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Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis

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Clinical and Experimental Allergy

Summary

Background Addition of H₁ antagonists to intranasal corticosteroid treatment of allergic rhinitis (AR) is common in clinical practice and recommended by guidelines, despite some evidence that the additive benefits are negligible.

Objective To assess additional benefits of 5 mg levocetirizine dihydrochloride in seasonal AR patients using 200 mcg fluticasone propionate nasal spray once daily.

Methods In a double-blind placebo-controlled crossover study of 27 patients, following 2 weeks without treatment, subjects used fluticasone with levocetirizine or identical placebo for 2 weeks each. Assessments were the Juniper mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ), domiciliary peak nasal inspiratory flow (PNIF), total nasal symptoms (TNS) scores and nasal nitric oxide concentrations. Effects were interpreted and tested against minimal clinically important differences.

Results Add-on effects for levocetirizine vs. placebo excluded any clinically significant benefits: mean effects (one sided 95% confidence intervals) were mini-RQLQ -0.11 (-0.34), PNIF $+0.57$ ($+5.23$), and TNS -0.11 (-0.60). Numbers needed to treat (95% confidence intervals) by outcome were mini-RQLQ 14 (5 to 49), PNIF 4 (3–7), and TNS 3 (2–6). No significant within or between treatment effects were seen for nasal nitric oxide.

Conclusion Contrary to current practice, the present results demonstrate that for the majority of patients, antihistamine add-on to effective nasal steroid treatment is inappropriate. Further work is required to confirm that this is also true in the most severe cases, and the available evidence needs to be put into guidelines and implemented.

Keywords clinical relevance, fluticasone propionate, levocetirizine dihydrochloride, minimal clinically important difference, seasonal allergic rhinitis

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Introduction

Both antihistamines and nasal steroids are commonly used in the treatment of allergic rhinitis (AR). There is good evidence of efficacy for monotherapy with either, but the response is frequently incomplete and patient satisfaction is poor, so combination therapy is often started. The ARIA guidelines [1] comment 'The treatment of allergic rhinitis implies symptom reduction by drugs and attempts to interfere in the inflammatory cascade by

anti-inflammatory drugs or specific immunotherapy ... theoretically, combining interventions at different levels should improve the clinical outcome'. The same report described differential effects for intranasal corticosteroids and antihistamines on symptoms, so it would seem intuitive that additive effects could exist.

A literature search (Medline, Cochrane, Embase and ancestor references) was conducted for evidence supporting add-on of antihistamines for patients using topical nasal steroids in AR.

In a recent review, Akerlund et al. [2] highlighted the lack of evidence to support newer guidelines that recommend the add-on of antihistamine to nasal steroid therapy.

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A review by Howarth [3] observed that there was no evidence from 'limited studies available' to support superiority of combination therapy compared with topical corticosteroid alone.

Ratner et al. [4] evaluated 2 week treatments with loratadine (10 mg once daily) and nasal fluticasone (200 mcg once daily) alone or in combination in moderate to severe seasonal AR and found no evidence of 'meaningful' additional benefits on symptoms scores and quality of life.

Di Lorenzo et al. [5] compared the use of nasal fluticasone (200 mcg once daily) alone and in combination with cetirizine (10 mg once daily) in moderate to severe seasonal AR, showing that combination therapy resulted in a statistically significant but small improvement in nasal itching and combined symptom scores. No significant improvements were seen for congestion, rhinorrhoea, sneezing, or percentage of eosinophils and eosinophil cationic protein in nasal washings.

Notably, none of the studies identified in our search conducted equivalence or non-superiority analyses comparing effects to defined limits of clinical relevance, and so were not able to conclude that combination therapy is clinically inappropriate.

Combination therapy is certainly more expensive, and has the inherent risks of polypharmacy, including poor compliance, interactions and additional side-effects, which although rare and usually mild, do include sedation, palpitations, arrhythmias and hypersensitivity reactions.

We therefore conducted a double-blind placebo-controlled crossover study of the effects of fluticasone propionate alone or in combination with levocetirizine. Outcome assessments included both objective and subjective measures. The primary outcome was the Juniper mini-RQLQ [6]. We conducted a non-superiority analysis for levocetirizine vs. placebo as add-on to fluticasone treatment, with reference to minimal clinically important differences (MCIDs) for each outcome.

