Cystic fibrosis

Macrolide antibiotics and cystic fibrosis

D G Peckham

Do the macrolides have a role in the treatment of cystic fibrosis?

There is growing interest in the potential use of macrolide antibiotics as anti-inflammatory agents in cystic fibrosis. This stems from the dramatic success of long term erythromycin in the treatment of diffuse panbronchiolitis (DPB), a condition with a high prevalence in Japan but rare elsewhere.[1–3] Clinically, DPB exhibits some similarities to cystic fibrosis including chronic productive cough, exertional dyspnoea, chronic sinusitis, mucoid *Pseudomonas aeruginosa* colonisation, and bronchiectasis. The introduction of erythromycin as a treatment for DPB has had a dramatic impact on mortality, increasing 10 year survival from 12.4–21.9% to over 90% in those colonised with *P aeruginosa*.[3 4] Similar success has been reported with clarithromycin, roxithromycin, and azithromycin.[1 3] While the aetiology of both conditions may be very different, it is the similarities which beg the question "do the macrolides have a role in the treatment of cystic fibrosis?"

The macrolide antibiotics are an intriguing group of drugs with both anti-inflammatory and antibacterial properties.[4] Their mode of action in DPB is thought to be mediated by mechanisms other than antibacterial as the effect occurs below the minimum inhibitory concentration required for bacteria such as *Haemophilus influenzae* and *P aeruginosa*.[1 3]

There are several theoretical reasons why the macrolides could modulate the disease process in cystic fibrosis. Firstly, airway inflammation, as in DPB, is recognised as a major factor in the pathogenesis of cystic fibrosis lung disease.[5–7] Anti-inflammatory drugs such as high doses of non-steroidal anti-inflammatory agents and prednisolone have been shown to slow the decline of lung function in patients with cystic fibrosis.[8–10] Several studies suggest that the macrolides also possess important anti-inflammatory activity which appears to be mediated by an inhibition of neutrophil chemotaxis, reduction of neutrophil elastase, and modification of pro-inflammatory cytokines with suppression of interleukin (IL)-1β, IL-6, IL-8, and tumour necrosis factor (TNF)-α production.[1 2 4 11] Secondly, they reduce sputum viscoelasticity and airway adhesion of *P aeruginosa*.[2 12 13] Certain macrolides have the innate ability to increase the killing of mucoid *P aeruginosa*, a mechanism that may be mediated by their ability to disrupt the integrity of the protective biofilm and impair the transformation of non-mucoid *P aeruginosa* to the more virulent mucoid phenotype.[14–16]

The clinical evidence to support the use of macrolides in the treatment of cystic fibrosis is poor. Most of the studies have only been published in abstract form and are usually anecdotal with small numbers of patients. Frederiksen *et al* reported a larger randomised, double blind, placebo controlled, crossover study of the effect of twice daily clarithromycin in cystic fibrosis.[17] Various parameters were measured including pulmonary function but, unexpectedly, 20 of 41 patients were excluded from the study so that no conclusions could be drawn. Importantly, failure to complete the study was not related to the active arm.

> "Treatment with azithromycin was associated with significantly fewer courses of intravenous antibiotics, maintenance of lung function, reduction in median CRP levels, and improvement in quality of life scores"

In this issue of *Thorax* Wolter *et al* report their findings of the first published prospective, randomised, placebo controlled trial investigating the clinical effect of macrolides in the treatment of cystic fibrosis.[18] A total of 49 adults with cystic fibrosis completed the 3 month trial of 250 mg azithromycin versus placebo. Treatment with azithromycin was associated with significantly fewer courses of intravenous antibiotics, maintenance of lung function, reduction in median C reactive protein (CRP) levels, and improvement in quality of life scores. While there was no difference in baseline microbiology, *Staphylococcus aureus* was isolated from 41.3% of patients at the start of the study. This suggests that some of the clinical response seen in the azithromycin group may have been mediated through the antibacterial activity of the drug. Similar results have been reported in children. In a non-randomised open labelled study Pirzada *et al* compared the effect of 250 mg azithromycin in 18 children with cystic fibrosis and 18 age and sex matched controls over a mean of 0.78 years.[18] The azithromycin treated group showed significant improvement in lung function and weight gain. The drug was well tolerated and no significant side effects were observed.

In the only other study to be formally published, Jaffe *et al* reported their findings from an open study of seven children with cystic fibrosis given 250 mg azithromycin for more than 3 months.[20] Although azithromycin was associated with a significant increase in lung function, the results are difficult to interpret.

