Rhinology, 38, 142–146, 2001

Effects of leukotriene receptor antagonist therapy in patients with chronic rhinosinusitis in a real life rhinology clinic setting*

Andrew M. Wilson[1], Paul S. White[2], Quentin Gardiner[2], Ramez Nassif[2], Brian J. Lipworth[1]

The Rhinology Joint Medical/Surgical Megaclinic
[1] Asthma & Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, University of Dundee, Dundee, Scotland, UK
[2] Department of Otolaryngology, Ninewells Hospital & Medical School, University of Dundee, Dundee, Scotland, UK

SUMMARY

Although there is evidence from randomised controlled trials that leukotriene receptor antagonists are efficacious in chronic rhinosinusitis there are still little data on their use in everyday real life clinical practice. We report on a pragmatic case series of 32 patients referred from primary care with uncontrolled chronic rhinosinusitis (allergic or non-allergic) who have been treated with montelukast in our joint medical/surgical rhinology clinic. Patients' symptoms were scored according to "facial pain", "headache", "nasal blockage", "nasal discharge", "sense of smell" and "daily activity", and measurements of peak inspiratory nasal flow were made, before and after the introduction of montelukast 10mg/day. There were significant ($p<0.05$) improvements in subjective scoring for headache, nasal discharge & blockage, sense of smell and daily activity but not for facial pain, when montelukast was added along with other alterations in chronic rhinosinusitis medication (all receiving intra-nasal corticosteroids). Subgroup analysis of 10 patients, were the addition of montelukast was the only change to medical therapy, showed significant ($p<0.05$) improvements in headache, nasal discharge and blockage and their daily activity. There was no significant improvemens in nasal peak inspiratory flow or spirometry. In conclusion, montelukast may be a useful therapeutic option in addition to standard therapy (ie intra-nasal corticosteroids or anti-histamines) when treating patients with chronic rhinosinusitis in a real life clinical setting.

Keywords: montelukast, chronic rhinosinusitis, symptom scores, inspiratory flow, clinical setting

INTRODUCTION

Chronic rhinosinusitis is a common condition, with increasing prevalence, occurring in up to 20% of the population (Lundback, 1998). Although the condition does not result in hospitalisation or mortality, it is distressing to patients and may result in absenteeism from work (Blaiss, 2000). Topically delivered intra-nasal corticosteroids are widely recognised to be the first-line anti-inflammatory treatment for allergic chronic rhinosinusitis, as reflected in guidelines (Lund, 1994). They exert their anti-inflammatory activity in a non-selective way by affecting a wide range of inflammatory and structural cells.

Leukotrienes are important inflammatory mediators in the pathogenesis of allergic and non-allergic chronic rhinosinusitis (Bisgaard et al., 1986; Okuda et al., 1988; Naclerio et al., 1991). Their effects can now be inhibited specifically by leukotriene receptor antagonists (Lipworth, 1999). Although they are not currently licensed for the treatment of chronic rhinosinusitis, randomised controlled studies have shown clinical efficacy with leukotriene receptor antagonists (Donnelly et al., 1995; Grossman et al., 1997; Shirasaki et al., 1998). Furthermore, Knapp et al. (1990) showed that 5-lipoxygenase inhibition reduced allergen induced nasal congestion and levels of leukotrienes in nasal lavage fluid. However, these drugs have been shown to be less efficacious than intra-nasal corticosteroids. For example in seasonal allergic rhinosinusitis, zafirlukast has been shown to be inferior to intra-nasal beclomethasone dipropionate on nasal symptoms and biopsy (Pullerits et al., 1999), and intranasal budesonide to be superior to montelukast in terms of peak nasal

* Received for publication: November 13, 2000; accepted: March 28, 2001

inspiratory flow, symptoms and nitric oxide (Wilson et al., 2000).

