Author’s response to reviews

Title: Attitudes and actions of asthma patients on regular maintenance therapy: The INSPIRE study

Authors:

Martyn R Partridge (m.partridge@imperial.ac.uk)
Thys van der Molen (t.van.der.molen@med.umcg.nl)
Sven-Erik Myrseth (Sem@LHL.NO)
William W Busse (wwb@medicine.wisc.edu)

Version: 3 Date: 24 May 2006

Author’s response to reviews:

BMC Pulmonary Medicine Manuscript ID 1056937412997903

Reviewers’ comments and author responses

I wish to express my appreciation to the reviewers for their constructive comments on the manuscript. I have attempted to respond to the comments point by point, as indicated in the table below.

Reviewer 1

Major compulsory revisions

C1 Study population. The study population included more females (65%) than males. Is there an explanation for the discrepancy in the ratio of female to male participants? Did gender or smoking status (21%, n=714 were current smokers) influence any of the outcome measures?

R1 With regard to the study population, we would agree that there appears to be a slight predominance of females in this study, but this does reflect the fact that the prevalence of asthma in adults is higher amongst females than males. Indeed, the use of Health Service resources such as hospital treatments are higher amongst females, as is the number of deaths from asthma. Any further excess may reflect the fact that we have recruited a large number of these patients from the primary care setting and we know that, amongst adults in the 20-65 age range at least, females consult their physician more often than males. In addition, typically more females than males agree to participate in patient surveys and clinical trials, and thus the higher number of females recruited into this study correlates with this trend. It should be noted that the participating physicians were asked to recruit the next 10 valid patients (i.e. those patients who fulfilled the stated inclusion and exclusion criteria for the study) visiting the clinic for an appointment or to pick up a prescription, in order to minimise bias in the recruitment of patients as far as possible.

The point about whether smoking prevalence affected any of the outcome measures is extremely interesting, particularly in the light of the work done by the reviewer himself, in which it was shown that patients who smoked required a higher dose of ICS in order to achieve the same effect as those who did not smoke. Smoking status was not a primary question in our study, but studying the 21% of the sample who did smoke, it does look as though those who smoke were more likely to have had a severe period of worsening asthma in the past year. However, as this was not a pre-planned research question in this project and the study was not designed to investigate patients’ smoking status, we would be a little reluctant to include these data in the manuscript on this occasion. We do agree that smoking status and asthma morbidity and treatment is a very interesting research area, and if we had considered it upfront we could have been able to investigate this further.

C2 Management of exacerbations. Although action plans contain advice to increase the dose of ICS at the start of an exacerbation, it cannot be concluded that this component of the plan accounts for the reduction in symptoms and unscheduled use of healthcare resources (refs 20 & 27). Furthermore, 2 studies have failed to demonstrate any benefit by increasing the dose of ICS at the start of an exacerbation (refs 18, 19). The Foresi study (ref 21) refers to subjects taking low-dose ICS and involved a five-fold increase in the dose of ICS at the time of the exacerbation. Based on these data I would question whether the authors can conclude that subjects "adjust treatment (ICS) in an inappropriate manner". I believe the authors need to be much more circumspect about their interpretation of this aspect of the survey.

R2 We do very much respect the reviewer’s comments regarding our assumption that increasing maintenance therapy promptly is beneficial. This is an ongoing debate and one that we have frequently discussed in public meetings. The Harrison et al (Lancet 2004;363:271-275) and Fitzgerald et al (Thorax 2004;59:550-556) papers are both often interpreted as counting against the prompt adjustment of medication by patients. However, we would like to stress that in a large proportion of the self management
education trials that have been published to date and included in the Cochrane review, when self-management advice involved doubling or trebling the dose of inhaled steroids in a study, the results showed overwhelmingly improved outcomes, including reduced unscheduled use of healthcare, hospitalisation, time off work and school, and night-time wakening. The use of rescue steroid tablets in those studies was much less compared with the dose of inhaled steroids in the original Lahdensuo paper (BMJ 1996;312:748-752), which also reported poor patient compliance. There is, therefore, something of a dichotomy between self-management studies in which increasing the dose of inhaled steroids is advocated and appears to be beneficial, and the Harrison and Fitzgerald studies which have concentrated the intervention solely upon the doubling of inhaled steroids. This implies that self-management education in some way encourages those patients who were not already using inhaled steroids to start using this treatment when their asthma worsens, or that doubling the dose of inhaled steroids is insufficient and a greater increase is required to achieve an observed effect (we cited the Foresi et al study [Chest 2000,117:440-446] to explain this point), or that increasing inhaled steroids only works within the context of self-management education and patient adherence to action plans. Alternatively, the absence of an effect in the Harrison and Fitzgerald studies may have been because the dose was too little too late. In the Fitzgerald study in particular, there could have been at least a 48-hour delay before there was any adjustment in the dose of inhaled steroids.

