Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis

Ian M Balfour-Lynn, Nigel J Klein, Robert Dinwiddie

Abstract

Background—Controlling lung inflammation may be the key to improving morbidity and mortality in cystic fibrosis. 

Objective—To assess the effects of inhaled corticosteroids on lung inflammation in cystic fibrosis. 

Design—Double blind placebo controlled randomised sequence crossover trial. Fluticasone propionate (400 µg/day) was given as a dry powder inhaler for six weeks with a four week washout period before crossover. 

Outcome measures—Sputum inflammatory markers (interleukin-8, tumour necrosis factor-α (TNF-α) and neutrophil elastase—both free and bound to α1-antiprotease), sputum interleukin-10, lung function, and symptomatology. 

Subjects—Twenty three children from a regional cystic fibrosis centre were enrolled into the study, with mean age 10.3 years (range 7 to 17 years) and mean baseline forced expiratory volume in one second (FEV1) of 64% (range 21% to 102%) predicted for sex and height. One patient was excluded for non-compliance to the study protocol. 

Results—No significant benefit was shown for the use of fluticasone propionate in any of the outcomes. For sputum interleukin-8 there was an estimated true treatment median difference of 142 pg/ml (95% confidence interval (CI) 8 to 2866 pg/ml) in favour of placebo; while for maximal expiratory flow at 25% (MEF25%) remaining forced vital capacity predicted for sex and height there was a 15 percentage points (pp) (95% CI 4 to 26 pp) mean treatment difference in favour of placebo. Sputum interleukin-10 was undetected in any samples and unaffected by fluticasone propionate. Neither atopic status, baseline FEV1, nor concomitant DNase therapy had any effect on response to treatment. 

Conclusions—Lack of benefit from fluticasone propionate was most likely due to failure of the drug to penetrate the viscid mucus lining the airways. It is suggested a large multicentre trial with higher doses given for a longer time by a different delivery system is required to assess efficacy. 

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Keywords: cystic fibrosis; corticosteroids; inflammation; randomised controlled trial
Methods

SUBJECTS

Children with previously diagnosed cystic fibrosis were enrolled from a single centre. Inclusion criteria were age between 6 and 17 years, ability to reliably perform spirometry and use a Diskhaler (Glaxo Wellcome UK), and guaranteed sputum production. Their routine medication was not altered and no one was started on DNase during the study period. Exclusion criteria were the use of systemic or inhaled corticosteroids within the previous six months, clinical diagnosis of asthma, use of sodium cromoglycate or long acting \( \beta \)-agonists within six weeks, and lower respiratory tract infection requiring antibiotics within the previous three weeks. Other exclusion criteria were cystic fibrosis related diabetes, portal hypertension, allergic bronchopulmonary aspergillosis, or isolation of *Burkholderia cepacia* in sputum. Atopic status was determined by positive personal history of atopy (rhinitis or eczema) as detected by the ISAAC questionnaire, or serum IgE > 100 ku/l, or positive skin prick tests to house dust mite, grass pollen, cat and dog fur (presence of at least two weals greater than 3 mm at 20 minutes).

STUDY DESIGN

The trial was conducted in a double blind placebo controlled randomised crossover sequence. After a baseline visit (V0), there were two treatment periods of six weeks’ duration with a four week washout period; patients were assessed before and after each period (V1–V4). Each received 400 µg/day fluticasone propionate in two doses via Diskhaler (dry powder inhaler) or matched placebo provided by Glaxo Wellcome UK. All unused disks were returned and counted to assess patient compliance to the study protocol. The study was approved by the hospital ethics committee; parents or patients, or both, gave written informed consent.

Primary outcome measures were change from baseline in the sputum inflammatory markers interleukin-8, TNF-\( \alpha \), and neutrophil elastase (free and bound to \( \alpha \)-antiprotease). Covariates were atopic status and disease severity as assessed by baseline forced expiratory volume in one second (FEV\(_1\)). Secondary outcomes were lung function and symptomatology as well as patient tolerance of fluticasone propionate. Adverse events were monitored closely, especially infectious respiratory exacerbations and oral candidiasis.