We wished to evaluate effects of a leukotriene receptor antagonist (montelukast) in patients with severe, uncontrolled chronic rhinosinusitis in a real life clinic setting. This report discusses a series of 50 patients who attended the joint medical and surgical rhinology clinic at Ninewells Hospital between October 1998 and October 1999 and were prescribed a montelukast for the management of their chronic rhinosinusitis. Patients had been prescribed a leukotriene receptor antagonist by either a surgeon or physician working together. Treatment response was measured according to a validated symptom scoring system (Lund and Kennedy, 1995) and peak nasal inspiratory flow rate which has been shown to be comparable to rhinomanometry (Gleeson et al., 1986; Holmstrom et al., 1990).

MATERIAL AND METHODS

Patients

The case notes of 50 consecutive patients who received leukotriene receptor antagonists after primary care referral for management of their severe uncontrolled chronic rhinosinusitis were reviewed. The data from 18 patients was not suitable for serial analysis (before vs after) as the follow-up measurements were incompletely documented in the notes. None of the patients had previously been prescribed a leukotriene receptor antagonist. Of the 32 remaining patients, 24 had been given a diagnosis of asthma and in 22 a diagnosis of chronic rhinosinusitis by their primary care doctor prior to referral. Seventeen had a primary care diagnosis of nasal polyps. Nine patients had a prior diagnosis of septal deviation and 3 patients of chronic sinusitis.

All patients underwent rigid nasendoscopy in the rhinology clinic prior to commencement of the treatment. This confirmed nasal polyposis in all 17 patients who a primary care diagnosis and identified one extra patient with previously undiagnosed polyps. Significant septal deviation was identified in 11 patients. The septal deviation was considered significant if it was greater than 50% with or without turbinate contact. Nasal discharge was identified in 7 patients and the nasal mucosa was swollen and oedematous in 16 patients.

Patients recorded their symptoms according to a 10 point scale under the following headings: “facial pain”, “headache”, “nasal blockage”, “nasal discharge”, “lack of sense of smell” and “daily activity”. In each case 0 indicated no symptoms, or no impairment of smell or quality of life; and 10 represented severe symptoms.

Nasal peak inspiratory flow rate (nPIFR) was measured using an In-check™ flow meter (Clement Clarke International Ltd, Harlow, UK). After blowing their nose, patients inspired forcefully from residual volume to total lung capacity with their mouth closed. All measurements were made while in the sitting position with a good seal around a purpose built facemask.

The forced expiratory volume in one second (FEV1), forced mid expiratory flow rate (FEF25-75) and peak expiratory flow rate (PEFR) were performed according to criteria of the American Thoracic Society (American Thoracic Society, 1987) using a Vitalograph compact spirometer (Vitalograph Ltd, Buckinghamshire, UK). Forced expiratory manoeuvres were performed from total lung capacity to residual volume. The best test value was taken from three consistent measurements (a coefficient of variation of less than 5% was considered acceptable). The pneumotachograph head was calibrated daily using a precision syringe (Vitalograph Ltd., Buckinghamshire, UK).

The median duration of follow-up was 14 weeks with a range 6 weeks to 12 months. In all cases montelukast 10mg once daily was used instead of zafirlukast as it is the preferred drug of its class in our department due to its once daily dosing regimen, and lack of pharmacokinetic interactions and unaltered food bioavailability.

Statistical Analysis

The effect of treatment response was assessed by comparing measurements before and after the introduction of the leukotriene receptor antagonist by a paired Student’s t-Test ($p<0.05$, two tailed). Assessment was made regardless whether there was a pre-existing diagnosis of asthma or not.

An overall assessment was made of response to treatment in all 32 evaluable subjects all of whom were receiving intra-nasal corticosteroids. A subgroup analysis was then performed in 17 patients who had no change to their prescription of intra-nasal corticosteroid, although in 7 patients there was a modification of their histamine receptor antagonist therapy. In 4 of the 7 patients an anti-histamine had been started in the remaining 3 their anti-histamine was discontinued. A second sub-group analysis was performed on the group of 10 patients who had no change to any medication other than the addition of a leukotriene receptor antagonist. Of these 10 patients, 9 patients were not given an antihistamine and one patient was already receiving this therapy. The analysis was performed using Excel 97 (Microsoft, California, USA).