We do acknowledge the reviewer's point, but for the reasons stated above we think that it is a reasonable conclusion to suggest that patients are missing an opportunity to adjust their therapy early enough. In addition, there is now evidence from cellular, lung function and exhaled marker endpoints to suggest that inhaled steroids work much more quickly than previously thought.

We hope that our response adequately answers the reviewer's comment. We are happy to alter the manuscript if required, but as exemplified by the length of our response to the comment, we believe that we can only discuss this issue more fully in this paper by lengthening the discussion section to a considerable extent.

Reviewer 2

General
C1 The authors have gathered interesting data on a large number of adults with asthma, all (at least theoretically) taking regular inhaled ICS (plus or minus LABA). In general, the picture seems pretty miserable from the point of view of asthma guidelines and decades of attempting to optimize asthma medication and minimize asthma morbidity to levels that we know are possible. The population studied emerges as suspicious of ICS and minimalist in their use, and prepared to put up with a lot in their dedication to independence and self-determination in their asthma management. They pursue a "sine-wave" of asthma control: the best they achieve is pretty poor but they also have frequent and significant asthma worsenings - one gets the impression of a pretty chaotic and anarchistic therapeutic lifestyle! The key here is the extent to which these patients' asthma and needs for regular disease-modifying therapy has ever been properly assessed, and whether their adherence with their therapeutic regimen can really be as good as they claim in Fig5 (I note that there is no mention that I can see of this in the text). Either their assessment and/or drug regimen is pretty ordinary, or they are pretty awful patients!
R1 We agree that it is disappointing to see that, despite apparently being prescribed and taking regular maintenance therapy, many patients still had persisting morbidity. Although this study enabled us to make this observation, we may not be able to interpret all the causes for this level of morbidity from our study alone. Of course, non-compliance to medication may be a problem and we accept that reported medication usage is often a poor reflection of patient compliance. It is our opinion, however, that the existence of poor patient compliance does not detract from the inferences we have made regarding the poor level of asthma control in this study. We showed that high disease morbidity persists in patients who were prescribed regular maintenance therapy -- findings that correlate with those observed previously in patients who had not been receiving regular maintenance therapy (Rabe et al 2004).

C2 The core questions here are who exactly are these patients, and who exactly are these treating doctors in this study, and why were the patients seeing the doctor at this particular time? Was it because they were in fact going through a bad phase? Are these patients and doctors typical? How general sable are the data? Nothing about the study is really random in terms of selection (in spite of what is claimed).
No selection criteria for the doctors included are given, or what sort of practices they have, or what sort of medicine they practice. The end-product is not very good - the implication is that none of us are, but I think that needs more evidence than is provided here.
R2 We thank the reviewer for the points raised. Unlike previous studies, this study recruited patients who had received a physician's diagnosis of asthma and the very fact that the patients were recruited following a recent clinic attendance almost certainly acknowledges some bias in the type of patients recruited.
However, we would like to emphasise that these were routine patient consultations/prescription pick-ups.
In response to the reviewer's comment, additional information regarding the quotas imposed on physician selection and the type of physicians recruited has now been added on page 4 of the manuscript. The mean number of times that patients had visited their physician in the last year has also been included on page 7.

C3 What were the doctors and/or patients paid for their recruitment/involvement? Are there any objective benchmarks/metrics/inputs/outputs/demographics to say how typical they are respectively?
R3 Yes, both physicians and patients who were recruited into the study were paid for their time and involvement. This has now been clarified on page 4 of the paper. The criteria for physician recruitment, patient screening, and the quotas imposed on the physicians and patients were intended to enable the recruitment of representative samples of physicians and patients. Additional details regarding the recruitment process have now been included on pages 4 and 7 of the manuscript.

C4 Why were both PCPs and specialists involved, would it not have been better to limit to one or the other? Did this make any difference if analysis was done separately? How many patients were "consulting" and how many "just getting a prescription" - does this matter to outcomes? As implied above, was the very fact that these highly individualistic patients attending their doctor at all at this particular time, have any deterministic effect upon the data from the week before, or indeed their recollection of events/attitudes.
R4 The reviewer makes a very valid point regarding the recruitment from both primary care physicians and specialists and feels that it would have been better to limit to one or the other medical professional. The reason why we specifically recruited patients using both primary care physicians and specialists was to avoid bias being introduced. We recruited patients via primary care physicians and specialists differently in each country in order to provide a true reflection of where most asthma care was undertaken in the participating countries so that our patients were as representative as possible. It was never the intention to compare outcomes according to the level of care given, but this has been done in previous studies in France and the USA. We did not record whether the patient was attending the clinic/hospital for a consultation or simply to obtain a prescription because the primary objective was to recruit 10 sequential patients from each practice. On page 14 of the discussion section (paragraph 1), we acknowledge the fact that recent attendance at the physician's clinic/hospital may have meant that we attracted a slightly more severe or unstable group of patients. We hope that this response adequately addresses the reviewer's comment.