Methods

Patients

Participants were identified from our own database of patients in the Dundee area, Scotland. Inclusion criteria were male or female patients, aged 16–75 years, with seasonal (intermittent or persistent) AR, and skin prick-positive responses to grass pollen. Exclusion criteria were any other conditions affecting nasal airway patency, including septal deviation greater than 50%, and grade 2 polyps (extending below the upper edge of the inferior turbinate), pregnancy, lactation or any medical condition or screening blood result that might compromise participant safety.

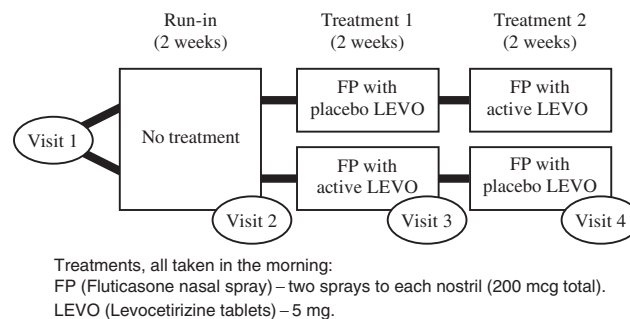


Fig. 1. Study flow diagram.

Study design

The study (see Fig. 1) was conducted in four visits to the research laboratory in the months of June and July 2004 – the Dundee peak grass pollen season. All participants gave informed consent, and the protocol was given a favourable opinion by the multi-centre research ethics committee for Scotland.

Visit one (screening) determined inclusion and exclusion status. A medical history was taken, and routine blood tests (full blood count, urea and electrolytes, and liver function tests), nasal endoscopy and skin prick tests to common aeroallergens were performed (including mixed grass, positive and negative controls). Participants stopped any usual therapy with decongestants, antihistamines, anti-leukotrienes and nasal steroids, and were given sodium cromoglicate nasal spray and eye drops as rescue medication. Use of rescue medication was avoided for 24 h before each visit.

Participants attended visit 2 after 2 weeks without their usual treatments to establish baseline measurements.

For the remainder of the study, they took two sprays each side (200 mcg total) every morning of fluticasone nasal spray and either placebo or 5 mg levocetirizine tablets. An independent pharmacy encapsulated both tablets in an identical manner to blind the study. Fluticasone and levocetirizine doses were chosen to represent routine clinical practice. A crossover design was used; so all subjects received 2 weeks of combination therapy with fluticasone and levocetirizine and 2 weeks of monotherapy with fluticasone (and placebo) in a randomized order. Visit 3 was conducted after the first treatment and visit 4 after the second.

Measurements

All outcomes were measured or calculated for baseline (visit 2) and after each treatment period (visits 3 and 4).

Juniper mini Rhinoconjunctivitis Quality-of-Life Questionnaire. The mini-RQLQ [6] is a validated shortened version of the Juniper rhinoconjunctivitis quality-of-life questionnaire [7]. There are 14 questions in five domains

(activities, practical problems, nose, eye and other symptoms). Each question is scored for the preceding week as an integer from 0 (not troubled) to 6 (extremely troubled). The global mini-RQLQ score is the average (mean) of all question scores.

Domiciliary morning peak nasal inspiratory flow rate. PNIF measurements were noted each morning in a subject diary – each taken as the best of three from an In-Check[®] PNIF meter (Clement Clarke International Ltd, Harlow, UK). This is analogous to a reversed peak flow meter connected to a face mask to establish the maximal airflow rates on forced nasal inspiration. Subjects were instructed in the correct method, and the technique was assessed at screening, to ensure a seated posture, horizontal positioning of the meter, correct restoration of the reading to zero, a closed mouth, and an adequate mask seal while making a maximal nasal inspiration.

Domiciliary morning total nasal symptoms score. TNS scores were also recorded in the diary each morning. The TNS score is the sum of scores for nasal run, blockage, itch and sneeze, each measured on an interval scale of 0, 1, 2 or 3 representing no symptoms, mild, moderate or severe symptoms, respectively. This results in an integer score for TNS of 0 to 12.

