis in humans (Rozanski 2014). In the present study, the owner refused further examinations, including BAL fluid analysis. However, based on the history taking, the patient had rarely been walked outside, had not been exposed to smoke or other inhaled irritants and had not been responsive to regular deworming and preventive antibiotics. Therefore, infections and foreign bodies were less likely, and allergic bronchitis was the most likely cause of chronic bronchitis in this patient.

Treatment goals for dogs with chronic bronchitis are a dampening of airway inflammation and relieving associated clinical signs to halt the progression of disease and airway remodelling (Rozanski 2014). Glucocorticoids are the mainstay therapy of chronic bronchitis and asthma, because they effectively suppress the inflammatory response by inhibiting the production of various inflammatory mediators (Barnes and Adcock 2003; Nafe et al. 2010). Prednisone is the most commonly used glucocorticoid medication to control clinical signs (Rozanski 2014). However, in this patient, administering glucocorticoid therapy did not manage the cough effectively, even with the concurrent administration of an antihistamine, a bronchodilator and a cough suppressant. Furthermore, the dog's elevated hepatic enzyme levels showed that it was suffering from the adverse effects of glucocorticoid therapy. Therefore, we considered alternative anti-inflammatory medicines to replace the long-term glucocorticoid administration for the refractory cough.

Some studies (Piatti et al. 2003; Byers 2005) suggest that zafirlukast may be effective in treating allergic bronchitis and rhinitis in humans and cats. However, no study exists on the successful long-term management of chronic bronchitis with zafirlukast in the dog. In the present study, zafirlukast effectively controlled intractable cough associated with chronic bronchitis. After monotherapy with zafirlukast for four weeks, the cough was significantly alleviated and was nearly resolved.

The orally active leukotriene receptor antagonist zafirlukast is effective in treating asthma in humans as a monotherapy or as a combination therapy with glucocorticoid medications (Drazen et al. 1999; Senter et al. 2002). The leukotrienes may have major roles in the pathogenesis of asthma and in other forms of allergic inflammation (Liu and Yokomizo 2015). Leukotrienes are proinflammatory mediators that have an important role in the pathophysiology of asthma (Drazen et al. 1999). They are also powerful bronchoconstrictors and specific chemoattractants for eosinophils (Sharma and Mohammed 2006). Asthma, atopic dermatitis, anaphylaxis and other allergies are included in type 1 hypersensitivity; therefore, leukotrienes are also crucial in late-phase hypersensitivity reactions and in the slow reaction of anaphylaxis (Drazen et al. 1999; Senter et al. 2002; Liu and Yokomizo 2015). Therefore, many reports exist concerning the administration of leukotriene receptor antagonists to treat human patients with asthma and allergic rhinitis (Drazen et al. 1999; Jeffery 2001). In these patients, leukotriene antagonists effectively attenuate airway constriction, the recruitment of eosinophils, airway responsiveness, mucus hypersecretion and chronic airway remodelling (Drazen et al. 1999; Jeffery 2001). Various reports have demonstrated that leukotriene receptor antagonists reduce the number of eosinophils in peripheral blood (Reiss et al. 1998; Laviolette et al. 1999), BAL fluid (Wenzel et al. 1995; Calhoun et al. 1998), bronchial biopsy tissue (Ramsay et al. 2009) and nasal lavage fluid (Piatti et al. 2003). Therefore, leukotriene receptor antagonists may have a potent effect on preventing the worsening of asthma and the loss of lung function (Jeffery 2001). In veterinary patients, the efficacy of zafirlukast is not well established. Some reports indicate that zafirlukast may be effective for treating canine atopic dermatitis and feline asthma (Senter et al. 2002; Reinero et al. 2005; Goodman et al. 2008). One study (Becker et al. 1995) reported that the application of a leukotriene biosynthesis inhibitor, MK-0591, in allergic dogs significantly blunted the acute allergic response and relieved the symptoms of asthma. In the present study, zafirlukast was very effective in controlling intractable cough, and we assume that the agent had a decisive effect on the patient's symptoms. Therefore, we also presume that the chronic cough was closely associated with

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type 1 hypersensitivity reactions such as asthma and allergic bronchitis.

Zafirlukast is also well tolerated in humans. However, pharyngitis and headache are the most common adverse effects and administering four times the approved dose increases alanine transaminase activity (Kelloway 1997; Reinero 2011). In one study (Finkel et al. 1999), systemic lupus erythematous was reported as an adverse effect of zafirlukast treatment. Veterinary experience and the number of veterinary studies on zafirlukast are very few; however, vomiting after oral dosing in some dogs has been reported (Senter et al. 2002). In preclinical toxicity studies (Senter et al. 2002), doses of 500 mg/kg did not cause any deaths. Thus, zafirlukast may be a safe and well-tolerated drug in dogs (Senter et al. 2002).

To the best of our knowledge, this is the first case report of the successful long-term management of chronic cough with zafirlukast in a dog. Furthermore, after ruling out infections, the administration of zafirlukast can be considered for dogs with a refractory and ill-defined cough or in glucocorticoid-intolerant dogs with chronic bronchitis.

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