Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial

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Summary

Background Postinfectious cough is common in primary care, but has no proven effective treatments. Cysteinyl leukotrienes are involved in the pathogenesis of postinfectious cough and whooping cough (pertussis). We investigated the effectiveness of montelukast, a cysteinyl leukotriene receptor antagonist, in the treatment of postinfectious cough.

Methods In this randomised, placebo-controlled trial, non-smoking adults aged 16–49 years with postinfectious cough of 2–8 weeks' duration were recruited from 25 general practices in England. Patients were tested for pertussis (oral fluid anti-pertussis toxin IgG) and randomly assigned (1:1) to montelukast 10 mg daily or image-matched placebo for 2 weeks. Patients chose whether to continue study drug for another 2 weeks. The randomisation sequence was computer-generated and stratified by general practice. Patients, health-care professionals, and researchers were masked to treatment allocation. Effectiveness was assessed with the Leicester Cough Questionnaire to measure changes in cough-specific quality of life; the primary outcomes were changes in total score between baseline and two follow-up stages (2 weeks and 4 weeks). The primary analysis was by intention to treat with imputation by last observation carried forward. Recruitment closed on Sept 21, 2012, and follow-up has been completed. This trial is registered with EudraCT (2010-019647-19), UKCRN Portfolio (ID 8360), and ClinicalTrials.gov (NCT01279668).

Findings From April 13, 2011, to Sept 21, 2012, we randomly assigned 276 patients to montelukast (n=137) or placebo (n=139). 70 (25%) patients had laboratory-confirmed pertussis. Improvements in cough-specific quality of life occurred in both groups after 2 weeks (montelukast: mean 2·7, 95% CI 2·2–3·3; placebo: 3·6, 2·9–4·3), but the difference between groups did not meet the minimum clinically important difference of 1·3 (mean difference –0·9, –1·7 to –0·04, p=0·04). This difference was not statistically significant in any sensitivity analyses. After 2 weeks, 192 of 259 participants from whom data were available elected to continue study drug (99 [77%] of 129 participants on montelukast; 93 [72%] of 130 on placebo). After 4 weeks, there were no significant between-group differences in cough-specific quality of life improvement (montelukast: 5·2, 4·5–5·9; placebo: 5·9, 5·1–6·7; mean difference –0·5, –1·5 to 0·6, p=0·38) or adverse event rates (21 [15%] of 137 patients on montelukast reported one or more adverse events; 31 [22%] of 139 on placebo; p=0·14). The most common adverse events reported were increased mucus production (montelukast, n=6; placebo, n=2), gastrointestinal disturbance (montelukast, n=3; placebo, n=5), and headache (montelukast, n=2; placebo, n=6). One serious adverse event was reported (placebo, n=1), which was unrelated to study drug (shortness of breath and throat tightness after severe coughing bouts).

Interpretation Montelukast is not an effective treatment for postinfectious cough. However, the burden of postinfectious cough in primary care is high, making it an ideal setting for future antitussive treatment trials.

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Introduction

Postinfectious cough is commonly encountered in primary care and can affect nearly 40% of adults after an acute respiratory tract infection.[1] Postinfectious coughs present as subacute coughs and are thought to be caused by airway inflammation, epithelial disruption, and hyper-responsiveness.[2] Cysteinyl leukotrienes are likely to be important in postinfectious cough. In non-atopic adults, infection with rhinovirus increases expression of 5-lipoxygenase and 5-lipoxygenase-activating protein, which are both involved in the production of cysteinyl leukotrienes.[3] Increased cysteinyl leukotriene concentrations are reported in the nasal secretions of adults infected with respiratory syncytial virus (RSV), rhinovirus, or influenza A virus[4] and in the lung tissues of mice[5] and rats[6] infected with RSV. Raised concentrations are also observed in children with RSV bronchiolitis[7] and virus-induced wheeze.[8] Cysteinyl leukotrienes promote virus-induced airway inflammation by activating pulmonary dendritic cells[5] and potentiating the effects of inflammatory neuropeptides.[6] Respiratory viruses can also sensitise airways to leukotrienes by increasing production of interferon-γ,[8] thereby increasing cysteinyl leukotriene type 1 receptor expression.[9]

The expression of cysteinyl leukotriene type 1 receptors can also be upregulated by T helper cell type 2 (Th2)-type cytokines.[10] In adults, rhinovirus infection activates both Th1 and Th2-like cytokine responses. The balance between these responses might help to determine clinical outcome. Strong Th2-like cytokine responses are

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associated with increased symptom severity and increased time to virus clearance from sputum.[11] These factors might be important in the pathogenesis of persistent virus-induced symptoms including postinfectious cough. Th1 cells have also been shown to increase Th2 cell-mediated airway inflammation in the mouse model.[12] Additionally, infection with whooping cough (pertussis), which is recognised to be an important cause of postinfectious cough,[13] is associated with increased production of the Th2-like cytokine interleukin-13 in the mouse model.[14] Interleukin-13 is known to upregulate cysteinyl leukotriene production and receptor expression.[15]

