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Efficacy of Desloratadine in Persistent Allergic Rhinitis – A GA²LEN Study

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Key Words

Activity impairment · ARIA · Desloratadine · Persistent allergic rhinitis · Quality of life, rhinitis · Randomized controlled trial · Work productivity

Abstract

Background: The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines proposed a classification for allergic rhinitis based on the duration of symptoms (intermittent or persistent) rather than on the time of allergen exposure (seasonal or perennial). There had been no placebo-controlled, randomized, clinical trial of desloratadine (DL) in patients with persistent allergic rhinitis to date. ***Objectives:*** To assess the efficacy and safety of DL in patients with persistent allergic rhinitis based on the ARIA classification. ***Methods:*** Patients 12 years of age and older with persistent allergic rhinitis were assessed over 85 days of treatment with DL 5 mg once daily (n = 360) or placebo (n = 356). The primary endpoint was the AM/PM reflective total 5-symptom score (T5SS) averaged over days 1–29. Secondary endpoints included AM/PM instantaneous T5SS and individual symptoms, therapeutic response, symptom severity assessed by a visual analogue scale and quality of life. ***Results:*** The mean reduction in AM/PM reflective T5SS was significantly greater with DL than placebo over days 1–29 (–3.76 vs. –2.87, $p < 0.001$) and on each individual day ($p < 0.05$). The mean AM instantaneous T5SS was significantly reduced with DL compared with placebo as early as day 2 (–1.90 vs. –1.46; $p < 0.001$). The therapeutic response and improvement in quality of life were significantly greater with DL than placebo ($p < 0.001$ for each). The frequency of treatment-related adverse events was low and similar between DL (10.0%) and placebo (8.4%). ***Conclusions:*** This study showed DL to be effective and safe in the treatment of persistent allergic rhinitis.

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Introduction

In 2001, allergic rhinitis was classified by the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines into four categories [1], mild and moderate/severe intermittent, and mild and moderate/severe persistent, depending on the severity of symptoms and quality of life, and the duration of symptoms. It is important to note that the terms intermittent allergic rhinitis (IAR) or persistent allergic rhinitis (PER) are not interchangeable with the terms seasonal or perennial allergic rhinitis. The recent ARIA update has confirmed this classification because it is closer to the patient's needs and to real life than the previous one [2].

In the ARIA documents, a stepwise pharmacologic treatment is proposed based on the ARIA categories. There is no correlation between the ARIA categories and the previous classification of rhinitis (seasonal or perennial) [3, 4]. In its last edition, the ARIA panel members proposed that the results from randomized clinical trials (RCTs) conducted in the earlier classifications could not be extended to PER [2]. Two RCTs with oral H_1-antihistamines have been carried out in PER [5, 6], but there is no RCT in PER with desloratadine (DL). In RCTs in allergic rhinitis patients, assessment of treatment efficacy has been based on symptoms, quality of life [5, 7] and visual analogue scales (VAS) [7–10]. DL is effective and safe in the treatment of allergic rhinitis. It was shown to improve symptoms and quality of life in seasonal [11–17] and perennial allergic rhinitis [18, 19]. It was recently found to be effective and safe in the treatment of IAR (ACCEPT-1 study) [20]. However, it had not been previously tested in ARIA-defined PER.

The aim of the ACCEPT-2 (Aerius Control: Clinical and Evaluative Profile of Treatment-2) Study was to evaluate the efficacy and safety of DL in patients with PER defined by ARIA guidelines. The study report follows the CONSORT statement [21]. The ACCEPT studies also provided an opportunity to collaborate with GA^{2}LEN (Global Allergy and Asthma European Network) [20, 22], a consortium of leading European research centers specializing in allergic diseases.