Nasal nitric oxide levels. Nitric oxide levels are an objective marker of airway eosinophilic inflammation [8]. A Niox[®] nitric oxide analyzer (© 2000 Aerocrine AB, Solna, Sweden) was used at each visit to sample nitric oxide levels, using a method consistent with the joint statement [9] of the American Thoracic Society and the European Respiratory Society.

Statistical analysis and data presentation

The study was powered (at > 90%) to detect ($P < 0.05$) a 0.7 U change (the MCID) in the primary outcome variable – the mini-RQLQ. The within subject standard deviation used was 0.32, as calculated in the instrument's initial validation [6]. Analyses were performed using Minitab, Copyright © 2004, Minitab Inc. PA, USA and SPSS for Windows (v11) Copyright © 2004, SPSS Inc. Chicago, IL, USA.

Each outcome was assessed for normality using Shapiro–Wilk tests and by eye, with consideration of previous data sets and the literature. All outcomes were considered normally distributed.

For PNIF and TNS, analysis was conducted on mean measurements for the final week of each period (treatment or run-in); for all other outcomes single (visit based) measurements were used.

Before non-superiority testing, differences within group (vs. baseline) were tested to demonstrate efficacy

for all outcomes (null hypothesis – in the wider population no treatment effect exists). Non-superiority testing was then conducted for levocetirizine vs. placebo add-on therapy (null hypothesis – in the wider population the additional benefit of levocetirizine treatment vs. placebo is greater than the MCID).

Confidence intervals were calculated for both these comparisons – two-sided 95% confidence intervals for efficacy and one-sided 95% confidence intervals for non-superiority.

Finally, the number needed to treat (NNT) for one subject to experience a benefit greater than the MCID for each outcome was calculated.

Minimal clinically important difference determination

The MCID for the mini-RQLQ (± 0.7 U) was determined in its development by an anchor-based approach. MCIDs for PNIF (± 6.23), TNS (± 0.52) and nasal nitric oxide (± 68.7) were calculated using a distribution-based approach – each MCID is one-fifth of the outcome's standard deviation at baseline (see Table 3). Anchor- and distribution-based approaches are described in the discussion.

Data presentation

A summary by treatment period for each measurement taken is given in Table 2. Treatment effects for all outcomes (Table 3) were plotted (Fig. 3) using a scale on which +1 U represents an improvement of one MCID, thus enabling different outcomes to be plotted together and interpretations to be made of the statistical and clinical significance of treatment effects within and between groups. The plots also allow a comparison of the strength of signal and noise for all outcomes used. Interpretation of these plots is described in the discussion and in Fig. 5.

Results

Patient demographics (see Table 1)

Thirty-one subjects were initially enrolled for the study. Four subjects chose to withdraw for personal reasons. Eleven men and 16 women with mean (SD) age of 45.9 (15.0) and 44.2 (15.9) years respectively completed per protocol. Sixteen subjects received fluticasone with levocetirizine (combination) followed by fluticasone with placebo (monotherapy), 11 the opposite. Adverse events were recorded as (by treatment period) 1 $\times$ minor epistaxis (during combination therapy), 1 $\times$ URTI and 1 $\times$ lethargy (during monotherapy). No serious adverse events occurred.

Table 1. Demographics

Participant	Age	Sex	Sensitivities	Mini-RQLQ	FEV ₁ % Predicted
1	31	F	GHC	4.21	–
2	63	M	GH	1.64	–
3	55	F	G	1.93	–
4	37	M	GTW	1.50	–
5	48	M	GWHAF	4.86	–
6	55	M	GH	1.79	91
7	33	F	GC	2.07	–
8	28	M	GTWHDC	2.79	–
9	66	M	GWHAF	2.54	–
10	47	F	GTC	1.07	–
11	60	F	GH	3.07	–
12	32	M	GTW	1.43	–
13	57	F	GWA	1.86	–
14	58	F	GWH	2.29	–
15	65	F	GH	3.14	–
16	23	F	GWHC	3.50	–
17	61	F	GWH	1.50	–
18	60	M	GHC	1.57	–
19	30	M	GTWHCD	2.50	–
20	29	M	GTWHF	3.36	87
21	44	F	GDC	1.71	–
22	49	M	GW	3.00	–
23	18	F	GW	2.43	–
24	25	F	GWHC	4.29	–
25	49	F	GTWHAFDC	5.64	–
26	54	F	GHC	2.71	96
27	27	F	GTWHAFDC	1.43	90
28	18	F	GHC	2.21	–
29	21	F	GTW	4.71	101
30	57	M	GTW	4.86	–
31	39	F	GWHC	2.71	–