SPUTUM INFLAMMATORY MARKERS

Sputum was collected into a sterile container, placed onto ice, and weighed. A previously described method was adapted for specimen preparation. An equal volume of 20% N-acetylcysteine (ml for gram) was added to the sputum which was left on ice for 20 minutes. This was then vortexed at 4°C before centrifuging at 4°C for 15 minutes at 3000 \( \times \) g. The supernatant was decanted and stored in aliquots at –80°C.

After thawing, supernatants were centrifuged at 13000 \( \times \) g at 4°C for 10 minutes. For cytokine determination, supernatants were mixed with an equal volume of protease inhibitors (sodium fluoride 20 mM, aprotinin 2%, phenylmethylsulphonyl fluoride 2 mM (Sigma), and 5% human serum known to have undetectable cytokine concentrations). This combination was found to completely inhibit free elastase activity in all sputum samples. Samples were analysed by ELISA for interleukin-8 (using a commercially available kit, Biotrak, Amersham), and TNF-\( \alpha \) and interleukin-10 using capture and detector antibodies from PharMingen (San Diego, California, USA), streptavidin-alkaline phosphatase (Amersham) and developed with p-nitrophenyl phosphate dihydrate (Sigma). Free elastase was measured by a modification of a previously described method. Sputum supernatants were diluted 1:20 with 0.1M Tris, 0.5 mol/l sodium chloride and 0.05 mmol/l EDTA. This was added to an equal volume of substrate solution (120 µg N-methoxy succinyl-ALA-ALA-PRO-VAL-p-nitroanilide (Sigma) per ml Tris salt buffer). Optical densities were measured at 405 nm on a Dynatech MRX ELISA plate reader and calibrated using purified human neutrophil elastase (Sigma). Elastase: \( \alpha \)-antiprotease complexes were measured by ELISA as previously described. After dilution, lower limits of detection were 40 pg/ml for interleukin-8, 30 pg/ml for TNF-\( \alpha \), 250 pg/ml for interleukin-10, 0.05 u/ml for free neutrophil elastase and 1 ng/ml for bound neutrophil elastase.

LUNG FUNCTION

Lung function was assessed by standard spirometry using a compact spirometer (Vitagraph, Buckingham). At each visit, forced vital capacity (FVC), FEV\(_1\), and maximal expiratory flow at 25% remaining FVC (MEF\(_25\%\)) were recorded as per cent predicted for sex and height. Resting oxygen saturation was measured using a Biox 3700e pulse oximeter (Ohmeda, USA). On subsequent clinic visits, lung function was recorded within two hours of the baseline reading and bronchodilators were withheld for four hours before each test.

SYMPTOM SCORES

At the end of each week, the patient or parent recorded symptom scores for cough, sputum production, and wheeze for the previous seven days (combined to provide overall mean respiratory score). At each visit, overall scores for general wellbeing and appetite were recorded. These were indicated on a 10 cm linear analogue scale, which was measured to establish symptom severity.

STATISTICAL METHODS

Analysis was performed by the Applied Statistics Research Unit Ltd at the University of Kent at Canterbury using the SAS System (Release 6.09). Change from baseline for each inflammatory marker was compared using non-parametric Wilcoxon rank sum test for crossover design (Koch’s method). Per cent predicted lung function at the end of each
Table 1  Baseline lung function (mean % predicted with range) and mean coefficient of variation (%) with adjusted mean (95% CI) at end of treatment with fluticasone propionate and placebo. Also included are estimated mean treatment differences (fluticasone propionate minus placebo) with 95% CI. Values of p > 0.05 are considered non-significant (NS)