Patients and Methods

Participants

Patients were included in the study after written informed consent was obtained. The study conformed to Good Clinical Practices and was approved by local ethics committees. All patients fulfilled the following inclusion criteria: age 12 years or older, either sex, at least a 2-year history consistent with symptoms of allergic rhinitis defined according to the International Consensus on Rhinitis [23] and PER according to the ARIA classification [1] (symptoms of allergic rhinitis present >4 days per week for >4 consecutive weeks per year). Patients had to have moderate-to-severe symptoms. On the day of inclusion, at the start of the run-in period, the reflective total 5-symptom score (T5SS) was at least 8. For a patient to be randomized, the sum of the daily averages of the diary recordings of the 12-hour AM plus PM reflective T5SS collected during 4 days and the AM reflective T5SS on the morning of randomization had to be ≥40. Allergy had to be confirmed by a positive skin prick test to common aeroallergens carried out according to the GA^{2}LEN skin test study [24]. None of the patients were to have received any medication for allergic rhinitis for specified periods (washout) prior to randomization. Maintenance regimens of immunotherapy were permitted.

Interventions

DL (5 mg once daily) or placebo was administered orally in identical tablets each morning within 1 h after waking up. The study consisted of two periods: The run-in period lasted for 4–14 days. If patients had sufficient symptoms (≥40) for 4 days, they were randomized to DL 5 mg or placebo for 12 weeks. Visits occurred on day 1 (baseline visit) and days 15, 29, 43, 57 and 85 after randomization during the treatment period.

Rescue medications were allowed after the first 4 weeks. They consisted of nasal and/or ocular cromoglycate at the minimum dose required to control symptoms. If a patient required the use of rescue medication for >4 consecutive days, he/she was eliminated from the study.

Objectives

The aim of the present study was to assess the efficacy and safety of DL in patients aged ≥12 years suffering from ARIA-defined PER. This multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group phase IV study of DL (5 mg, once daily, in the morning) was conducted in compliance with Good Clinical Practices. The study was conducted at 83 sites in 15 countries (Belgium, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Italy, The Netherlands, Portugal, Russia, Spain, Sweden and Turkey) from September 5, 2006 to November 21, 2007. The primary outcome measure was the reflective T5SS in the intent-to-treat population from days 1 to 29. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; days 1–29) [25] and T5SS from days 1 to 85 were key secondary outcome measures. Instantaneous T5SS (days 1–29 and days 1–85), individual symptom scores (days 1–29 and days 1–85), VAS levels (days 1–29 and days 1–85) [26, 27], RQLQ (days 1–85) and patients' assessment of response (days 29 and 85) were secondary endpoints, and the Work Productivity and Activity Impairment Questionnaire (WPAI-AS; days 29 and 85) [28, 29] was used as an exploratory outcome measures.

Outcomes

Symptom Severity Rating Scale Assessment. Severity scores for five (T5SS) individual allergic rhinitis signs/symptoms (nasal congestion/stuffiness, sneezing, rhinorrhea/nasal discharge, nasal pruritus and eye itching) were recorded in the patients' daily diaries in the morning and evening. Each sign/symptom was scored from 0 (none) to 3 (severe) twice daily, once in the morning (AM) within 1 h of waking up and prior to dosing (reflective) and once

in the evening (PM), approximately 12 h later. In both the AM and PM T5SS, symptom severity was assessed over the previous 12 h (reflective) and at the time of the assessment (instantaneous). The T5SS is the sum of the ratings for the individual scores.

Symptom Severity VAS Assessment. The 24-hour reflective VAS rating was recorded in the patients' daily diaries each morning within 1 h of waking up and prior to dosing (AM) at the baseline visit and for each treatment day. Scores ranged from not at all bothersome (0 mm) to very bothersome (100 mm) [26, 27, 30].

Patients' Evaluation of Therapeutic Response to Treatment. The patients' response to treatment was assessed by the patient alone on days 15 and 29, and at the final visit (day 85). Evaluation included the entire period from the start of treatment (baseline) up to and including the final visit. The assessment was scored using a 5-point scale: complete relief, marked relief, moderate relief, slight relief or no relief.

RQLQ. The standardized version of the 28-question RQLQ-S [25] was completed by patients >18 years of age at baseline, on day 29 and at the final visit.

Interference with Sleep and Activities of Daily Living. At the run-in visit, during the run-in period (days –4 to –1) and continuing through to the final visit (day 85), patients recorded in their daily diaries (at the same time as recording the T5SS ratings) the two interference rating scores, namely:

- once daily (AM) evaluations of interference with sleep caused by allergic rhinitis symptoms during the previous night, and
- once daily (PM) evaluations of interference with activities of daily living caused by allergic rhinitis symptoms during that day.