Montelukast is a cysteinyl leukotriene type 1 receptor antagonist that is reported to improve cough[16] and prevent exercise-induced bronchoconstriction[17] in asthma. A trial comparing montelukast with ketotifen in the treatment of postinfectious cough[18] had inconclusive findings due to the use of poorly defined outcome measures, including subjective clinical efficacy ratings and an unvalidated four-point cough score. In another trial, montelukast was associated with significantly greater resolution of post-RSV bronchiolitis symptoms (cough, wheeze, shortness of breath) compared with placebo.[19] However, this finding was based on a post-hoc analysis of participants retrospectively defined as having persistent symptoms (ie, mean percentage of symptom-free days 30% or less during the first 2 weeks of treatment). A systematic review of treatments for pertussis-induced cough did not identify any trials of leukotriene receptor antagonists.[20]

We aimed to establish the effectiveness of montelukast in the treatment of postinfectious cough and explore in a subgroup analysis the efficacy of montelukast in the treatment of pertussis-induced cough.

Methods

Participants

For this randomised, placebo-controlled trial, health-care professionals at 25 general practices in the Thames Valley and southwest England recruited patients aged 16–49 years with postinfectious cough. Postinfectious cough was defined as cough of 2–8 weeks' duration triggered by an acute respiratory tract infection or with no established diagnosis (since the initial infection can cause very mild or no symptoms). Health-care professionals screened patients' eligibility for trial participation. Exclusion criteria were contraindication to montelukast, chronic severe disease associated with cough (eg, cystic fibrosis, bronchiectasis, cardiac failure), known immunodeficiency or immunocompromise, current smoker or recent ex-smoker (ie, gave up smoking less than 6 months ago), pregnancy, breastfeeding, regular treatment known to be associated with causing cough (eg, angiotensin-converting enzyme inhibitors), and participation in another clinical research study. Written informed consent was obtained from each participant. The trial was approved by Southampton and South West Hampshire Research Ethics Committee (10/H0502/37).

Randomisation and masking

Patients were randomly assigned to receive montelukast sodium 10 mg tablets or image-matched placebo tablets (main excipient lactose monohydrate; Merck, Sharp & Dohme, West Point, PA, USA) with a 1:1 allocation within each general practice. The randomisation sequence was computer-generated and retained by an independent statistician and stratified by general practice with a fixed block size of four. Participants, health-care professionals, and research staff were masked to treatment allocation, since montelukast and placebo tablets and bottles were identical in appearance.

Procedures

On study entry (day 0), health-care professionals recorded participants' date of birth, sex, duration of cough, self-administered drugs for cough, and household smoking status. Participants were also asked if they had experienced wheeze or nasal symptoms (sneezing, blocked nose, runny nose, itchy nose) since their cough started. Each participant was asked to rate how bothersome their nasal symptoms had been on a 100 mm visual analogue scale (VAS; 0=not at all bothersome, 100=extremely bothersome). An oral fluid sample was obtained from each participant and tested at the Health Protection Agency (London, UK; now Public Health England). Laboratory-confirmed pertussis was defined as an oral fluid anti-pertussis toxin IgG titre of 70 arbitrary units or more.[21]

Participants received study drugs in a bottle containing 28 montelukast 10 mg or placebo tablets. All participants were asked to take one tablet daily from days 1–14 and avoid taking self-administered treatment for cough. After 2 weeks, participants chose whether to continue their study drug.

At baseline, 2 weeks, and 4 weeks, participants were asked to complete the Leicester Cough Questionnaire (LCQ). The range of possible LCQ total scores is from 3 to 21, with a higher score indicating a better cough-specific quality of life.[22] Additionally, participants were asked to rate on a seven-point Likert scale how often during the past 2 weeks their cough got worse with exercise (1=every time I exercise, 7=never). Participants were also asked to record daily cough severity on a 100 mm cough VAS (days 0–14), number of paroxysms of cough (days 0–14), and study drug intake (days 1–14).

Health-care professionals recorded data for adverse events and cessation of cough at 2 weeks and 4 weeks. Data were extracted from participants' medical records on pertussis vaccinations, medical conditions, previous interventions, and further interventions for the cough (consultations, prescribed drugs, and investigations) up to 4 weeks after study entry.

The primary outcomes were LCQ total score changes between baseline and two follow-up points (2 weeks and

4 weeks). Changes in LCQ physical, psychological, and social domain scores between baseline and both follow-up points were secondary outcomes. Other secondary outcomes were overall cough severity, paroxysmal cough severity, cessation of cough, cessation of exercise-induced cough, further interventions for cough, and adverse events. We measured overall cough severity and paroxysmal cough severity by calculating areas under the curve (AUC) from days 1–14 for cough VAS scores and number of paroxysms of cough, respectively. Cessation of exercise-induced cough was defined as a score of 6 (rarely) or 7 (never).