Sensitivities represent: G, grasses; T, trees; W, weeds; H, house dust mite; A, aspergillus; F, feathers mix; D, dog; C, cat. Mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ) is the score recorded at screening. Percentage predicted FEV₁ was only recorded for asthmatics.

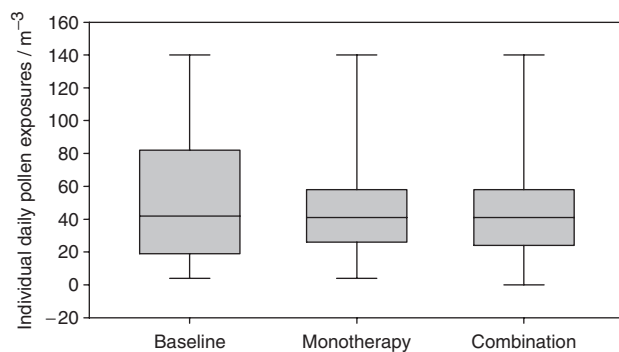


Fig. 2. Pollen exposures by treatment period. Boxplots –boxes show 2nd and 3rd quartiles, whiskers show minima and maxima.

Pollen Exposure (see Fig. 2)

Dundee pollen profiles have been published in this journal previously [10–12]. The 2004 pollen counts (52 m⁻³, SEM

Table 2. Means (and standard errors) for all outcomes at baseline and following each randomised treatment

Outcome (units)	Baseline	Monotherapy	Combination
Mini-RQLQ (units)	2.5 (0.22)	1.7 (0.25)	1.6 (0.24)
PNIF (L/min)	118 (5.8)	130 (5.7)	131 (6.3)
TNS (units)	4.7 (0.46)	2.6 (0.51)	2.5 (0.53)
Nasal NO (ppb)	810 (64)	763 (77)	758 (67)

Mini-RQLQ, mini Rhinoconjunctivitis Quality-of-Life Questionnaire; PNIF, peak nasal inspiratory flow; TNS, total nasal symptoms score; NO, nitric oxide.

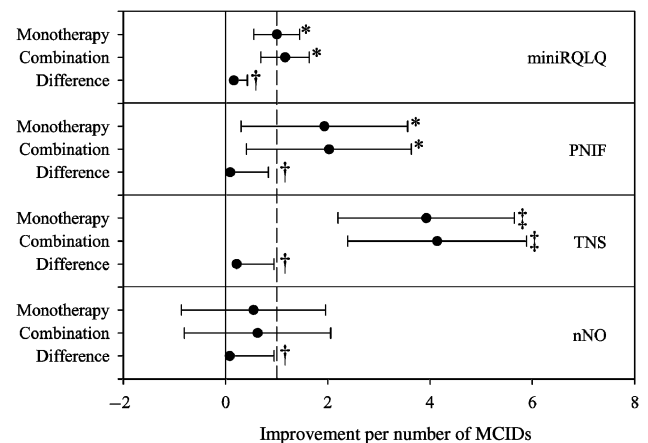


Fig. 3. Outcome improvements for each randomized treatment and differences between treatments. Results for monotherapy (fluticasone and placebo), combination (fluticasone and levocetirizine) and differences (add-on benefits) are plotted on a scale to depict changes relative to minimal clinically important differences (MCIDs). For within treatment effects two-sided 95% CIs are shown: †denotes statistically and clinically significant improvements. *denotes statistically significant improvements of uncertain clinical significance. For between treatment differences the one-sided 95% CIs are shown: †denotes non-superiority of combination therapy.

3.6) were not significantly different to previous years ($P = 0.67$). Individual daily pollen exposure is presented by treatment period in Fig. 2.