<table>
<thead>
<tr>
<th></th>
<th>FVC (%)</th>
<th>FEV1 (%)</th>
<th>MEF25 (%)</th>
<th>Oxygen saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>75 (45 to 107)</td>
<td>64 (21 to 102)</td>
<td>35 (8 to 73)</td>
<td>95 (90 to 98)</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>7</td>
<td>9</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>78 (74 to 83)</td>
<td>65 (61 to 69)</td>
<td>25 (15 to 36)</td>
<td>95.0 (94.6 to 95.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>78 (73 to 82)</td>
<td>67 (63 to 71)</td>
<td>40 (30 to 50)</td>
<td>95.4 (95.0 to 95.8)</td>
</tr>
<tr>
<td>Estimated mean treatment difference</td>
<td>0.5 (−6 to 7)</td>
<td>−2 (−8 to 4)</td>
<td>−15 (−26 to −4)</td>
<td>−0.4 (−1.0 to 0.1)</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>NS</td>
<td>0.009</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2  Baseline sputum inflammatory markers (median with interquartile range) and mean coefficient of variation (%) with median (95% CI) change from baseline after treatment with fluticasone propionate and placebo. Also included are estimated median treatment differences (fluticasone propionate minus placebo) with 95% CI. Values of p > 0.05 are considered non-significant (NS)

<table>
<thead>
<tr>
<th></th>
<th>Interleukin-8 (pg/ml)</th>
<th>TNF-α (pg/ml)</th>
<th>Free neutrophil elastase (u/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>376 (306 to 437)</td>
<td>375 (198 to 583)</td>
<td>62 (40 to 80)</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>54</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>8 (−161 to 217)</td>
<td>14 (−90 to 103)</td>
<td>−1 (−8 to 14)</td>
</tr>
<tr>
<td>Placebo</td>
<td>−67 (−1152 to 37)</td>
<td>25 (−122 to 117)</td>
<td>1 (−15 to 7)</td>
</tr>
<tr>
<td>Estimated median treatment difference</td>
<td>142 (8 to 2866)</td>
<td>27 (−104 to 167)</td>
<td>5 (−9 to 31)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.03</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

treatment, and change from baseline in symptom scores were compared using parametric analysis of covariance. The covariates used were atopic status, baseline per cent predicted FEV1, and colonisation with Pseudomonas aeruginosa. In addition, for FVC and MEF25%, variables, their mean baseline values were also used. Values from the run-in and washout period were used to detect any first order and second order carryover effects. If carryover was detected, analysis was based on the first treatment period only. Significance was judged at the 10% level for carryover effects and at the 5% level for treatment and period effects. All statistical tests were two sided. Effect of atopic status and use of DNase on treatment difference in change from baseline of inflammatory markers was assessed using subgroup analyses and employing the non-parametric method of Koch; while effect on treatment difference in end of treatment lung function was assessed by analysis of covariance. Pre-existing lung function was calculated using baseline per cent predicted FEV1, (mean of FEV1, measured at V0 and V1). For the inflammatory markers, regression analysis was performed plotting baseline FEV1, against the log ratio before and after treatment levels for each treatment, and for lung function, baseline FEV1, was plotted against after treatment lung function. Retrospective sample size calculations for crossover studies based on the observed variability were performed for a power of 80% and a 5% significance level.

Results

Twenty three patients were enrolled into the study and randomised, but one patient failed to comply with treatment so the efficacy sample used for analysis consisted of 22 patients. The two sequence groups were comparable in terms of demographic and baseline clinical characteristics. There were 11 boys and 12 girls with a mean age of 10.3 years (range 7–17 years). Fifteen (65%) were homozygous for ΔF508 gene mutation, seven (30%) were heterozygous for ΔF508, and one child was heterozygous for G551D mutation. Mean (SD) centiles predicted for sex and age were 40% (36%) for weight and 43% (34%) for height. Table 1 shows mean baseline lung function. Seventeen (74%) patients reported daily cough and 22 (96%) daily sputum production; seven (30%) patients wheezed, although only two on a daily basis. Three were bronchodilator responsive (increase in FEV1 >15% after inhaled β-agonist), none of whom reported wheezing. Ten (43%) patients were considered atopic. Previous sputum microbiology revealed 96% had been infected with Staphylococcus aureus, 87% with P aeruginosa, and 48% with Haemophilus influenzae. At the start of the study, 61% had positive sputum culture for S aureus, 52% for P aeruginosa, and 4% (one patient) for H influenzae. Oral antibiotics were started in 18 (78%) patients during the trial and nebulised antibiotics started in five (22%). Five (22%) patients required intravenous antibiotics. Antibiotic usage was the same for patients in both treatment sequences. Nine (39%) patients were on nebulised DNase at the start of the trial and continued its use; none started DNase during the trial.