Study drug adherence was defined as taking at least 50% of tablets, because plasma concentrations of montelukast in healthy adults have been shown to reach and maintain a steady state by day 2 of a 7-day treatment course (montelukast 10 mg daily)[23] and all trial participants were asked to take a minimum of 14 tablets of study drug. Furthermore, on the basis of clinical experience, we judged that any treatment effect would be most pronounced during the first week, when cough was most severe.

Statistical analysis

Allowing for a 25% dropout rate, our target sample size was 288 participants, giving an effective sample size of 216 participants. This number would give more than 80% power to detect the minimum clinically important difference in LCQ total score change (1·3), assuming a SD of 3·3 and two-tailed α of 0·05. The minimum clinically important difference is the smallest change in LCQ score which patients perceive to be clinically significant.[24]

We analysed data using STATA version 12SE. We did not do an interim analysis. We summarised continuous baseline characteristics of all randomly assigned participants using means and SDs (parametric data) or medians and IQRs (non-parametric data). We summarised categorical variables using numbers and percentages. We estimated overall recruitment rate and prevalence of laboratory-confirmed pertussis with 95% CIs and calculated attrition rates in each group.

Primary outcome and LCQ domain score data were analysed by intention to treat with imputation by last observation carried forward as specified in our statistical analysis plan. This imputation method is recommended as a conservative approach in cases where the condition is expected to improve spontaneously over time.[25] We calculated mean changes in LCQ total scores with 95% CIs using analysis of covariance (ANCOVA) adjusted for baseline scores and other baseline covariates (age, sex, atopy, pertussis status, pertussis vaccination status, duration of cough, paroxysmal cough severity, and exercise-induced cough severity). Baseline data for paroxysmal cough severity were obtained from participants' responses to LCQ item 11 (frequency of coughing bouts).

Per-protocol analyses were done for our primary outcomes in trial participants who met study eligibility criteria, showed study drug adherence, reported taking no self-administered drugs for cough and completed baseline and both follow-up Leicester Cough Questionnaires. Prespecified sensitivity analyses involved complete case analysis, adjustment for multiple comparisons (using α=0·025), multiple imputation to impute missing LCQ total and domain scores (univariate, linear regression with five datasets), mean values to impute missing baseline data, and best and worst possible prognosis in both groups.

Changes in LCQ domain scores, overall cough severity, and paroxysmal cough severity were also analysed with ANCOVA adjusted for baseline scores and other baseline covariates as previously listed. Logistic regression analyses adjusted for these same baseline covariates were done to assess between-group differences in cessation of cough and exercise-induced cough after 2 and 4 weeks. Proportions of patients who reported adverse events and underwent further interventions for cough during the 4 weeks after study entry were compared with χ² tests. We did exploratory analyses of our primary outcomes,
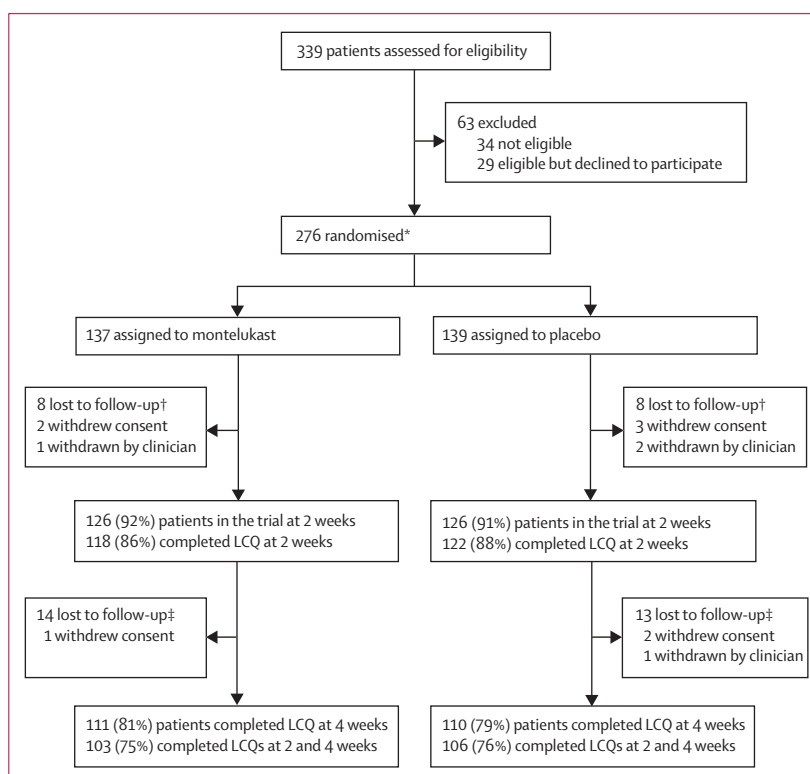