Work Productivity Questionnaire. At the baseline visit and weekly through to the final visit, the allergic-rhinitis-specific WPAI-AS was completed by the patients [28, 29].

Study Drug Compliance. Compliance was assessed by comparing the number of tablets dispensed at the baseline visit with the number returned at the interim visits and at the final visit. Patients were considered non-compliant if they had taken <80 or >120% of drugs.

Adverse Events

Adverse events were recorded at each visit on the case report form and were coded using the Medical Dictionary for Regulatory Activities [31].

Sample Size

A sample size of approximately 800 patients (400 on DL 5 mg and 400 on placebo) was calculated to provide at least 90% power to detect a 0.8-point treatment difference from baseline reflective T5SS averaged over days 1–29, with a 5% two-sided level of significance and an assumed standard deviation of 3.5. A 0.8-point treatment difference is a 10% improvement over placebo, assuming a baseline score of 8.0 points.

Randomization

Patients were randomized in a 1:1 ratio to the two treatment arms by means of a computer-generated randomization schedule.

Statistical Analysis

A two-way analysis of variance (ANOVA) with treatment and side effects as covariates was used to examine treatment differences in T5SS, RQLQ, individual diary symptoms, interference with sleep and daily activities, the VAS assessment and WPAI-AS. The Mantel-Haenszel test was used for the patients' evaluation of therapeutic response.

Multiplicity. The study has one primary endpoint and one key secondary endpoint for one treatment comparison (DL vs. placebo). The key secondary endpoint was tested only if the primary endpoint had been statistically significant. Therefore, the overall α of 5% was preserved. The results of the additional secondary and exploratory endpoints were examined only to confirm the results of the primary analysis. Thus, no multiplicity adjustments to the overall α were applied to the additional secondary endpoints.

Missing Data. All randomized patients with non-missing baseline data and at least some data obtained after baseline were included in the analysis (intent-to-treat principle). However, patients with a missing evaluation at a given visit or time point were excluded from the analysis for that evaluation. For visit and diary evaluations, several impact analyses were performed to assess the influence of early discontinuations, such as looking at patients who completed the study and substitution of worst-case values for missing data, as previously reported in detail [20].

Since there was a larger dropout rate in the placebo group after 30 days of treatment, we have carried forward the last values for each patient so that the sample size remains constant in each group (LOCF: last observation carried forward). For each individual, missing values are replaced by the last observed value of that variable. Using LOCF, once the data set was complete in this way, it was analyzed as if it were fully observed.

Results

Participant Flow and Number Analyzed

In total, 931 patients were screened and 716 patients were randomized and valid for inclusion in the safety protocol. A total of 301 patients treated with DL and 261 treated with placebo completed the study. The study groups are shown in figure 1.

Baseline Data

The baseline demographic data at the run-in period were similar in both groups (table 1).

Patient Compliance

Only 11 patients in the DL group and 6 in the placebo group were not compliant and were therefore excluded from the analysis.

Outcome and Estimation

Table 2 represents the intent-to-treat analysis. There was a 39.0% improvement in the primary endpoint (T5SS reflective, days 1–29) in the DL group and a 30.0% improvement in the placebo group ($p < 0.001$). The secondary outcome (RQLQ) was significantly improved in the