While the study by Wolter *et al* supports the potential role of macrolides in the treatment of cystic fibrosis, larger double blind, placebo controlled trials are needed which can differentiate between the anti-inflammatory and antibacterial properties of these agents. With the potential ability of the macrolides to alter the complex bacteria/epithelial/biofilm interaction, it is possible that they may have a role both in reducing the incidence of new *P aeruginosa* colonisation and improving conventional early eradication treatment.[21]

Thorax 2002;**57**:189–190

Author's affiliation
D G Peckham, Regional Adult CF Unit, Seacroft Hospital, Leeds LS14 6UH, UK

Correspondence to: Dr D Peckham, Regional Adult CF Unit, Seacroft Hospital, Leeds LS14 6UH, UK

REFERENCES

1 **Koyama H**, Geddes DM. Erythromycin and diffuse panbronchiolitis. *Thorax* 1997;**52**:915–8.
2 **Jaffe A**, Bush A. Anti-inflammatory effects of macrolides in lung disease. *Pediatr Pulmonol* 2001;**31**:464–73.
3 **Hoiby H**. Diffuse panbronchiolitis and cystic fibrosis: East meets West. *Thorax* 1994;**49**:531–2.
4 **Black PN**. Anti-inflammatory effects of macrolide antibiotics. *Eur Respir J* 1997;**10**:971–2.
5 **Armstrong DS**, Grimwood K, Carzino R, *et al*. Lower respiratory tract infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**:1571–2.
6 **Kahn TZ**, Wagener JS, Bost T, *et al*. Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med* 1995;**151**:1075–82.

7 **Konstan MW**, Hilliard KA, Norvell TM, *et al*. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. *Am J Respir Crit Care Med* 1994;**150**:448–54.
8 **Konstan MW**, Byard PJ, Hoppel CL, *et al*. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995;**332**:848–54.
9 **Auerbach HS**, William M, Kirkpatrick JA, *et al*. Alternate day prednisolone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;ii:686–8.
10 **Eigen H**, Rosenstein BJ, Fitzsimmons S, *et al*. Cystic Fibrosis Foundation Prednisolone Trial Group. A multicenter study of alternate day prednisolone therapy in patients with cystic fibrosis. *J Pediatr* 1995;**126**:515–23.
11 **Bell SC**, Wolter JM, Seeney SL, *et al*. Azithromycin reduces TNF-α release from lipopolysaccharide (LPS) in cystic fibrosis (abstract). *Pediatr Pulmonol* 2000;Suppl 20:261.
12 **Tai S**, Sudo E, Sun F, *et al*. Effect of azithromycin on sputum rheology in cystic fibrosis patients (abstract). *Pediatr Pulmonol* 1999;Suppl 19:264.
13 **Fisher JJ**, Baumon U, Gudowius P, *et al*. Azithromycin reduces epithelial adherence of P aeruginosa in patients with cystic fibrosis (abstract). *Pediatr Pulmonol* 1999;Suppl 19:265.
14 **Yasuda H**, Ajiki Y, Koga, T, *et al*. Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. *Antimicrob Agents Chemother* 1993;**37**:1749–55.
15 **Kobayashi H**. Biofilm disease: its clinical manifestation and therapeutic possibilities of macrolides. *Am J Med* 1995;**99**:26–30.
16 **Kobayashi O**, Moser C, Jensen PO, *et al*. Azithromycin treatment inhibits induction of mucoid phenotype in susceptible BALB/c mice with chronic Pseudomonas aeruginosa lung infection (abstract). In: *Proceedings of XIIIth International Cystic Fibrosis Congress, Stockholm, Sweden* 2000:164.
17 **Frederiksen B**, Koch C, Hoiby N, *et al*. Clinical efficacy of clarithromycin in CF patients with chronic lung infection. *Abstracts of the 24th European Cystic Fibrosis Conference, Vienna, Austria* 2001:P208.
18 **Wolter J**, Seeney S, Bell S. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002;**57**:212–6.
19 **Pirzada OM**, Taylor CJ. Long-term macrolide antibiotics improve pulmonary function in cystic fibrosis (abstract). *Pediatr Pulmonol* 1999;Suppl 19:263.
20 **Jaffe A**, Jackie F, Rosenthal M, *et al*. Long-term azithromycin may improve lung function in children with cystic fibrosis. *Lancet* 1998;**351**:420.
21 **Frederiksen B**, Koch C, Hoiby N. Antibiotic treatment at time of initial colonisation with Pseudomonas aeruginosa postpones chronic infection and prevents deterioration in pulmonary function in patients with cystic fibrosis. *Pediatr Pulmonol* 1997;**23**:330–5.

Asthma

Psychological factors in asthma control and attack risk

L M Osman

The risk of asthma episodes may depend on a complex relationship between psychological factors and the experience of a recent attack.