Figure 1: Trial profile
LCQ=Leicester Cough Questionnaire (primary outcome measure). *Eight patients were randomised in error, four to montelukast (one outside age range; one on angiotensin-converting enzyme inhibitor therapy; one with previous splenectomy; and one who gave up smoking less than 6 months ago), and four to placebo (all outside age range); number of patients analysed for primary outcome was 136 for montelukast and 139 for placebo (one patient assigned to montelukast did not complete the Leicester Cough Questionnaire at baseline). †Did not complete Leicester Cough Questionnaire at 2 weeks or 4 weeks and were not withdrawn from the study. ‡Completed Leicester Cough Questionnaire at 2 weeks, but not at 4 weeks, and were not withdrawn from the study.

overall cough severity, and paroxysmal cough severity adjusted for baseline scores in participants with laboratory-confirmed pertussis.

This trial is registered with EudraCT (2010-019647-19), UKCRN Portfolio (ID 8360), and ClinicalTrials.gov (NCT01279668).

Role of the funding source

Neither the funding source nor Merck, Sharp & Dohme were involved in study design, data collection, analysis or interpretation, report writing, or submission for publication. KW, KT, and RP had full access to all study data. KW had final responsibility for the decision to submit for publication.

Results

Between April 13, 2011, and Sept 21, 2012, we screened 339 patients of whom 276 were randomly allocated to receive montelukast (n=137) or placebo (n=139). This sample size allowed for a 22% dropout rate. Figure 1 summarises recruitment and follow-up of participants. Eight participants who did not meet trial eligibility criteria were randomly assigned to groups in error (montelukast, n=4; placebo, n=4). Recruitment rate was 90% (268/297 eligible patients, 95% CI 86·9–93·6) in patients meeting trial eligibility criteria. Attrition rates did not differ significantly between groups at 2 weeks (11 [8%] of 137 participants on montelukast; 13 [9%] of 139 participants on placebo; p=0·70) or 4 weeks (15 [11%] participants on montelukast; 16 [12%] on placebo; p=0·88).

At 2 weeks, 116 (85%) of 137 participants in the montelukast group and 118 (85%) of 139 participants in the placebo group adhered to study drug. 192 of 259 patients from whom data were available elected to continue study drug (montelukast, n=99 of 129; placebo, n=93 of 130). 61 participants in each group took 14 or more study drug tablets. Table 1 summarises the baseline characteristics of participants. Both groups reported severe impairment in cough-specific quality of life based on LCQ total scores. 70 (25%, 95% CI 20·2–30·5) of 276 participants had laboratory-confirmed pertussis.

Table 2 summarises changes in LCQ total and domain scores. Large improvements in cough-specific quality of life based on LCQ total score changes were reported in both groups at 2 weeks (montelukast: mean 2·7, 95% CI 2·2–3·3; placebo: 3·6, 95% CI 2·9–4·3). The adjusted mean between-group difference was statistically significant (–0·9, 95% CI –1·7 to 0·04, p=0·04), but not clinically significant (LCQ minimum clinically important difference=1·3). Large improvements in cough-specific quality of life were also reported at 4 weeks (montelukast: mean 5·2, 95% CI 4·5–5·9; placebo: mean 5·9, 95% CI 5·1–6·7), but the adjusted mean between-group difference was neither clinically nor statistically significant (–0·5, 95% CI –1·5 to 0·6, p=0·38). Between-group differences in LCQ total score changes after 2 and 4 weeks were neither clinically nor statistically significant in any per-protocol or sensitivity analyses (appendix).

Improvements in all three LCQ domains were observed in both groups at 2 and 4 weeks. At 2 weeks, the adjusted mean between-group difference in LCQ physical domain score change (–0·2, 95% CI –0·5 to 0·01, p=0·04), and that in LCQ psychological domain score change (–0·3, 95% CI –0·6 to –0·01, p=0·03) were both statistically but not clinically significant.

Montelukast was associated with lower overall cough severity than placebo (mean AUC of daily cough VAS scores: montelukast 483·9, 95% CI 439·0–528·9; placebo