Within- and between-treatment effects (see Tables 2–4, Fig. 3)

Juniper mini rhinoconjunctivitis quality-of-life questionnaire. Statistically significant improvements were seen for change from baseline for both monotherapy ($P < 0.0001$) and combination therapy ($P < 0.0001$). The mean (one-sided 95% CI) for the difference between combination and monotherapy (i.e. levocetirizine add-on effects) was -0.11 (to -0.30), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the

Table 3. Baseline data, MCID calculations and change by treatment group for all outcomes

Outcome (U)	Baseline Mean (95% CI)	SD at baseline	MCID (SD/5)	Monotherapy	Combination therapy	LEVO add-on effect
MiniRQLQ (U)	2.46 (2.03 to 2.90)	1.17 [†]	0.7 [†]	-0.70 (-1.02 to -0.39), $P < 0.0001$	-0.82 (-1.15 to -0.49), $P < 0.0001$	-0.11 (to -0.30), $P < 0.0001$
PNIF (L/min)	118 (107 to 130)	31.2	6.23	12.0 (1.9 to 22.2), $P < 0.05$	12.6 (2.6 to 22.6), $P < 0.05$	0.57 (to 5.23), $P < 0.05$
TNS (U)*	4.56 (3.61 to 5.50)	2.58	0.52	-2.02 (-2.91 to -1.13), $P < 0.0001$	-2.13 (-3.04 to -1.23), $P < 0.0001$	-0.11 (to -0.51), $P < 0.05$
nNO (ppb)	810 (682 to 938)	344	68.7	-37.4 (-134.5 to 59.6), $P = 0.44$	-43.1 (-142 to 55), $P = 0.37$	-5.6 (to -65.3), $P < 0.05$

Effect data are presented as means (95% confidence intervals) and P -values. P -values are the probability of non-efficacy vs. baseline except for add-on effects where P -values are the probability of superiority for combination therapy of 1 minimal clinically important difference or more.

*Individual symptom score data are presented in Table 4.

[†]Calculated in the instruments development.

LEVO, 5 mg daily Levocetirizine Dihydrochloride; Mini-RQLQ, mini Rhinoconjunctivitis Quality-of-Life Questionnaire; MCID, minimal clinically important difference; PNIF, peak nasal inspiratory flow; TNS, total nasal symptoms score; NO, nitric oxide.

additional mini-RQLQ benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, two experienced a benefit with levocetirizine add-on that was greater than the MCID – NNT 14 (95% CI 5–49).

Domiciliary morning peak nasal inspiratory flow rate. Statistically significant improvements were seen for change from baseline for monotherapy ($P < 0.05$) and combination therapy ($P < 0.05$). The mean (one-sided 95% CI) for the difference between combination therapy and monotherapy (i.e. levocetirizine add-on effects) was 0.57 (5.23), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the additional PNIF benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, eight experienced a benefit with levocetirizine add-on greater than the MCID: i.e. NNT 4 (95% CI 3 to 7).

Domiciliary morning Total Nasal Symptoms score. Statistically significant improvements were seen for change from baseline for monotherapy ($P < 0.0001$) and combination therapy ($P < 0.0001$). The mean (one-sided 95% CI) for the difference between combination therapy and monotherapy (i.e. levocetirizine add-on effects) was -0.11 (-0.51), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the additional TNS benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, nine experienced a benefit with levocetirizine add-on greater than the MCID: i.e. NNT 3 (95% CI 2–6). A breakdown by individual symptom scores is given in Table 4.

Nasal nitric oxide levels. No statistically significant improvements were seen for change from baseline for monotherapy ($P = 0.44$) or combination therapy ($P = 0.37$). Thus, we were unable to demonstrate a signal

for nasal nitric oxide measurements at all, so no further conclusion should be drawn.

Sequence analysis

A comparison of randomization groups showed no statistically significant differences for carry-over ($P = 0.58$) or period ($P = 0.29$) effects on the primary outcome.

Discussion

In the present study, we set out to determine whether combination therapy with nasal fluticasone and oral levocetirizine was any more effective than fluticasone monotherapy. In view of the previous evidence, instead of hypothesizing a difference, we set out with the hypothesis that monotherapy could be considered no worse than combination therapy, i.e. non-inferior.

In AR, it is important to measure outcomes not only related to nasal airflow obstruction (PNIF, acoustic rhinometry or rhinomanometry), but also symptoms such as blockage, rhinorrhoea, itch and sneeze and the effects on global quality of life [13].