In a series of Australian studies Yellowlees,[1] Ruffin,[2] and Campbell[3] have found high rates of anxiety and panic disorder among patients who have suffered near fatal asthma episodes. In the UK Ayres and coworkers have found a high lifetime prevalence of psychiatric symptoms and psychiatric morbidity in patients with brittle asthma.[4 5] Both the Australian studies and that by Ayres *et al* report a consistent pattern of high levels of denial of asthma and delay in seeking help in acute attacks. The confidential enquiries into asthma deaths[6–8] suggest that psychological factors including denial and delay contribute to some deaths. Patients who had died from asthma were more likely to be those who found it difficult to cooperate with medical management.

However, these studies only refer to a small minority of asthma patients, are post hoc, and may be relevant only to a special group of asthmatic subjects. It is not easy to translate these findings for very severe high risk subjects to moderate asthmatics in general practice.

Anxiety is not always found to be higher among patients with poorly controlled asthma. Barboni *et al*[9] compared patients with near fatal asthma with a group of matched controls and found no difference in psychiatric anxiety scores between the two groups. Boseley *et al*[10] found no significant difference in anxiety between adherent and non-adherent patients. Some anxiety may be useful in self-management. Spinhoven *et al*[11] found that anxious subjects were more accurate in detecting a fault in forced expiratory volume in 1 second (FEV_1) on bronchial challenge than non-anxious subjects; they hypothesised that anxiety might produce greater vigilance. On the other hand, greater accuracy of perception of variability in asthma might lead to greater anxiety.

Delay and denial have frequently been identified in qualitative studies of the attitudes of asthma patients to self-management. In one study[12] in which 30 general practice patients with a diagnosis of asthma prescribed regular inhaled steroids were interviewed, about half the patients accepted their asthma and used regular daily inhaled steroids or had a pragmatic approach to asthma control using inhaled steroids intermittently but reporting that this strategy was successful. The other 50% of interviewees did not accept that they had asthma and were classified as "deniers". Their self-definition commonly was that they had a "bad chest" which resulted in intermittent illness but was not a permanent condition. None of the "deniers" used their prescribed inhaled steroid. Denial was related to seeing asthma as a stigmatised illness and also to seeing themselves as people who could "cope". To these subjects, acceptance of a self-definition of having asthma and using a preventer regularly would mean that they were "not coping".

Janson and Becker[13] prospectively followed 95 patients with asthma and assessed the reasons for the type of action taken when acute episodes occurred. They found that a delay in seeking help was common due to attitudes ranging from fear of steroids to the need to "tough it out"; however, they also found that a small but significant minority identified a pivotal episode in their dealing with acute asthma which changed their attitude to self-management.

The post hoc studies described at the beginning of this article present us with a believable association between denial, psychological morbidity, and a high risk of adverse outcome but they have the limitation of working backwards from a non-representative group. The qualitative studies support the belief that denial and delay are linked to patient willingness to cooperate actively in asthma self-management, but leave unanswered the question of the objective risk of acute episodes associated with different psychological patterns and attitudes to management. Among patients with moderate asthma, are "deniers" more at risk of acute episodes than patients who accept their asthma? In Janson's study was there any evidence that the patients who described themselves as having a pivotal experience that changed their attitudes to their asthma actually did demonstrate more successful asthma control?

Few studies have looked at the prospective consequences of psychological attitudes. In the 1980s Kaptein[14] showed

that patients admitted with asthma who had high anxiety scores were more likely to be re-admitted within 6 months. One recent study by Adams *et al*[15] in hospital outpatients has shown that the prospective risk of admission was related to greater use of strategies such as "hoping for a miracle" to cure asthma.

In this issue of *Thorax* the paper by Greaves *et al*[16] complements the findings by Adams *et al* and presents new data on how the effect of psychological factors on the risk of asthma episodes may depend on a complex relationship between psychological factors and the experience of a recent attack. We might expect patients who have had recent attacks to have low confidence, a high fear of attack, and a high risk of future attacks. Conversely, we would expect patients who have successfully controlled asthma for more than a year to have low anxiety/fear, high confidence, and a low risk of future attacks. Greaves *et al* show that the story is not so simple. Past attack experience does not completely explain patient differences in panic fear and confidence, and high confidence in a patient has different implications for the risk of an acute attack depending on whether the patient has a history of well controlled or poorly controlled asthma. They conclude that fear of attack is undesirable in patients with good asthma control but is good in patients with poor control. Similarly, confidence in control is good if asthma is well controlled, but too much confidence is bad if asthma is poorly controlled. Dirks *et al*[17] found more than 20 years ago that hospitalisation was more common in both patients with very high and very low levels of anxiety. The persistence of this pattern is striking as medical management of asthma has changed dramatically since the 1980s.