Sputum inflammatory markers

Table 2 shows sputum interleukin-8, TNF-α, and free neutrophil elastase baseline levels (taken at V1) with median change after treatment with fluticasone propionate and placebo. Figure 1 shows treatment changes for individual patients. For interleukin-8, estimated true treatment median difference (fluticasone propionate-placebo) was 142 pg/ml in favour of placebo (with 95% confidence interval (CI) for difference of 8 to 2866 pg/ml). This was a statistically significant difference with p=0.03. There was little change from baseline for sputum TNF-α or free neutrophil elastase during either fluticasone propionate or placebo, with no significant difference between the two treatments. In 16 out of 23 patients, at baseline, bronchodilator responsiveness was undetectable (<10 ng/ml), in the others, it ranged from 2–42 (median 10) ng/ml. Analysis of change in bound neutrophil elastase is invalid.
due to the large number of samples with undetectable levels (80/110). Neither atopic status, baseline FEV1, nor concomitant DNase therapy had any significant effect on response to treatment. An estimate of coefficient of variation for the markers was calculated using values from the initial visit (V0) and the first visit (V1) before treatment. Table 2 shows that these were highest for interleukin-8. Sputum interleukin-10 was undetectable in all samples; no effects were seen after giving corticosteroids.

**LUNG FUNCTION**

No effect of treatment was seen on either FVC or FEV1 (see table 1). For MEF25%, there was a significant second order carryover effect (p=0.02) so analysis was based on the first treatment period only (12 patients on fluticasone propionate, 10 on placebo). Adjusted mean per cent predicted MEF25% was higher after treatment with placebo than fluticasone propionate (table 1). The estimated difference between the treatments (fluticasone propionate - placebo) was −15pp (95% CI −26 to −4 pp) which was statistically significant with p=0.009. Resting oxygen saturation was unaffected by either treatment (table 1). Neither atopic status, baseline FEV1, nor concomitant DNase therapy had any significant effect on response to treatment. From the measurements at V0 and V1, mean coefficient of variation for lung function was highest for MEF25% (see table 1).

**SYMPTOM SCORES**

Table 3 shows baseline symptom scores with mean changes after treatment. Mean overall respiratory score, wellbeing, and appetite scores were all unaffected by treatment.

**ADVERSE EVENTS**

Two patients (9%) experienced an adverse event which was possibly drug related during treatment with fluticasone propionate. One child coughed immediately after taking fluticasone propionate for five minutes on one occasion, while another developed peeling skin on the fingers for three days, the cause of which was unknown. Overall 18 (78%) patients had adverse events during treatment with fluticasone propionate and 15 (65%) while on placebo. These were mainly upper respiratory tract infections (52%), or cystic fibrosis chest exacerbations (20%).

**POWER STUDIES**

Retrospective sample size estimation for crossover studies have been calculated, based on the variability observed in this study. For change from baseline in sputum inflammatory markers the sample size estimation assumed the data were normally distributed, which was not actually the case, even after taking a log transformation. For interleukin-8, to detect a difference of 150 pg/ml, it was estimated that huge numbers of patients were needed. In fact, the huge variability of interleukin-8 was due to a small number of patients and furthermore, with non-parametric analysis a statistically significant difference in interleukin-8 was obtained in our study. To obtain a difference of 125 pg/ml TNF-α, 46 patients would be needed, and for a difference of 20 u/ml free neutrophil elastase, 18 patients. To obtain a difference of 15% improvement over placebo in percent predicted FVC, FEV1, and MEF25%, a study would need 28, 42, and 98 patients respectively. To detect a treatment difference in mean symptom scores of 1.5 requires 14 patients.