Both the mini-RQLQ and RQLQ have strong discriminative and evaluative measurement properties (defined by Guyatt *et al.* [14]), and the mini-RQLQ is significantly more responsive than the earlier rhinoconjunctivitis quality-of-life questionnaire [6, 7].

We have previously shown that PNIF is a representative and repeatable (cv. 8%) [15] measure of nasal airflow obstruction, and that it is more sensitive than acoustic rhinometry for monitoring response to histamine nasal challenges [16]. Nasal nitric oxide is considered a reproducible (cv. 13% [17]), non-invasive and easily obtained nasal inflammatory marker.

For our drug interventions we chose to study levocetirizine add-on to fluticasone nasal spray over a 2-week period to represent the current best treatment. Fluticasone is among the most commonly used of the nasal steroids available in our rhinology clinic, and has a high

Table 4. Baseline data, MCID calculations and change by treatment group for individual symptom scores

Outcome (U)	Baseline		MCID (SD/5)			
	Mean (95%CI)	SD at baseline		Monotherapy	Combination therapy	LEVO add-on
BN (U)	1.24 (0.95 to 1.54)	0.79	0.16	-0.60 (-0.63 to -0.10), $P < 0.0005$	-0.49 (-0.74 to -0.24), $P < 0.0005$	0.11 (to -0.04), $P < 0.005$
RN (U)	1.00 (0.70 to 1.29)	0.78	0.16	-0.37 (-0.63 to -0.23), $P < 0.01$	-0.40 (-0.66 to -0.14), $P < 0.005$	-0.04 (to -0.19), $P = 0.1$
IT (U)	1.16 (0.86 to 1.46)	0.79	0.16	-0.55 (-0.85 to -0.25), $P < 0.001$	-0.58 (-0.88 to -0.28), $P < 0.001$	-0.03 (to -0.16), $P = 0.06$
SN (U)	1.31 (1.04 to 1.57)	0.72	0.14	-0.51 (-0.79 to -0.23), $P < 0.001$	-0.66 (-0.96 to -0.36), $P < 0.0005$	-0.15 (to -0.31), $P = 0.54$

Effect data are presented as means (95% confidence intervals) and P-values. P-values are the probability of non-efficacy vs. baseline except for add-on effects where P-values are the probability of superiority for combination therapy of 1 minimal clinically important difference or more. LEVO = 5 mg daily levocetirizine dihydrochloride; BN, blockage; RN, rhinorrhoea; IT, Itching; SN, sneezing; MCID, minimal clinically important difference.

glucocorticoid potency and binding affinity [18, 19], while levocetirizine was chosen as potentially the most effective [20–23] and longest acting 'new generation' [24] antihistamine with a negligible potential for cardiac toxicity at standard doses [13].

It is not possible in any study to demonstrate that a treatment has absolutely no effect or that there is absolutely no difference between treatments, because the breadth of the confidence interval for such differences is only 0 when the sample size is infinite: for this reason, in contrast to efficacy studies, studies hypothesizing equivalence or non-superiority must first define limits within which any change observed can be considered irrelevant. For example, accepting that a change in PNIF of less than ± 2 L/min is of no clinical relevance: 2 L/min is then the MCID for PNIF. An MCID can be defined as '*the smallest difference in score in the domain of interest which patients would perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management*' [25].

Exactly how a value should be determined for an MCID is a matter of debate. Perhaps most commonly, it is decided on the merits of 'clinical experience', with a distinguished writer simply dictating what he/she feels is

of relevance or otherwise. Two more objective methods have been developed. In an 'anchor-based' approach, changes in an outcome of interest are assessed and compared with 'a global or overall question measuring wellbeing or treatment effect' [26]. For example, in developing their mini-RQLQ [6], Juniper et al. used a global-rating scale as illustrated in Fig. 5. They found that when assessing the global-rating scale alongside changes in the mini-RQLQ, the mean change in their quality-of-life instrument for those patients that described either a 1 or 2 U change (positive or negative) on the global scale was 0.7 U, and thus established the MCID of the mini-RQLQ.