RESULTS

The mean (SE) baseline characteristics for the symptoms of the whole group of 50 patients were: facial pain 2.5 (0.4), headache 3.2 (0.5), nasal blockage 7.7 (0.4), nasal discharge 6.3 (0.5), hyposmia 6.3 (0.6), daily activity 7.3 (0.3). The spirometry was as follows PEF 88.1 (3.0) % predicted, FEV_1 86.5 (2.6) % predicted, FEF_{25-75} 65.1 (3.2) % predicted, nPIFR: 103.8 (5.8) l/min, nasal oral index 0.77 (0.04). When assessing the spirometry for patients with a history of asthma the PEF 87.3 (3.2) % predicted, FEV_1 83.4 (4.3) % predicted FEF_{25-75} 62.2 (3.9) % predicted; and without asthma PEF 91.7 (3.2) % predicted FEV_1 101 (4.3) % predicted, FEF_{25-75} 78.4 (4.3) % predicted.

The use of montelukast when combined by alterations in other medication (usually intra-nasal corticosteroids) for chronic rhinosinusitis (n=32) resulted in significant improvement in patients experience of headache, nasal discharge & blockage, their sense of smell and daily activity but not for facial pain (Table 1). Subgroup analysis of patients who had not altered the dose or type of intra-nasal corticosteroid (n=17) also showed symptomatic improvement in their headache, nasal discharge and blockage and their daily activity (Table 1). There were sim-

ilar findings in patients who had no change to their medication when seen at the clinic apart for the addition of a leukotriene receptor antagonists (n=10) (Table 1, Figure 1).

There was no significant improvement in the spirometry or nasal inspiratory flow rate for the group as a whole or for either of the subgroups (Table 2). However when looking at the group of 24 patients who were diagnosed with asthma there was a significant ($p<0.05$) improvement in peak expiratory flow rate from 86.4 (5.1) to 91.8 (4.5) % predicted. There was no improvement in FEV1 or FEF25-75.

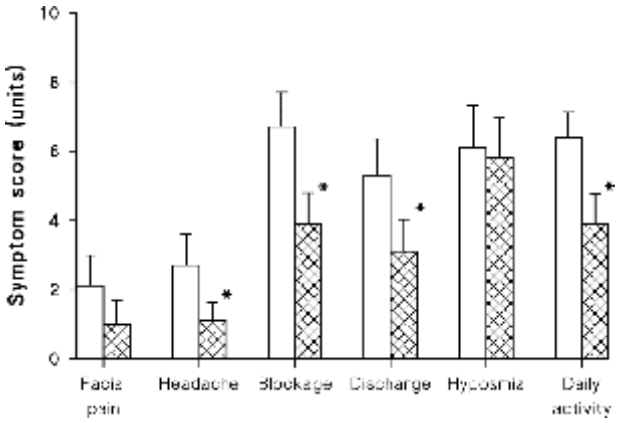

Figure 1. Mean (with standard error) scores (from 0 to 10) for facial pain, headache, nasal blockage (blockage), nasal discharge (discharge), hyposmia and daily activity before (open) and after(shaded) the introduction of leukotriene receptor antagonist therapy in the 10 patients who had no other alteration to their medication. Astericks denotes significant ($p<0.05$) difference after treatment.

DISCUSSION

We have shown that montelukast 10mg once daily was effective in managing patients referred with uncontrolled symptoms of chronic rhinosinusitis including nasal blockage, nasal discharge, headache and daily activity. Similar results were found when only analysing those patients who had no intervention other than the addition of montelukast. These results are in keeping with the findings of Parnes and Chuma who found symptomatic improvement in patients with sinonasal polyposis with zafirlukast and zileuton (Parnes and Chuma, 2000).