**Discussion**

This study has not shown any significant benefit in terms of sputum inflammatory markers, lung function, or symptomatology when an inhaled corticosteroid (400 µg/day fluticasone propionate) was given by dry powder inhaler to children for six weeks. However,
Table 3  Baseline symptom scores out of a maximum of 10 points (mean with range) with adjusted mean (95% CI) change from baseline at end of treatment with fluticasone propionate and placebo. Also included are estimated mean treatment differences (fluticasone propionate minus placebo) with 95% CI. Values of p > 0.05 are considered non-significant (NS)

<table>
<thead>
<tr>
<th></th>
<th>Respiratory</th>
<th>Wellbeing</th>
<th>Appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.4 (0.9 to 5.9)</td>
<td>6.7 (3.2 to 9.3)</td>
<td>6.7 (0.1 to 9.4)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>0.5 (–0.3 to 1.2)</td>
<td>–0.4 (–1.0 to 0.2)</td>
<td>–0.3 (–1.3 to 1.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>–0.3 (–1.0 to 0.4)</td>
<td>–0.6 (–1.1 to 0)</td>
<td>–0.8 (–2.2 to 0.6)</td>
</tr>
<tr>
<td>Estimated mean treatment difference</td>
<td>0.8 (–0.3 to 1.8)</td>
<td>0.1 (–0.7 to 1.0)</td>
<td>0.9 (–0.6 to 2.4)</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

with all the theoretical reasons why inhaled corticosteroids should be beneficial in cystic fibrosis, the disappointing result needs to be explained, and there are a number of possibilities. Firstly, there may have been a problem with the outcome measures used. The primary aim was to determine the effect on lung inflammation, so inflammatory markers were measured in the sputum which is non-invasive and easy to collect. Sputum markers can give highly variable results, however, since sputum is a non-homogeneous material and each cough produces a sample from a different part of the lung. Cystic fibrosis sputum is also a difficult substance to work with in the laboratory due to its viscosity. Furthermore, a recent longitudinal study has shown that sputum cytokine concentrations can vary several fold in the same patient over time, without discernable change in clinical status or lung function. Few studies have found correlations between cytokine concentrations and clinical status and data on the effect of antibiotics on sputum cytokines is limited. Although this throws into doubt the clinical use of sputum markers, it does not invalidate their use in a trial of anti-inflammatory treatment where inflammation is the primary outcome.

With the difficulties in using sputum, many studies, particularly in the USA, measure markers in BAL fluid. BAL is invasive, however, and this would be a problem in a study requiring repeated samples. BAL also has methodological problems, particularly related to the effects of dilution and variability. Numerous studies have looked for surrogate markers of inflammation in blood. Aside from the problem of repeated venepuncture in children, none have been shown to be highly predictive of acute changes, and there is often a wide overlap between levels found in health and disease. Besides, cytokines tend to act locally in low concentrations so their direct measurement in tissue fluids of the site of production is preferable to measurement of blood levels, which often do not reflect concomitant changes found in sputum or BAL fluid.

Aside from the concerns over sputum, it is also possible there was a problem with the actual marker substances even though they had all been previously shown to be raised in cystic fibrosis. The levels of TNF-α from this study are in general agreement with those found by others. The interleukin-8 levels on the other hand varied widely, both between and within studies with large ranges obtained. In this study it can be seen that the majority of samples fell within a fairly narrow band, although in some patients huge differences were found for interleukin-8. This may explain the unexpected and possibly random finding that placebo was superior to fluticasone propionate in reducing sputum interleukin-8 levels. There was also a large variability between the two baseline samples, and the reason this was so high compared with that found with the TNF-α, may be due to the less restricted range of cells capable of producing interleukin-8. This may artefactually increase interleukin-8 concentrations in some sputum samples, for example, in the presence of a large number of epithelial cells. Results from this and other studies indicate caution is needed before using sputum interleukin-8 as an inflammatory marker in cystic fibrosis.

The fact that FVC and FEV₁ were unaffected by six weeks of corticosteroids is not surprising, given the fluctuating nature of cystic fibrosis lung disease. Although four weeks is long enough to detect an effect of fluticasone propionate in asthmatic children, the nature of cystic fibrosis means it is likely a longer study would be necessary to detect an effect on lung function. The baseline variability for FVC and FEV₁ was reasonable in our study, particularly when compared with the known variability of cystic fibrosis lung function. The variability of MEF 25% was high, but it is known to be an intrinsically more unstable measurement. This, together with the fact that due to carryover effect on MEF 25%, only the first treatment sequence was analysed, may explain why the MEF 25% was unexpectedly (and possibly randomly) significantly higher after placebo compared with fluticasone propionate.