The second, more commonly used 'distribution-based approach' compares magnitude of the change seen with the variability of the measure in question. For example, if the standard deviation of PNIF measurements in the population in general is 10 L/min, we can take a proportion of this to represent our MCID. Cohen [27] defined a 'small change' (which has been interpreted as an MCID) as $0.2 \times$ the sample standard deviation of the measure at baseline.

Once an MCID has been used to set the limits of clinically irrelevant changes, the confidence interval for any change can be compared not only to 0 (as in efficacy testing) but also to +1 MCID or -1 MCID. Figure 5 illustrates the interpretation of confidence intervals for a change in relation to zero and MCIDs.

As a general rule, anchor-based MCIDs are to be favoured to the relatively empirical distribution-based MCIDs. For the mini-RQLQ used in our study, an anchor-based MCID had been determined in its original validation [6]. For the other outcomes, we applied the more commonly used 'distribution-based' approach. Where anchor-based MCIDs are not available, these are certainly to be preferred to best guess approaches or the regrettably common conclusions of no difference when a comparison with 0 shows $P > 0.05$ – the correct conclusion in such scenarios is usually that the study was under-powered.

Using these methods, we have gone beyond the analyses conducted previously and have been able not only to test for a difference within or between groups, but also to demonstrate its clinical relevance or irrelevance. We first

- 7 – A very great deal worse
-6 – A great deal worse
-5 – A good deal worse
-4 – Moderately worse
-3 – Somewhat worse
-2 – A little worse
-1 – Almost the same, hardly any worse at all
0 – No change
+1 – Almost the same, hardly any better at all
+2 – A little better
+3 – Somewhat better
+4 – Moderately better
+5 – A good deal better
+6 – A great deal better
+7 – A very great deal better

Fig. 4. Global rating of change questionnaire, reproduced by kind permission of Prof. E. Juniper. 'Since your last visit, has there been any change in activity limitation/symptoms/emotions/overall quality of life, related to your allergic rhinitis?' Use the scale shown above.

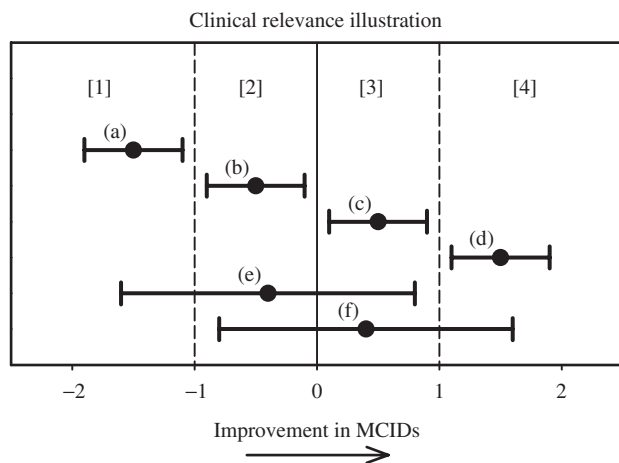


Fig. 5. Interpretation of results with regard to minimal clinically important differences (MCIDs) and clinical relevance. The illustration shows confidence intervals for 6 hypothetical changes plotted on a scale of MCIDs of change. For example, if the MCID for peak nasal inspiratory flow rate were 2 L/min, a change of 4 L/min would be plotted at 2 on the scale. Changes to the right of zero are improvements; changes to the left are deteriorations. Regions [1] and [4] contain clinically significant deteriorations and improvements respectively, while Regions [2] and [3] contain clinically insignificant deteriorations and improvements respectively. Thus, confidence intervals (a) and (d) demonstrate effects (deterioration and improvement, respectively) that are both statistically and clinically significant: they not only exclude zero effect, but also any effect smaller than the MCID. In contrast, confidence intervals (b) and (c) demonstrate effects (deterioration and improvement, respectively) which although statistically significant, are of no clinical relevance: they are entirely contained within ± 1 MCID. Confidence intervals (e) and (f) illustrate non-superiority and non-inferiority, respectively.

demonstrated not only that randomized treatment with fluticasone alone or in combination with levocetirizine produced a statistically significant improvement from baseline (95% confidence interval excluded 0) but also that this improvement was clinically relevant (mean was greater than 1 MCID). Further, there were no statistically significant differences between randomized treatments, and non-superiority of levocetirizine vs. placebo was demonstrated with respect to MCIDs for mini-RQLQ, PNIF and TNS (one-sided 95% confidence intervals excluded any benefit of 1 MCID or more).