Leukotrienes are important inflammatory mediators involved in the pathogenesis of chronic rhinosinusitis (Busse, 1996; Howarth, 2000). Nasal challenge with leukotrienes have been shown to increase nasal resistance and patients symptoms of sneezing and nasal itch (Bisgaard et al., 1986). They are also present in higher concentrations after nasal allergen challenge. Numata et al. (1999) have shown that after allergen challenge there was improvement in acoustic rhinometry measurement of nasal volume with a leukotriene receptor antagonist (pranlukast) but this was not significant with an anti-histamine (mequitazine).

There is interest in patients with a triad of asthma, nasal polyps and aspirin sensitivity. Indeed 15 of our patients had both nasal polyps and a history of asthma, and 8 had a documented history of aspirin sensitivity. It is recognised that these patients have increased release of leukotrienes into nasal secretions (Picado et al., 1992) and from peripheral leukocytes (Mewes et al., 1996); and recently it has been shown that this is due to alternations in leukotriene metabolism within nasal mucosal epithelium (Picado et al., 1999; Kowalski et al., 2000). Furthermore, leukotriene receptor antagonists have been shown to be beneficial in treating the nasal symptoms of these patients (Ulualp et al., 1999)

Table 1. Mean (with standard error) scores (from 0 to 10) for facial pain, headache, nasal blockage, nasal discharge, hyposmia and daily activity before and after the introduction of leukotriene receptor antagonist therapy. Data is shown for all patients, for patients who had no change to their intra-nasal corticosteroid therapy and for patients who no alteration in their therapy apart from the addition of montelukast. Significance levels for difference before and after treatment are shown

		Facial pain	headache	nasal block	discharge	hyposmia	Daily activity
All patients	Before	3.0 (0.5)	3.4 (0.6)	7.8 (0.5)	6.5 (0.6)	6.7 (0.7)	7.5 (0.4)
32 patients	After	2.1 (0.5)	2.0 (0.4)	5.1 (0.6)	3.4 (0.6)	5.2 (0.7)	4.9 (0.6)
		p=0.11	p<0.005	p<0.001	p<0.001	p<0.05	p<0.001
No change to intranasal corticosteroid	Before	3.3 (0.7)	3.6 (0.8)	7.3 (0.7)	5.1 (0.9)	6.3 (1.0)	7.5 (0.6)
17 patients	After	1.9 (0.7)	1.8 (0.5)	5.2 (0.8)	3.5 (0.7)	5.9 (0.9)	5.0 (0.8)
		p=0.14	p<0.05	p<0.05	p<0.05	p=0.46	p<0.005
No change to medication	Before	2.1 (0.9)	2.7 (0.9)	6.7 (1.0)	5.3 (1.1)	6.1 (1.2)	6.4 (0.7)
10 patients	After	1.0 (0.7)	1.1 (0.5)	3.9 (0.9)	3.1 (0.9)	5.8 (1.2)	3.9 (0.9)
		p=0.39	p<0.05	p<0.05	p<0.05	p=0.75	p<0.05

		PEFR	FEV1	FEF_{25-75}	nPIFR
All patients	Before	86.7 (4.2)	85.1 (3.3)	64.0 (4.4)	97.1 (6.2)
32 patients	After	90.3 (3.8)	85.3 (2.8)	63.2 (4.0)	100.2 (6.2)
		p=0.28	p=0.91	p=0.72	p=0.89
No change to intranasal corticosteroid	Before	85.1 (4.7)	82.6 (3.8)	64.7 (6.7)	100.8 (7.1)
17 patients	After	87.7 (5.0)	83.9 (2.8)	65.8 (5.9)	98.5 (9.3)
		p=0.49	p=0.93	p=0.96	p=0.38
No change to medication	Before	92.7 (5.1)	88.9 (4.2)	76.0 (10.1)	102.5 (8.8)
10 patients	After	90.5 (6.3)	86.8 (3.7)	73.5 (9.5)	100.0 (12.6)
		p=0.79	p=0.30	p=0.74	p=0.34