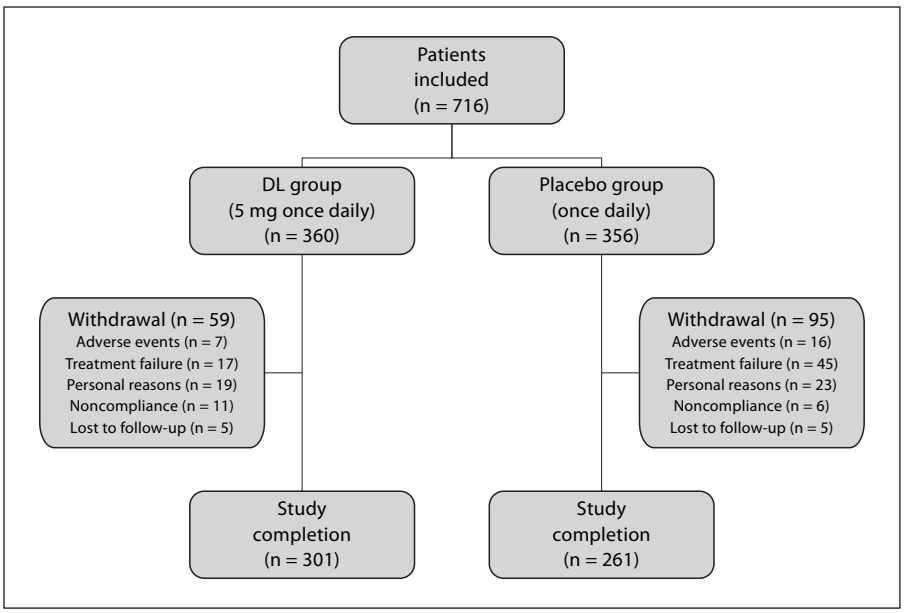

Fig. 1. Flowchart of patient randomization and dropout.

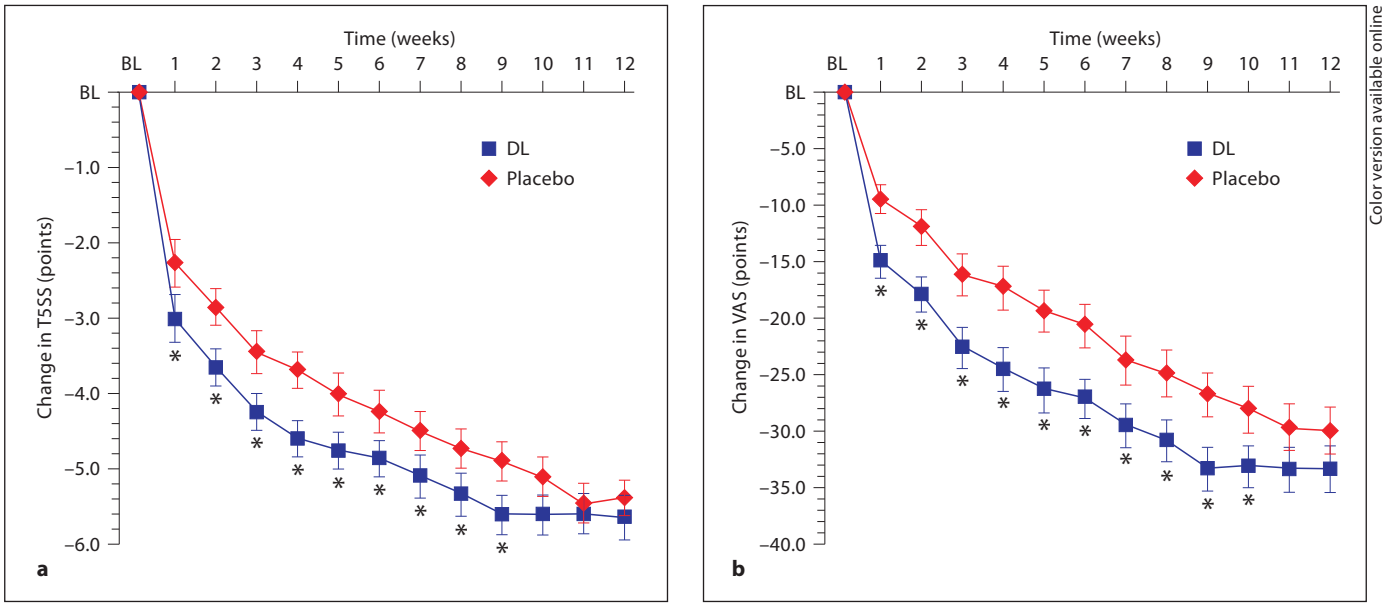

Fig. 2. Evolution of reflective T5SS (**a**) and symptom severity by VAS (**b**). Least significant (LS) mean change during weeks 1–12 in 24-hour versus baseline (BL) T5SS (**a**) and VAS (**b**) obtained from an ANOVA model with treatment and side effects as covariates in the model (* $p \leq 0.018$).

DL group in comparison to the placebo group. All secondary and exploratory outcomes were also significantly improved by DL up to 85 days. The efficacy of DL was found for both the instantaneous and reflective symptom assessments.