	Montelukast (n=137)	Placebo (n=139)
Age (years)	37·9 (9·6)	37·8 (9·5)
Sex (female)	82 (60%)	97 (70%)
Smoker(s) in household	18 (13%)	15 (11%)
Pertussis*	31 (23%)	39 (28%)
Pertussis vaccination status (three doses)†	52 (38%)	58 (42%)
Atopy‡	22 (16%)	19 (14%)
Clinical features		
Duration of cough (weeks)	5·0 (1·9)	4·8 (1·8)
Duration of cough ≤4 weeks	62 (45%)	70 (50%)
Nasal symptoms§	102 (74%)	99 (71%)
Nasal symptom severity (VAS score, mm)	49 (19–78)	55 (22–76)
Wheeze	83 (61%)	88 (63%)
Exercise-induced cough severity¶	3·9 (1·9)	3·4 (1·9)
Previous interventions for current postinfectious cough		
≥2 primary care consultations	42 (31%)	53 (38%)
Chest radiograph	13 (9%)	13 (9%)
Antibiotics	45 (33%)	54 (39%)
Self-administered treatment		
Dextromethorphan	29 (21%)	31 (22%)
Codeine/pholcodeine	15 (11%)	19 (14%)
Antihistamines	7 (5%)	8 (6%)
Outcome variables		
LCQ total score‖	10·8 (3·0)	10·1 (2·8)
LCQ physical domain score‖	3·8 (1·0)	3·6 (1·0)
LCQ psychological domain‖	3·7 (1·1)	3·4 (1·0)
LCQ social domain‖	3·4 (1·2)	3·1 (1·2)
Cough severity, day 0 (VAS score, mm)**	58 (37–72·5)	62 (37–74)
Number of paroxysms of cough, day 0††	8 (4–20)	9 (5–20)

Data are number (%), mean (SD), or median (IQR). VAS=visual analogue scale (100 mm); cough VAS: 0=no cough, 100=worst cough ever; nasal symptom severity VAS: 0=not at all bothersome, 100=extremely bothersome. LCQ=Leicester Cough Questionnaire; range of possible scores 3–21. *Oral fluid anti-pertussis toxin IgG titre ≥70 arbitrary units. †Number of childhood vaccination records available: montelukast, n=84; placebo, n=85. ‡Diagnosis of asthma, hay fever, allergic rhinitis, or atopic eczema listed as active problem in participant's medical record. §Itchy nose, runny nose, blocked nose, or sneezing. ¶Montelukast, n=133; placebo, n=139; participants rated on seven-point Likert scale how often their cough got worse when they exercised: 1=every time I exercise, 2=most times when I exercise, 3=several times when I exercise, 4=some times when I exercise, 5=occasionally when I exercise, 6=rarely, 7=never. ‖Montelukast, n=136; placebo, n=139. **Montelukast, n=120; placebo, n=125. ††Montelukast, n=117; placebo, n=122.

Table 1: Baseline characteristics

540·5, 95% CI 487·8–593·1), but the adjusted mean between-group difference was not statistically significant (–23·8, 95% CI –83·5 to 35·9, p=0·44). Montelukast was also associated with lower paroxysmal cough severity than placebo (mean AUC of daily number of paroxysms of cough: montelukast 151·1, 95% CI 107·3–194·9; placebo 171·3, 95% CI 131·4–211·2), but the adjusted mean between-group difference was also not statistically significant (15·0, 95% CI –22·0 to 51·9, p=0·43).

The likelihood of cough cessation at 2 and 4 weeks was similar in both groups (adjusted odds ratio [OR] 1·0, 95% CI 0·6–1·8, at both stages). Treatment with montelukast also did not significantly improve the likelihood of exercise-induced cough cessation at 2 weeks (adjusted OR 1·4, 95% CI 0·8–2·8) or 4 weeks (1·4, 95% CI 0·7–2·6). Similar proportions of participants in both groups underwent further interventions for cough (25 [18%] of 137 patients on montelukast; 24 [17%] of 139 on placebo; p=0·83).

Table 3 summarises adverse events. The proportions of patients reporting one or more adverse events did not differ significantly between groups (21 [15%] of 137 participants on montelukast; 31 [22%] of 139 participants on placebo; p=0·14). Seven participants reported two adverse events (montelukast, n=2; placebo, n=5) and one reported four adverse events (placebo, n=1). Only one serious adverse event was reported, which was unrelated to study drug (placebo, n=1). The participant reported shortness of breath and throat tightness after taking one tablet of study drug. This event was initially treated as an anaphylactic reaction. However, the participant subsequently reported having these symptoms after severe coughing bouts, even before commencing study drug.

In participants with laboratory-confirmed pertussis, montelukast was associated with lower overall and paroxysmal cough severity than placebo (appendix). However, the differences between groups were of uncertain clinical relevance. Differences in LCQ total score changes between baseline and both follow-up stages were neither clinically nor statistically significant.

Having observed large clinical improvements in cough-specific quality of life at 2 weeks, we decided post hoc to explore the earlier timecourse of postinfectious cough by summarising daily cough VAS scores and numbers of paroxysms of cough from days 0–14 (figure 2). Rapid, immediate improvements in cough VAS scores were observed in both groups after starting study drug (day 1). Daily numbers of paroxysms of cough remained stable until day 3, but subsequently followed a fluctuating course with an overall improving trend.