Table 2. Mean (with standard error) scores (from 0 to 10) for peak expiratory flow rate (PEFR), force expiratory volume in 1 second (FEV1), mid expiratory flow rate (FEF25-75), nasal peak inspiratory flow rate (nPIFR) and nasal oral index (NOI), before and after the introduction of leukotriene receptor antagonist therapy. Data is shown for all patients, for patients who had no change to their intra-nasal corticosteroid therapy and for patients who no alteration in their therapy apart from the addition of montelukast. Significance levels for difference before and after treatment are shown

It is interesting that our patients had sub-normal spirometry values. Even with analysing the data for patients without a history of asthma the measure of small airways obstruction (FEF25-75) showed only two thirds of the predicted value. In this respect it is recognised that there is an association between upper and lower airways inflammation (Grossman, 1997). Mechanisms of this phenomenon include a neural reflex between upper and lower airways (Kaufman and Wright, 1969; Kaufman et al., 1970; Fontanari et al., 1996) and increased incidence of mouth breathing due to nasal obstruction (Griffin et al., 1982).

There was no improvement in patients' spirometry or nasal flow measures. In the subgroup of patients with asthma there was improvement in their peak expiratory flow rate but not other spirometric measures. It is recognised that "one-off" measurements or airway function are likely to be less representative of disease control than integrated daily measures, as chronic rhinosinusitis disease severity varies either spontaneously or in response to allergen exposure and treatment. For example, in a study comparing the effect of intranasal corticosteroid and combined mediator blockage there was a significant difference with both treatments compared to placebo with domiciliary nasal inspiratory flow rate, but not with acoustic rhinometry or rhinomanometry (Wilson et al., 2001). In this respect domiciliary measures of nasal inspiratory flow have been shown to correlate with patients symptoms (Wilson et al., 2000).

In conclusion, we have shown that montelukast was effective at controlling symptoms of chronic rhinosinusitis when used along with other chronic rhinosinusitis medication, in the clinical setting and its addition to standard medication (intranasal corticosteroids, anti-histamines) resulted in a significant improvement of symptoms. These results are in keeping with previous laboratory studies demonstrating clinical efficacy. Further larger clinical studies should be performed to determine which patients will benefit most from this form of therapy, as for example in patients with nasal polyps and associated rhinosinusitis.

ACKNOWLEDGEMENT

This study was funded by a University of Dundee grant and received no support from the pharmaceutical industry. BJL has received financial support for clinical studies and postgraduate lectures from Merck, who make montelukast

REFERENCES

1. American Thoracic Society (1987) Standardisation of spirometry - update. Am Rev Respir Dis 136: 1285-1298.
2. Bisgaard H, Olsson P, Bende M (1986) Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. Clin Allergy 16: 289-297.
3. Blaiss MS (2000) Cognitive, social, and economic costs of allergic rhinitis Allergy Asthma Proc 21: 7-13.
4. Busse WW (1996) The role of leukotrienes in asthma and allergic rhinitis Clin Exper Allergy. 26: 868-879.
5. Donnelly AL, Glass M, Minkwitz MC, Casale TB (1995) The leukotriene D4-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. Am J Respir Crit Care Med 151: 1734-1739.
6. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y (1996) Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J Appl Physiol 81: 1739-1743.