When individual symptoms were assessed, all nasal symptoms (including nasal congestion) were significantly improved in the DL group compared with placebo.

For the primary efficacy variable, DL was significantly more effective than placebo starting on day 1 and continuing through to week 9 (fig. 2a). However, the maxi-

Table 1. Demographic data

	DL 5 mg	Placebo	p value
Patients, n	360	356	
Males, %	42	44	NS
Age, years	34.0 ± 12.1	33.9 ± 12.3	NS
Asthma, n	38 (18.2%)	35 (16.5%)	NS

mum effect was observed after 1 week of treatment for the primary outcome measure (fig. 2a). For the VAS assessments, DL was significantly more effective than placebo starting on day 1 and continuing through to week 10 (fig. 2b). The loss of significance between DL and placebo during the last few weeks of the study can be attributed to the significantly higher dropout rate in the placebo group during the last few weeks of the study. In an analysis in which the last values for each patient are carried forward from the time they leave the study to day 85, the DL group shows significant improvement versus placebo throughout the entire study (online suppl. table 1, www.karger.com/doi/10.1159/000316351).

Both treatments were well tolerated and the rate of severe adverse events was identical and very low in both groups. No life-threatening adverse event occurred. There were no clinically meaningful changes in laboratory tests, electrocardiograms and/or vital signs (table 3).

Discussion

In the present study, we found that DL is safe and effective in the treatment of PER as defined by ARIA [1]. This is the third study using the ARIA criteria for PER [5, 6]. Because the methods used are recommended for the study of medications in allergic rhinitis and the sample size is sufficient, this study will help to support future ARIA guidelines.

Validated methods were used to enroll patients and study the efficacy of DL. The primary outcome measure was the recommended total score of five symptoms. This score includes nasal congestion, which is improved by DL [11]. Other well-accepted outcome measures, including RQLQ and WPAI-AS, were also used. Assessment of symptom severity by VAS was also employed as a secondary outcome measure. Interestingly, all the primary, secondary and exploratory outcomes were significantly different compared with placebo over the 85-day study pe-

Table 2. Primary and secondary outcome variables (intent-to-treat analysis): least significant means ± SEM (ANOVA model with treatment and side effects)

	DL 5 mg	Placebo	p value
AM/PM T5SS (reflective)			
Baseline	9.63 ± 0.13	9.55 ± 0.21	
Days 1–29	–3.76 ± 0.22	–2.87 ± 0.21	<0.001
RQLQ total score			
Baseline	3.30 ± 0.08	3.15 ± 0.08	
Day 29	–1.35 ± 0.10	–0.95 ± 0.10	<0.001
Day 85	–1.66 ± 0.11	–1.39 ± 0.12	0.023
AM/PM T5SS (reflective)			
Baseline	9.63 ± 0.13	9.55 ± 0.21	
Days 1–85	–4.50 ± 0.23	–3.61 ± 0.23	<0.001
AM/PM T5SS (instantaneous)			
Baseline	9.35 ± 0.15	9.23 ± 0.14	
Days 1–29	–3.41 ± 0.22	–2.52 ± 0.22	<0.001
Days 1–85	–4.11 ± 0.24	–3.22 ± 0.23	<0.001
AM/PM rhinorrhea (reflective)			
Baseline	2.10 ± 0.04	2.08 ± 0.04	
Days 1–29	–0.81 ± 0.05	–0.62 ± 0.05	<0.001
Days 1–85	–0.98 ± 0.05	–0.77 ± 0.05	<0.001
AM/PM nasal congestion (reflective)			
Baseline	2.13 ± 0.04	2.10 ± 0.04	
Days 1–29	–0.69 ± 0.05	–0.53 ± 0.05	0.002
Days 1–85	–0.87 ± 0.05	–0.70 ± 0.05	0.002
AM/PM sneezing (reflective)			
Baseline	1.88 ± 0.04	1.84 ± 0.04	
Days 1–29	–0.83 ± 0.05	–0.62 ± 0.05	<0.001
Days 1–85	–0.96 ± 0.05	–0.76 ± 0.05	<0.001
AM/PM nasal itching reflective			
Baseline	1.89 ± 0.04	1.88 ± 0.04	
Days 1–29	–0.77 ± 0.05	–0.58 ± 0.05	<0.001
Days 1–85	–0.91 ± 0.05	–0.74 ± 0.05	0.002
AM/PM eye itching (reflective)			
Baseline	1.62 ± 0.05	1.64 ± 0.05	
Days 1–29	–0.67 ± 0.05	–0.52 ± 0.05	0.006
Days 1–85	–0.78 ± 0.05	–0.65 ± 0.05	0.016
Sleep interference			
Baseline	1.58 ± 0.05	1.59 ± 0.05	
Days 2–29	–0.54 ± 0.06	–0.42 ± 0.05	0.022
Days 2–85	–0.65 ± 0.06	–0.52 ± 0.06	0.023
Activity interference			
Baseline	1.89 ± 0.04	1.89 ± 0.04	
Days 1–29	–0.69 ± 0.05	–0.46 ± 0.05	<0.001
Days 1–85	–0.82 ± 0.06	–0.60 ± 0.06	<0.001
Symptom severity (reflective) (VAS)			
Baseline	61.2 ± 1.20	59.80 ± 1.19	
Days 2–29	–19.7 ± 1.52	–12.7 ± 1.50	<0.001
Days 2–85	–25.7 ± 1.64	–18.0 ± 1.61	<0.001
Subjects' evaluation of response			
Baseline	NA	NA	
Day 85	2.70 ± 0.10	3.11 ± 0.10	<0.001