Discussion

To our knowledge, we report the first double-blind randomised placebo-controlled trial of montelukast for the treatment of postinfectious cough (panel). Large improvements in cough-specific quality of life were reported in both treatment groups, showing the

	Montelukast, mean difference*	Placebo, mean difference*	Mean between-group difference† (unadjusted)	Mean between-group difference† (adjusted)‡
Baseline to 2 weeks				
Total§ (MCID=1·3)	2·7 (2·2 to 3·3)	3·6 (2·9 to 4·3)	–0·8 (–1·7 to 0·03), p=0·06	–0·9 (–1·7 to –0·04), p=0·04
Physical (MCID=0·2)	0·8 (0·6 to 0·9)	1·0 (0·8 to 1·2)	–0·2 (–0·5 to 0·04), p=0·11	–0·2 (–0·5 to 0·01), p=0·04
Psychological (MCID=0·8)	0·9 (0·7 to 1·1)	1·3 (1·0 to 1·5)	–0·4 (–0·7 to –0·05), p=0·02	–0·3 (–0·6 to –0·01), p=0·03
Social (MCID=0·2)	1·0 (0·8 to 1·3)	1·3 (1·0 to 1·6)	–0·3 (–0·6 to 0·1), p=0·14	–0·3 (–0·6 to 0·04), p=0·08
Baseline to 4 weeks¶				
Total§ (MCID=1·3)	5·2 (4·5 to 5·9)	5·9 (5·1 to 6·7)	–0·7 (–1·8 to 0·3), p=0·19	–0·5 (–1·5 to 0·6), p=0·38
Physical (MCID=0·2)	1·5 (1·3 to 1·8)	1·7 (1·4 to 1·9)	–0·1 (–0·5 to 0·2), p=0·38	–0·1 (–0·4 to 0·2), p=0·46
Psychological (MCID=0·8)	1·7 (1·5 to 2·0)	2·0 (1·8 to 2·3)	–0·3 (–0·7 to 0·1), p=0·11	–0·1 (–0·5 to 0·2), p=0·41
Social (MCID=0·2)	1·9 (1·6 to 2·2)	2·2 (1·9 to 2·5)	–0·3 (–0·7 to 0·1), p=0·21	–0·2 (–0·6 to 0·2), p=0·33

Data are mean difference (95% CI), (p value). MCID=minimum clinically important difference (ie, smallest change in score which patients perceive to be clinically significant). *Positive mean difference indicates an improvement in cough-specific quality of life. †Positive between group difference indicates greater improvement in montelukast group than in placebo group. ‡Adjustment for baseline scores, age, sex, duration of cough, pertussis status, pertussis immunisation status, atopy, paroxysmal cough severity, and exercise-induced cough severity. §Primary outcome. ¶192 participants elected to continue drug at 2 weeks (montelukast, n=99; placebo, n=93).

Table 2: Changes in Leicester Cough Questionnaire total and domain scores

	Montelukast (n=22)	Placebo (n=39)
Increased mucus production	6	2
Upper respiratory tract infection	4	2
Gastrointestinal disturbance	3	5
Headache	2	6
Skin rash, itching	2	4
Nasal symptoms	1	5
Difficulty breathing, wheezing	1	2
Dry mouth, increased thirst	1	1
Hoarse voice, dry throat	0	4
Chest or breast discomfort	0	3
Lower respiratory tract infection	0	2
Fainting	0	1
Other*	2	2

n=total number of events. *Montelukast group: hiccups (n=1), cough triggered by beauty or hair products (n=1); placebo group: difficulty sleeping (n=1), ankle swelling (n=1).

Table 3: Adverse events

self-limiting nature of postinfectious cough.[26,27] However, our results show that montelukast is not an effective treatment for postinfectious cough. Our findings can be generalised to most non-smoking young adults with postinfectious cough, since our trial was done in primary care (where most of these patients present) using a pragmatic clinical definition of postinfectious cough.
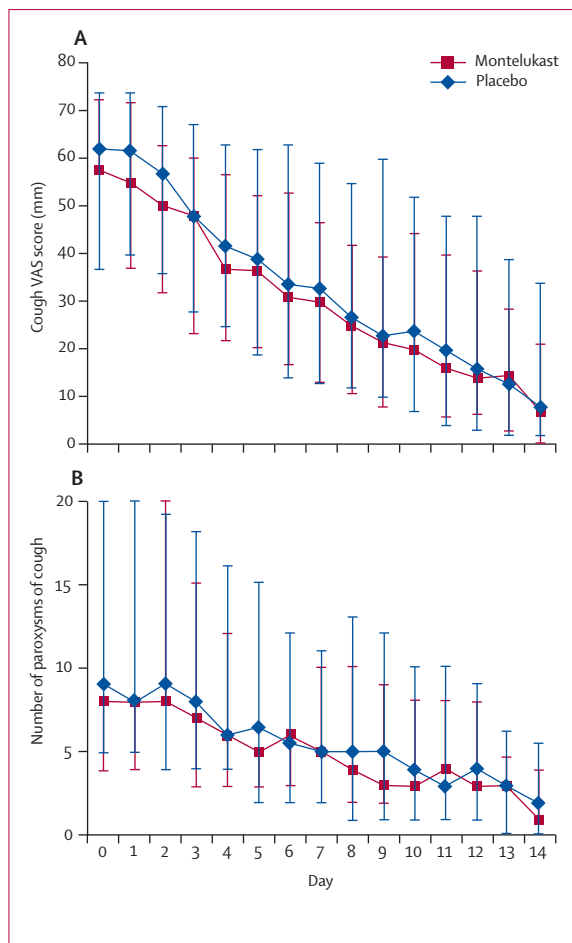
Figure 2: **Timecourse of postinfectious cough (days 0–14)**
(A) Daily cough visual analogue scale (VAS) scores completed by participants (0=no cough, 100=worst cough ever). (B) Daily number of paroxysms of cough reported by participants. Data are daily median values and IQRs. Day 0=baseline. Participants started taking study drug on day 1.