7. Gleeson MJ, Youlten LJ, Shelton DM, Siodlak MZ, Eiser NM Wengraf CL (1986) Assessment of nasal airway patency: a comparison of four methods Clin Otolaryngol Allied Sci 11: 99-107.
8. Griffin MP, McFadden ER Ingram RH (1982) Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. J Allergy Clin Immunol 69: 354-359.
9. Grossman J (1997) One airway, one disease Chest 111: 11S-16S.
10. Grossman J, Ratner PH, Nathan R, Adelglass J, De Jong PM (1997) Pranlukast (Ultair, SM 205312, ONO-1078), an oral leukotriene receptor antagonist, relieves symptoms in patients with seasonal allergic rhinitis (SAR) J Allergy Clin Immunol 99: s443.
11. Holmstrom M, Scadding GK, Lund VJ, Darby YC (1990) Assessment of nasal obstruction. A comparison between rhinomanometry and nasal inspiratory peak flow. Rhinology 28: 191-196.
12. Howarth PH (2000) Leukotrienes in Rhinitis. Am J Respir Crit Care Med. 161: s133-s136.
13. Kaufman J, Chen JC, Wright GW (1970) The effect of trigeminal resection on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man. Am Rev Respir Dis 101: 768-769.
14. Kaufman J, Wright GW (1969) The effect of nasal and nasopharyngeal irritation on airway resistance in man. Am Rev Respir Dis 100: 630.
15. Knapp HR (1990) Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. N Engl J Med 323: 1745-1748.
16. Kowalski ML, Pawliczak R, Wozniak J, Siuda K, Poniatowska M, Iwaszkiewicz J, Kornatowski T, Kaliner MA (2000) Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerent patients. Am J Respir Crit Care Med. 161: 391-398.
17. Lipworth BJ (1999) Leukotriene-receptor antagonists. Lancet 353: 57-62.
18. Lund VJ (1994) International consensus report on the diagnosis and management of rhinitis. International rhinitis management working group. Allergy 49 (Suppl 19): 1-34.
19. Lund VJ, Kennedy DW (1995) Quantification for staging sinusitis. Ann Otol Rhinol Laryngol 104 (Suppl 167): 17-21.
20. Lundback B (1998) Epidemiology of rhinitis and asthma. Clin Exper Allergy. 28 Suppl 2: 3-10.
21. Mewes T, Riechelmann H, Klimek L (1996) Increased in vitro cysteinyl leukotriene release from blood leukocytes in patients with asthma, nasal polyps, and aspirin intolerance. Allergy 51: 506-510.
22. Naclerio RM, Baroody FM, Togias AG (1991) The role of leukotrienes in allergic rhinitis: a review. Am Rev Respir Dis 143: S91-S95.
23. Numata T, Konno A, Yamakoshi T, Hanazawa T, Terada N, Nagata H (1999) Comparative role of peptide leukotrienes and histamine in the development of nasal mucosal swelling in nasal allergy. Ann Otol Rhinol Laryngol 108: 467-473.
24. Okuda M, Watase T, Mezawa A, Liu C (1988) The role of leukotriene D4 in allergic rhinitis. Ann Allergy 60: 537-540.
25. Parnes SM, Chuma AV (2000) Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear Nose Throat J 79: 24-25.
26. Picado C, Fernandez-Morata JC, Juan M, Roca-Ferrer J, Fuentes M, Xaubet A, Mullol J (1999) Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. Am J Respir Crit Care Med. 160: 291-296.
27. Picado C, Ramis I, Rosello J, Prat J, Bulbena O, Plaza V, Montserrat JM, Gelpi E (1992) Release of peptide leukotriene into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients Am Rev Respir Dis 145: 65-69.
28. Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J (1999) Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med. 159: 1814-1818.
29. Shirasaki H, Asakura K, Narita S, Kataura A (1998) The effect of a cysteinyl leukotriene antagonist, ONO-1078 (pranlukast) on agonist- and antigen-induced nasal microvascular leakage in guinea pigs. Rhinology 36: 62-65.
30. Ulualp SO, Sterman BM, Toohil RJ (1999) Antileukotriene therapy for the relief of sinus symptoms in aspirin triad disease. Ear Nose Throat J 78: 604-606.
31. Wilson AM, Dempsey OJ, Sims EJ, Coutie WJ, Patterson MC, Lipworth BJ (2000) Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exper Allergy. 30: 833-838.
32. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ (2001) A comparison of topical budesonide and oral montelukast seasonal allergic rhinitis and asthma. Clin Exper Allergy (in press).
33. Wilson AM, Orr LC, Sims EJ, Lipworth BJ (2001) Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exper Allergy. 31: 61-68.

Dr. B.J. Lipworth
Professor of Allergy and Respiratory Medicine
Ninewells Hospital and Medical School
University of Dundee
Dundee, Scotland
United Kingdom DD1 9SY

Tel: +44-1382 632983 (direct) 632180 (sec)
Fax: +44-1382 632983 (direct) 644972 (sec)