NA = Not applicable.

Table 3. Incidence of treatment-related adverse events reported by ≥1% of patients in either treatment group

	DL 5 mg (n = 360)	Placebo (n = 356)
Report of any adverse event	36 (10.0%)	30 (8.4%)
Adverse event leading to treatment discontinuation	7 (1.9%)	16 (4.5%)
Fatigue	7 (1.9%)	9 (2.5%)
Pruritus	4 (1.1%)	3 (0.8%)
Headache	6 (1.7%)	7 (2.0%)
Sedation/somnolence	8 (2.2%)	1 (0.3%)

riod. Statistical analysis followed the CONSORT statement and intent-to-treat analysis was carried out. However, in order to better assess the progress of treatment between weeks 9 and 12, we used LOCF. Because this method may induce bias, we only used it as a secondary outcome as there was a greater dropout rate in the placebo group. In the conduct of a clinical trial, all efforts should be directed towards minimizing the amount of missing data likely to occur in a long-term study, especially in the placebo group. Loss of values was therefore anticipated to a certain extent. The Committee for Proprietary Medicinal Products clearly delineates this problem [32]. Although the statistical analysis of a clinical trial generally requires the imputation of values to those data that have not been recorded, the LOCF method is acceptable if measurements are expected to be relatively constant over time, which is the case in this study. Sensitivity analyses were not needed since LOCF was not used for the primary endpoint [32]. Compared to previous studies on persistent rhinitis, the dropout rate was higher in the present study. However, at inclusion, patients appeared to have more severe disease according to the Rhinoconjunctivitis Total Symptom Score and RQLQ. Dropouts were observed, as expected, in patients with severe symptoms. The methodology appears to be acceptable for the European Medicinal Agency. The results of this study suggest that long-term trials may be affected by a high dropout rate, and, in some European countries, ethics committees will not accept that a placebo is given for periods exceeding 1 month. Thus, it is proposed that trials in persistent allergic rhinitis should not exceed 6 weeks.

The patients were well characterized according to ARIA. Few dropouts were observed in the DL group, and a greater number of dropouts were seen in the placebo group, with some reporting lack of efficacy. Compliance to the treatment was excellent.

DL was effective over a 24-hour period, as already shown. Improvements in daily diary symptom ratings were corroborated by VAS data, which improved by 31.4% in the DL group and 17.0% in the placebo group from day 1 to day 29. Interestingly, on day 29, the reductions in VAS levels in the DL and placebo groups were almost identical to those observed during the study of DL in IAR (ACCEPT-1, 14 days: –31.0 and –17.0%, respectively) [20]. These results indicate the significance of VAS changes in the evaluation of treatment for allergic rhinitis. As we have shown in the ACCEPT-1 study in IAR, between-group symptom scores appear to change less than VAS. This finding may be of importance since VAS is a composite score which could be used as a primary endpoint if further tested.