It is possible there were too few patients in this trial, although it was as large as most studies of this nature. The problem arose because of the variability of the outcomes used, as discussed above. The variability was apparent once the trial was completed, and it means that the number of patients needed to detect a large treatment difference is high. This study has highlighted the difficulties in carrying out intervention studies in a disease where the patients are already overburdened by their treatment regimens, and emphasises the need for multicentre trials in cystic fibrosis.
Controlled trial of inhaled corticosteroids

It was also possible that it was already too late for the children in this trial to benefit from inhaled corticosteroids. Lung inflammation is seen early in cystic fibrosis and damage to the lung tissue is relentless. Although most of the subjects studied here had reasonable lung function (mean FEV$_1$, 64% predicted), there was a wide range (FEV$_1$, 21% to 102% predicted), and indeed three patients had FEV$_1$, <40% predicted. In addition, they had to be regular sputum producers to enter the trial and this would bias the subjects towards those with worse lung disease. Not surprisingly, trials of inhaled corticosteroids restricted to adults have so far also been negative. It is likely that maximum benefit of anti-inflammatory therapy will only be seen when treatment is started early, maybe even at the time of diagnosis. The problem will be proving this benefit, as long term studies will be needed and outcome measures for infants with cystic fibrosis are notoriously difficult to use.

The likeliest reason, however, for the failure to show benefit from inhaled corticosteroids was that the drug did not penetrate the thick viscid sputum. This would reduce the steroid effect on the inflammatory cells contained in the sputum as well as the underlying respiratory epithelial cells. This is backed up by the fact that systemic corticosteroids seem to exert an anti-inflammatory effect in cystic fibrosis whereas inhaled corticosteroids have so far not proved to be of benefit. The first trial of inhaled corticosteroids, in 26 subjects, used a low dose (400 µg/day beclomethasone dipropionate for 16 weeks), and showed no beneficial effect on lung function or inflammatory markers. The next study, over 10 years later, on 12 adults (1600 µg/day budesonide for six weeks), showed an improvement in bronchial responsiveness only, with no change in lung function. Another study, on 49 hospitalised patients (1500 µg/day beclomethasone dipropionate for 30 days), showed an improvement over those on standard treatment alone in terms of thoracic gas volume only. Finally, a recently reported abstract on 36 adults (1000 µg/day fluticasone propionate for up to 24 months) showed a non-significant trend only towards improvement in lung function.

A dry powder inhaler was used in this study to facilitate checking of patient compliance; normally inhaled corticosteroids would be given by a metered dose inhaler with a spacer to reduce oral absorption. It is possible that corticosteroids would penetrate the tenacious sputum more effectively if the drug was delivered as a droplet by spacer or nebuliser, but this is only speculation. A further trial of inhaled corticosteroids is still warranted using a different delivery system. Unfortunately, there would most likely be problems with compliance if a new twice daily nebulised treatment was added to a patient’s existing regimen, particularly if no immediate benefit was felt. It is also possible that a higher dose should be used to counter the problems of penetrating the mucus. The dose of 400 µg/day fluticasone propionate used in this study was already above the current licensed dose. It is likely that at higher doses adrenal suppression would be seen in some patients but in a disease such as cystic fibrosis it may be acceptable to take increased risks as long as there is no other benefit from this during the present trial. Evidence is still needed before too many patients are given this form of treatment on empirical grounds, thus making further trials difficult to conduct. The main problem would seem to be in getting adequate doses of the drug into the relevant cells. The next stage should be a large multicentre trial with higher doses given for a longer time using a different delivery system.

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16 Richman-Eisenstat JBY, Jorens PG, Hébert CA, Ucles I, Nadell JA. Interleukin-8: an important chemoattractant in sputum of patients with chronic inflammatory airway
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