Mean improvements seen in the fluticasone group were all greater than the calculated MCIDs for the same outcomes. Nonetheless, even following fluticasone treatment, symptom and quality-of-life scores suggested clinically important persistent morbidity – the mean mini-RQLQ score following fluticasone alone was 1.7, which is more than twice the MCID. Similarly, mean residual symptom scores were 2.6 U (nearly five times the MCID). Thus, the lack of add-on efficacy of levocetirizine was not an erroneous finding because of total symptom control with nasal steroid alone. This is consistent with clinical experience and the available evidence that response is frequently incomplete and patient satisfaction poor [28].

From the plots provided (Fig. 3), it is possible to compare the strength of signal and noise for the different outcomes. At first glance, it would seem that TNS has the best signal to noise ratio; indeed it was the only outcome for which a clinically insignificant benefit was excluded in the comparisons with baseline. Unfortunately, these comparisons were not against placebo, which may account for their 'strength' of signal. This does not affect the interpretation of between group effects (including the primary outcome), which were placebo controlled. Equally, the relatively objective measures (PNIF and nasal nitric oxide) should be unaffected. It is also evident that the signal strength of nasal nitric oxide was less than that of the clinical outcomes. This is consistent with our previous use of the marker [11, 15, 29].

Pollen counts are highly variable and can lead to erroneous conclusions in seasonal allergy studies. In the current study, we saw the highest individual daily pollen exposures during the baseline periods (Median 42 m^{-3} interquartile range (IQR) 19–82), which could potentially have biased our findings, but only towards showing a greater efficacy for both monotherapy and combination therapy vs. baseline.

Differences between exposures for each treatment were prevented by the crossover design (Median 41 m^{-3} IQR 26–58 for monotherapy vs. 41 m^{-3} IQR 24–58 for combination therapy).

Carryover effects are another potential confounder to consider. The pollen season is short, and so no washout period was possible, but treatments were for 2 weeks, and the plasma half-life of levocetirizine is 7.9 h [30]; so this represents a 42 half-life washout. Further, a formal analysis showed no significant carryover effect.

Although we were able to dismiss the null hypothesis and conclude that for mean effects, levocetirizine add-on was non-superior to placebo for all outcomes, this does not rule out clinically relevant responses in a minority of subjects. In order to better assess this, we calculated the number of treatments necessary for one subject to experience a beneficial effect greater than +1 MCID. From these data, it would seem that at best one-third of patients treated with antihistamine add-on will experience any relevant improvement. It may be possible to identify subjects that are more likely to benefit (perhaps on severity grounds). The correlation between screening severity and treatment response that we observed (analysis not documented, $P=0.33$, $R=0.201$) was not significant and very weak, suggesting that if the most severely affected subjects do gain greater benefit from antihistamine add-on, the difference is likely to be small.

It could also be the case that full treatment effects are not established within 2 weeks; but longer treatment periods, run-in and wash-out would not be feasible within the constraints of our pollen season: a window of about 2 months. The literature on temporal effects of nasal steroid

and antihistamine use in AR surprisingly suggests that although effects of fluticasone are mostly established by 2 weeks [31], significant improvement does follow levocetirizine use between 4 and 24 weeks [32]; so it remains to be seen whether add-on effects for longer-term therapy may be of clinical relevance. This will be of greater significance in persistent AR, where longer-term treatments are possible, or in intermittent AR if treatment is started several weeks before the season.

There will always be pressure to offer some form of treatment to long suffering allergic rhinitics, and many practitioners will feel that an NNT of 3 or more, even as a best case scenario, is acceptable or even favourable, but it remains the case that for the majority of seasonal AR patients treatment risks and costs will outweigh benefits.

In conclusion, and contrary to common clinical practice, antihistamine add-on to nasal steroid treatment in AR leads to no clinically relevant benefit in the majority of patients. It is still to be determined whether this remains the case in long-term use and whether patient selection will improve the proportion of subjects deriving benefit from such treatment.

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