Symptoms were significantly improved by DL on day 1 and over the course of the 85-day study period. This study confirms previous ones [5, 6], but it consistently shows that PER is a robust model which can be used in clinical trials. It is difficult to ask patients to stay on placebo for a period of time >4 weeks and it may be proposed that PER should not be studied longer. The difference in Rhinoconjunctivitis Total Symptom Scores between DL and placebo groups was statistically significant. However, the improvement in the symptom score of only 8.7% is poor and confirms that oral H_1-antihistamine treatment results in a relatively low level of improvement in symptoms in RCTs. RCTs are not real-life trials and the magnitude of effects is likely to be smaller.

The symptoms of allergic rhinitis can considerably impair physical and emotional comfort and functional capacity. Patients rated symptom severity over the previous 24 h using a 100-mm VAS. The mean baseline VAS ratings were 61.24 in the DL group and 59.80 in the placebo group. These results show that most patients were in the moderate-severe category [26]. Compared to the IAR study (ACCEPT-1), VAS levels were slightly higher in the present study at baseline [20], in accordance with the level of severity set. At the end of the study, patients in the DL group showed a significantly greater improvement in VAS rating compared with placebo. In ACCEPT-1, the mean total score of the standardized version of the RQLQ-S at baseline was 2.96 in the DL group and 2.80 in the placebo group (out of a possible 6.0). In ACCEPT-2 (present study), RQLQ global scores were slightly more negative. These results confirm that patients presented moderate-severe PER [29].

In ACCEPT-2, at the end, the total RQLQ global score was significantly improved in the DL group compared to the placebo group.

Disordered sleep induced by allergic rhinitis, a bothersome issue on its own, also produces secondary effects on productivity, including next-day fatigue, school absence and poor task performance [33]. In the current study, improvements in sleep scores were significantly greater with DL than with placebo, and possibly related to improvements in congestion scores.

ACCEPT-2 confirmed the results of ACCEPT-1 [20] showing that symptom improvement with DL treatment has an economically relevant impact on the productivity of patients with PER. Improvement in work/school productivity and daily activity measured by the WPAI-AS was significantly increased with DL compared with placebo. Other studies have found an effect on work productivity [34], but there was no objective assessment. DL treatment significantly reduced work absenteeism and presenteeism associated with symptoms of allergic rhinitis (IAR and PER).

The rate of treatment-related adverse effects was similar between DL and placebo groups, confirming the results of previous studies that have found DL safe and effective [16, 19, 20]. Additionally, numerous studies have found DL to be relatively free of sedative side effects or effects on performance, even at excessive doses, most likely due to its apparent lack of penetration of the blood-brain barrier. The results of this study also corroborate these data, with a low incidence of somnolence being similar to that seen with placebo.

This GA^{2}LEN clinical trial confirms that the European Network of Excellence [22, 35] can therefore be used to perform and enroll well-characterized patients for a large-scale RCT.

Conclusions

The oral H_1-antihistamine DL is effective in reducing the total symptom burden and individual symptom scores associated with PER, with a safety profile similar to that of placebo, as previously shown for IAR. Improvements were also noted in various measures of quality of life and school/work productivity, issues that are of great importance to patients with allergies. This study will have an impact on the implementation of ARIA guidelines in future studies.

Participants of the ACCEPT-2 Study Group

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References

1 Bousquet J, Van Cauwenberge P, Khaltaev N: Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(5 suppl):S147–S334.

2 Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63(suppl 86):8–160.

3 Bauchau V, Durham SR: Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60:350–353.

4 Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, et al: Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005;35:728–732.

5 Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, et al: Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. J Allergy Clin Immunol 2004;114:838–844.

6 Fantin S, Maspero J, Bisbal C, Agache I, Donado E, Borja J, et al: A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. Allergy 2008;63:924–931.

7 Bousquet J, Lund VJ, Van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, et al: Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2003;58:733–741.

8 Van Cauwenberge P, Juniper EF: Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000;30:891–899.

9 Spector SL, Nicklas RA, Chapman JA, Bernstein IL, Berger WE, Blessing-Moore J, et al: Symptom severity assessment of allergic rhinitis: part 1. Ann Allergy Asthma Immunol 2003;91:105–114.