Minor essential revisions
C1 P5, para 3 is repeated verbatim in the next paragraph
R1 Thank you for bringing this typographical error to our attention. The repeated section has now been deleted.

C2 Should not the translation from English have been back-translated into English to test for validity? I thought that check was usual.
R2 We would agree with the reviewer that back translation is the ideal method to use for a patient survey. In this particular case, however, because of some previous problems we have had with translation and back translation of questionnaires, we arranged for the questionnaires to be translated into each of the appropriate languages required. This was followed by consultation with health professionals in those countries that were aware of the purpose and design of the study, in order to ensure that each of the questions was consistent in each language.

C3 The ACQ: the scores for control/non control seem remarkably low? It would be interesting to use the opportunity to calibrate the score against subjective experience - the way the score is used pre-determines, it seems to me, the poor outcome. How robust are the data in Ref 15, and how applicable to the current population?
R3 Thank you for your valuable comments on the use of the ACQ. In this study, a quantifiable measure was necessary in order to evaluate the level of patients' asthma control. The ACQ score ranges used to define 'well-controlled', 'not-well controlled' and 'uncontrolled' asthma in our study were based on the recently published study by Juniper et al (Respir Med 2006;100:616-624). As the Juniper et al study used data from the large GOAL study in patients with asthma (n=1323) and included extensive statistical analyses, we believe that these data were sufficiently robust to serve as a basis to develop a quantifiable measure. The score ranges and corresponding asthma control definitions were discussed with Elisabeth Juniper upfront before the commencement of the study in order to produce the most accurate measure possible. Although we accept that the scores are approximate and cannot correlate exactly with subjective definitions of asthma control, we believe that the ACQ measures utilised are scientifically sound and applicable to the study population.

C4 It would be very useful to know the actual dose(s) of ICS prescribed to the three control-level groups.
That might give some 'feel' for level of appropriate prescribed management for this level of disease activity. R4 We thank the reviewer for this comment, which is a very reasonable request. Clearly, if those patients who were on inhaled steroids alone contributed most to the uncontrolled group of patients with asthma, then one could argue that the problem is one of failure of doctors to implement guidelines and, for example, add a long-acting 2-agonist. However, we have not performed a sub-analysis of the data in this way and we certainly have not analysed the data in the way that the reviewer requests by looking at prescribed inhaled steroid doses. The reason we have not performed this sub-analysis is because of the difficulties of comparing different doses of different inhaled steroids and then deciding which is the more appropriate therapy for specific patients -- monotherapy with inhaled steroids administered at a high dose, or a lower dose of inhaled steroids administered in combination with a long-acting 2-agonist. Although such sub-analyses are possible and sometimes illuminating, our study evaluated patients who were definitely being prescribed maintenance therapy of an appropriate type. It was not the purpose of our study to attempt to quantify the magnitude of the appropriateness of patients' prescribed asthma therapy.

C5 The 'advert' for the sponsor's preferred style of use of ICS/LABA combination in Discussion, p13, 2nd para would best be left out. There are no data presented here to support that therapeutic philosophy, and a charge of 'marketing' would best be avoided (especially given the apparently close involvement of the commercial company in writing the paper). From the data, it seems far from clear where we go from here! R5 We are bemused as to why the reviewer has suggested that we have included an advertisement for the products of the company that sponsored the study. The text states that during periods of worsening asthma, treatment regimens (whereby patients increase their ICS/LABA maintenance dose in line with a self-management plan) have been demonstrated to improve asthma control compared with fixed-dose combination therapy, plus a short-acting beta-agonist. We have included two references published in reputable journals that support this treatment approach and we believe that statement is entirely relevant in a study showing, as we have done here, that there is plenty of time for patients to adjust their maintenance therapy in order to try to improve outcomes. The references that we have cited to support the statements have shown that when patients adjust their maintenance therapy, asthma control measures are improved. Unless we have misunderstood the point the reviewer is making, we think our statement is entirely relevant and is just the sort of 'way forward' advice which a reader of this article might wish for. Furthermore, we deliberately did not mention any one particular steroid/LABA product in the paper, even though the studies referenced involved the budesonide/formoterol combination.

C6 Table 1: use of rather vague terms such as "relatively" good/poor seem a pity; something rather more quantitative (VAS, for example) might have been better.

R6 Thank you -- we value this constructive criticism. It was our intention that the questions included in this study were immediately easy to understand for the patients and we tried very hard in order to use language that would enable this. The questionnaire was not designed to use a quantitative measure such as VAS in order to analyse the patients' responses to this specific question, although we agree that such a method may have been preferable and could be considered for future studies.

C7 Table 2, Statement 7: phraseology and use of the word "any" is odd and ambiguous. The data though, would suggest pretty poor attitudes to compliance/adherence, contrasting with subsequent claimed practice! Comment about this would be worthwhile. R7 Thank you for drawing our attention to this typographical error. The statement should read: "When I feel well, I believe there is no need to take my medication every day." This has now been corrected in Table 2 of the manuscript.