Postinfectious cough was associated with more severe impairment in cough-specific quality of life than chronic[24] or acute cough[28] particularly in the LCQ psychological domain. This finding might have been due to concerns about the cough failing to settle as quickly as an acute cough and failure to adapt to the cough because of its subacute rather than chronic nature. Placebo treatments have been associated with antitussive effects, which might be due to a combination of natural resolution, true placebo effect, and other factors, including patient beliefs about the drug and aspects relating to participation in a research study.[29] However, the placebo effect over and above montelukast that we recorded in this study is most likely due to chance, because it was not shown in any of our sensitivity analyses. A quarter of participants had laboratory-confirmed pertussis. Although recruitment coincided with a national pertussis epidemic, this proportion was still similar to that reported by a Canadian study, which

found laboratory evidence of pertussis in a fifth of adolescents and adults with acute or subacute cough.[13]

In patients with cough-variant asthma, montelukast has previously been associated with significantly greater reductions in daily cough frequency than placebo after 2 weeks (mean change from baseline 54·1% *vs* 15·2%, p<0·001) and 4 weeks (75·7% *vs* 20·7%, p<0·01).[16] Furthermore, zafirlukast, another cysteinyl leukotriene receptor antagonist, has been shown to suppress cough sensitivity to capsaicin and improve patient-reported cough scores.[30] Recent observational data suggest that the antitussive effect of montelukast in cough-variant asthma might be mediated by reductions in eosinophil production and cough reflex sensitivity rather than by direct cysteinyl leukotriene inhibition, although airway hyper-responsiveness at baseline might predict a better treatment response.[31] However, although increased cough reflex sensitivity[1] and airway hyper-responsiveness[32] have been shown in postinfectious cough, these patients have lower blood and nasal eosinophil counts than patients with asthma and similar sputum eosinophil counts to normal patients.[32]

Pertussis is associated with increased pulmonary eosinophil counts[5,14] and increased production of and prolonged sensitivity to bradykinin, which increases responsiveness to cough stimuli.[33] Montelukast also produces dose-dependent inhibition of bradykinin-induced tracheal smooth muscle contraction in guinea pigs.[34] However, we were only able to do an exploratory subgroup analysis in trial participants with laboratory-confirmed pertussis and were therefore unable to establish whether montelukast is an efficacious treatment for cough in patients with laboratory-confirmed pertussis.

Improvements in cough severity during the first week have been reported in trial participants with postinfectious cough.[26,27] However, these observations were of uncertain clinical significance because they were based on unvalidated patient-reported four-point cough scores (0=no cough, 3=severe cough). The cough VAS score minimum clinically important difference is 17 mm in acute cough.[35] We observed similar magnitudes of cough VAS score improvement in both groups at day 4, whereas paroxysmal cough initially followed a stable course before steadily improving. Prerandomisation assessment of cough stability[27] would therefore not be helpful in patients with postinfectious cough.

Although recruitment of patients with postinfectious cough is reported to be difficult,[27] our high recruitment and low attrition rates show that primary care is an ideal setting for antitussive treatment trials. Our high recruitment rate is likely to have been assisted by the severe impairment in cough-specific quality of life in our target population, the absence of any proven effective treatments for postinfectious cough, and the inclusion of a non-invasive oral fluid test to diagnose pertussis, which is not usually available as part of the routine clinical assessment of postinfectious cough. Detection of

anti-pertussis toxin IgG in oral fluid has 93% sensitivity and 94% specificity compared with serology,[21] which is positive in less than 1% of the general population.[36] We achieved low attrition rates by timing contact with health-care professionals to coincide with when participants were required to complete the LCQ.