10 Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, et al: Evaluation of impermeable covers for bedding in patients with allergic rhinitis. N Engl J Med 2003;349:237–246.

11 Nayak AS, Schenkel E: Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. Allergy 2001;56:1077–1080.
12 Berger WE, Schenkel EJ, Mansfield LE: Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. Ann Allergy Asthma Immunol 2002;89:485–491.
13 Baena-Cagnani CE, Berger WE, DuBuske LM, Gurne SE, Stryszak P, Lorber R, et al: Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. Int Arch Allergy Immunol 2003;130:307–313.
14 Berger WE, Lumry WR, Meltzer EO, Pearlman DS: Efficacy of desloratadine, 5 mg, compared with fexofenadine, 180 mg, in patients with symptomatic seasonal allergic rhinitis. Allergy Asthma Proc 2006;27:214–223.
15 Meltzer EO, Jalowayski AA, Vogt K, Iezzoni D, Harris AG: Effect of desloratadine therapy on symptom scores and measures of nasal patency in seasonal allergic rhinitis: results of a single-center, placebo-controlled trial. Ann Allergy Asthma Immunol 2006;96:363–368.
16 Pradalier A, Neukirch C, Dreyfus I, Devillier P: Desloratadine improves quality of life and symptom severity in patients with allergic rhinitis. Allergy 2007;62:1331–1334.
17 Canonica GW, Tarantini F, Compalati E, Penagos M: Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. Allergy 2007;62:359–366.
18 Simons FE, Prenner BM, Finn A Jr: Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol 2003;111:617–622.
19 Kim K, Sussman G, Hebert J, Lumry W, Lutsky B, Gates D: Desloratadine therapy for symptoms associated with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2006;96:460–465.
20 Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindslev Jensen C, et al: Efficacy of desloratadine in intermittent allergic rhinitis: a GA^{2}LEN study. Allergy 2009;64:1516–1523.
21 Moher D, Schulz KF, Altman DG: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001;357:1191–1194.
22 Van Cauwenberge P, Watelet JB, Van Zele T, Bousquet J, Burney P, Zuberbier T: Spreading excellence in allergy and asthma: the GA^{2}LEN (Global Allergy and Asthma European Network) project. Allergy 2005;60:858–864.
23 International Consensus Report on Diagnosis and Management of Rhinitis: International Rhinitis Management Working Group. Allergy 1994;49(19 suppl):1–34.
24 Heinzerling L, Frew AJ, Bindslev-Jensen C, Bonini S, Bousquet J, Bresciani M, et al: Standard skin prick testing and sensitization to inhalant allergens across Europe – a survey from the GALEN network. Allergy 2005;60:1287–1300.
25 Juniper EF: Measuring health-related quality of life in rhinitis. J Allergy Clin Immunol 1997;99:S742–S749.
26 Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Mechin H, Daures JP, et al: Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy 2007;62:367–372.
27 Bousquet PJ, Fabbro-Peray P, Janin N, Annesi-Maesano I, Neukirch F, Daures JP, et al: Pilot study assessing the impact of smoking on nasal-specific quality of life. Allergy 2004;59:1015–1016.
28 Reilly MC, Zbrozek AS, Dukes EM: The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–365.
29 Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, et al: Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol 2006;117:158–162.
30 Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J: Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol 2009 Jun;123:1349–1354.
31 Brown EG, Wood L, Wood S: The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109–117.
32 Committee for Proprietary Medicinal Products (CPMP): Points to consider on missing data. London, European Agency for the Evaluation of Medicinal Products, 2001, CPMP/EWP/1776/99.
33 Santos CB, Pratt EL, Hanks C, McCann J, Craig TJ: Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. Ann Allergy Asthma Immunol 2006;97:579–586; quiz 86–89, 671.
34 Bousquet J, Demarteau N, Mullol J, van den Akker-van Marle ME, Van Ganse E, Bachert C: Costs associated with persistent allergic rhinitis are reduced by levocetirizine. Allergy 2005;60:788–794.
35 Frew AJ: GA2LEN – The Global Allergy and Asthma European Network. Clin Exp Allergy 2005;35:122–125.