"Recent attack experience is an important mediator of patient behaviour and attitudes to asthma management"

The study by Greaves *et al*[16] suggests that there may "good" and "bad" denial of asthma symptoms. It is good for patients with well controlled asthma to be confident in their control and not to be fearful about their asthma, and this may be a form of "positive denial". Equally, lack of confidence in patients with stable asthma is not a good sign. Lack of confidence may be associated with depression and poor quality of life. In our own study in general practice patients with mild to moderate asthma[18] we found that poor quality of life was a prospective predictor of GP contact for asthma independent of asthma symptoms. Conversely, patients with high asthma confidence scores but who have poorly controlled asthma are expressing a belief in their ability to control episodes which is not warranted by their attack history. This is a denial of the need to change their self-management. This overconfidence is likely to be associated with poor compliance and delay in taking action during episodes. Chambers *et al*[19] found that the most frequent reason patients gave for non-use or intermittent use of inhaled corticosteroids was a belief that inhaled steroids were unnecessary during non-symptomatic periods. Factors associated with regular use of inhaled steroids were belief about the value of active participation with their doctor in self-care and belief that asthma was a serious health problem.

It would be of value to carry out further studies to determine whether the high confidence/high risk group in the study by Greaves *et al* is less compliant than the other groups described in the study .

Greaves *et al* suggest that the period immediately after a serious asthma episode may be a particularly important time for educating and negotiating with patients to change their self-management attitudes and behaviour. This is likely to be of critical importance for overconfident asthma patients who may comprise a significant minority of patients in general practice.

In conclusion, the study by Greaves *et al* makes clear that recent attack experience is an important mediator of patient behaviour and attitudes to asthma management. Future studies should be mindful of this.

Thorax 2002;**57**:190–191

Author's affiliation
L M Osman, Chest Clinic, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK

Correspondence to: Dr L M Osman, Chest Clinic, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK; l.osman@abdn.ac.uk

REFERENCES

1 **Yellowlees PM**, Ruffin RE. Psychological defences and coping styles in patients following a life-threatening attack of asthma. *Chest* 1989;**95**:1298–303.
2 **Ruffin RE**, Latimer KM, Schembri DA. Longitudinal study of near fatal asthma. *Chest* 1991;**99**:77–83.
3 **Campbell DA**, Yellowlees PM, McLennan G, *et al*. Psychiatric and medical features of near fatal asthma. *Thorax* 1995;**50**:254–9.
4 **Miles JF**, Garden GM, Tunnicliffe WS, *et al*. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. *Clin Exp Allergy* 1997;**27**:1151–9.
5 **Garden GM**, Ayres JG. Psychiatric and social aspects of brittle asthma. *Thorax* 1993;**48**:501–5.
6 **Mohan G**, Harrison BD, Badminton RM, *et al*. A confidential enquiry into deaths caused by asthma in an English health region: implications for general practice. *Br J Gen Pract* 1996;**46**:529–32.
7 **Burr ML**, Davies BH, Hoare A, *et al*. A confidential inquiry into asthma deaths in Wales. *Thorax* 1999;**54**:985–9.
8 **Bucknall CE**, Slack R, Godley CC, *et al*. Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994–6. *Thorax* 1999;**54**:978–84.
9 **Barboni E**, Peratoner A, Rocco PL, *et al*. Near fatal asthma and psychopathological characteristics: a group-control study. *Monaldi Arch Chest Dis* 1997;**52**:339–42.
10 **Bosley CM**, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J* 1995;**8**:899–904.
11 **Spinhoven P**, Peski-Oosterbaan AS, Van der Does AJ, *et al*. Association of anxiety with perception of histamine induced bronchoconstriction in patients with asthma. *Thorax* 1997;**52**:149–52.
12 **Adams S**, Pill R, Jones A. Medication, chronic illness and identity: the perspective of people with asthma. *Soc Sci Med* 1997;**45**:189–201.
13 **Janson S**, Becker G. Reasons for delay in seeking treatment for acute asthma: the patient's perspective. *J Asthma* 1998;**35**:427–35.
14 **Kaptein AA**. Psychological correlates of length of hospitalization and rehospitalization in patients with acute, severe asthma. *Soc Sci Med* 1982;**16**:725–9.
15 **Adams RJ**, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;**55**:566–73.
16 **Greaves CJ**, Eiser C, Seamark D, *et al*. Attack context: an important mediator of the relationship between psychological status and asthma outcomes. *Thorax* 2002;**57**:217–21.
17 **Dirks JF**, Kinsman RA, Horton DJ, *et al*. Panic-fear in asthma: rehospitalization following intensive long-term treatment. *Psychosom Med* 1978;**40**:5–13.
18 **Osman LM**, Calder C, Robertson R, *et al*. Symptoms, quality of life, and health service contact among young adults with mild asthma. *Am J Respir Crit Care Med* 2000;**161**:498–503.
19 **Chambers CV**, Markson L, Diamond JJ, *et al*. Health beliefs and compliance with inhaled corticosteroids by asthmatic patients in primary care practices. *Respir Med* 1999;**93**:88–94.