To ensure our results would be valid and clinically relevant, we used the LCQ to measure our primary outcomes. Although the LCQ minimum clinically important difference has not been established for postinfectious cough, it is likely to be between those for chronic cough (1·3)[24] and acute cough (2·5).[28] We ensured that our trial would have adequate power by calculating our sample size using the LCQ minimum clinically important difference for chronic cough.

Having observed large improvements in cough-specific quality of life in both groups at 2 weeks, we explored post hoc the earlier timecourses of improvements in cough VAS score and paroxysmal cough frequency. These have not previously been described in postinfectious cough. Our observations will therefore be instrumental in guiding their use in future trials.

Although one of our specified primary outcomes was LCQ total score change between baseline and 4 weeks, this outcome was less robust than the LCQ total score change between baseline and 2 weeks because around a quarter of participants elected to discontinue study drug after 2 weeks. Cough monitoring would have been useful to measure cough frequency objectively,[37] but was not possible because of resource constraints. For similarly pragmatic reasons, we also assessed exercise-induced cough using an unvalidated patient-reported score and obtained baseline covariate data on paroxysmal cough severity from LCQ item 11, although this item has not been validated for use in isolation.

We recruited participants using a clinical definition of postinfectious cough and restricted recruitment to young non-smoking adults because we regarded the risk of significant pathology in this population to be low. We did not have sufficient resources to routinely perform chest radiographs and other investigations to exclude significant pathology before study entry. Furthermore, exclusion of smokers from trials of antitussive treatments is standard practice because the relationship between smoking and cough reflex sensitivity is complex. Although some studies report that cough reflex sensitivity is diminished in smokers,[38] others report increased bronchial hyper-reactivity associated with smoking.[39,40]

Although general practice consultation rates for upper respiratory tract infections are known to be highest in children and young people, and consultation rates for lower respiratory tract infections to be highest in adults aged 65 years and older,[41] the epidemiology of postinfectious cough is poorly understood.[2] Although our trial included participants between 16 and 49 years of age for pragmatic reasons, postinfectious cough has been shown in children[42] and in older adult study

Panel: Research in context

Systematic review

We searched the Cochrane Library, Medline (for articles published from 1946 to week 31 of 2013), and Embase (for articles published from 1974 to week 31 of 2013) for randomised controlled trials and systematic reviews of leukotriene receptor antagonists for the treatment of postinfectious cough. The main search terms used were "persistent cough", "prolonged cough", "postinfectious cough", "post-infectious cough", "chronic cough", "montelukast", "Singulair", "zafirlukast", "Accolate", "pranlukast", "Onon", "Azlaire", and "leukotriene receptor antagonist*". No language restrictions were applied to our search. Our search did not find any randomised placebo-controlled trials of leukotriene receptor antagonists for the treatment of postinfectious cough. A Cochrane review of symptomatic treatments for cough due to whooping cough also found no randomised controlled trials of leukotriene receptor antagonists.[20]

Interpretation

This study is the first double-blind randomised placebo-controlled trial of montelukast for the treatment of postinfectious cough in adults. Montelukast was not associated with greater improvement in cough-specific quality of life than placebo after 2 or 4 weeks. To identify future potential antitussive treatments, improved understanding is needed of the timecourse and underlying mechanisms of postinfectious cough.

populations including individuals up to 76 years of age.[43] Our findings might therefore not be generalisable to these age groups. Future antitussive treatment trials should aim to include children younger than 16 years of age and adults older than 49 years of age and smokers with postinfectious cough in whom significant pathology has been excluded. To inform the design of future trials, further research is also needed to improve our understanding of the epidemiology of postinfectious cough, including patient age and ethnicity profiles, environmental factors, and socioeconomic aspects.

Although postinfectious cough is typically described as being of 3–8 weeks' duration,[2,43] and pertussis can be clinically diagnosed in patients who have been coughing for 2 weeks or longer,[44] our inclusion of patients with cough of 2–8 weeks' duration without definite infective signs might have increased clinical heterogeneity in our trial population. Some participants' cough might have been due to asthma. However, if our sample had included a high proportion of these patients, we would have expected to see a significantly greater improvement in the montelukast group. We also adjusted for atopy in our analysis of LCQ total and domain score changes, overall cough severity, and paroxysmal cough severity. Participant-reported wheeze associated with postinfectious cough at baseline would more likely have been virus-induced than asthma-related. Additionally, some participants might

have misinterpreted the term "wheeze". This issue is a well known limitation of patient-completed questionnaire items used to ascertain the presence of wheeze.[45,46] A large observational study has previously shown that gastro-oesophageal reflux is not an important cause of subacute cough in non-smoking adults.[43]

In conclusion, montelukast is not an effective treatment for postinfectious cough. However, the burden of postinfectious cough in primary care makes it an ideal setting for future trials. To identify potential antitussive treatments, improved understanding is needed of the underlying mechanisms of postinfectious cough.

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