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Original article

Efficacy of desloratadine in intermittent allergic rhinitis: a GA^{2}LEN study

Background: The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines proposed a classification for allergic rhinitis based on the duration of symptoms (intermittent, persistent) rather than on the time of allergen exposure (seasonal, perennial). There is no placebo-controlled, randomized clinical trial on intermittent allergic rhinitis (IAR) to date. Desloratadine (DL) is recommended for the first-line treatment of seasonal and perennial allergic rhinitis.
Objectives: To assess the efficacy and safety of DL in subjects with IAR based on the ARIA classification.
Methods: Patients over 12 years of age with IAR were assessed over 15 days of treatment with DL 5 mg once daily ($n = 276$) or placebo ($n = 271$). The primary endpoint was the AM/PM reflective total 5 symptom score (T5SS). Secondary endpoints included AM/PM instantaneous T5SS and individual symptoms, therapeutic response, symptom severity by visual analogue scale, and quality-of-life.
Results: The mean reduction of AM/PM reflective T5SS was significantly greater with DL than with placebo over 15 days (−3.01 *vs* −2.13, $P < 0.001$) and on each individual day ($P < 0.05$). Mean AM instantaneous T5SS was reduced significantly with DL compared to placebo as early as day 2 (−1.84 *vs* −0.89; $P < 0.001$). The therapeutic response and improvement in quality-of-life were significantly greater with DL than with placebo ($P < 0.001$ for each). The frequency of treatment-related adverse events was low and similar between DL (7.2%) and placebo (7.0%).
Conclusions: This is the first large trial to show that treatment can be effective in IAR. Desloratadine was effective and safe.

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Key words: ARIA; desloratadine; intermittent allergic rhinitis; quality-of-life; randomized controlled trial; work.

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Abbreviations: ACCEPT-1, Aerius Control: Clinical and Evaluative Profile of Treatment-1; AM/PM, average of daily AM and PM evaluations; ARIA, Allergic Rhinitis and its Impact on Asthma; DL, desloratadine; GA^{2}LEN, Global Allergy and Asthma European Network; IAR, intermittent allergic rhinitis; LS, least squares; MedDRA, Medical dictionary for Regulatory Activities; QoL, quality-of-life; PER, persistent allergic rhinitis; RCT, randomized clinical trial; RQLQ, Rhinoconjunctivitis quality-of-life questionnaire; T5SS, Total score for 5 symptoms (nasal congestion/stuffiness, sneezing, rhinorrhea/nasal discharge, nasal pruritus, and eye itching); VAS, visual analogue scale; WPAI-AS, Work Productivity and Activity Impairment – Allergy Specific.

In 2001, allergic rhinitis was classified by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines into four categories (1): mild and moderate/severe intermittent; and mild and moderate/severe persistent depending on the severity of symptoms, quality-of-life, and the duration of symptoms. The terms IAR or PER are not interchangeable with the terms seasonal or perennial allergic rhinitis. The recent ARIA update has confirmed that this classification is useful because it more closely reflects patients' needs and real life than the previous classification (2, 3).

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 (4, 5), and in its last edition, the ARIA panel members proposed not to extrapolate the results for treatment of intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER) from randomized clinical trials (RCTs) carried out with the old classification (3). Two RCTs with oral H_1-antihistamines have been carried out in PER (6, 7), but there is no RCT in IAR although one was incorrectly claimed to study IAR (8). A large RCT in intermittent rhinitis will have an impact on the revision of the ARIA guidelines.

The assessment of RCT efficacy in allergic rhinitis is usually based on symptoms, but it is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhea and nasal obstruction. It is also associated with significant impairments in social life (9–11) and work (12, 13). In some RCTs, quality-of-life has been used as a primary end point (6, 14). Moreover, visual analogue scales (VAS) are quantitative measures which have been used in RCTs in rhinitis (14–17) but there are no longitudinal studies on VAS measured each day of the trial.

Desloratadine (DL) is effective and safe in the treatment of allergic rhinitis. It was shown to improve symptoms and quality-of-life in seasonal (8, 18–23) and perennial allergic rhinitis (24, 25). However, it has not yet been tested in ARIA-defined IAR or PER.

The aim of the Aerius Control: Clinical and Evaluative Profile of Treatment (ACCEPT-1) study was to evaluate the efficacy and safety of DL in subjects with IAR as defined by the ARIA guidelines, to study the onset of efficacy and its duration over a 2-week treatment period.

The ACCEPT study also provided an opportunity to collaborate with GA^{2}LEN (26, 27), a consortium of leading European research centers specializing in allergic diseases, to characterize the patterns of sensitization to seasonal and perennial allergens at each study site.

Methods

Participants

Subjects 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 subjects fulfilled the following inclusion criteria: patients 12 years of age or older, of either sex, with at least a 2-year history consistent with symptoms of allergic rhinitis defined according to the International Consensus on Rhinitis (28) and meeting the criteria for IAR according to the ARIA classification (1) (symptoms of allergic rhinitis present <4 days/week or for <4 consecutive weeks/year). Patients had to have moderate/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 6. For a subject to be randomized, the sum of the daily averages of the diary recordings of the 12-h AM plus PM reflective T5SS collected during 4 days and the AM reflective T5SS on the morning of the randomization had to be ≥ 30. Allergy was defined by positive skin prick tests to common aeroallergens carried out according to the GA^{2}LEN skin test study (29). None of the patients had taken any medication for allergic rhinitis during the 14 days prior to randomization. Maintenance regimens of immunotherapy were permitted.

Interventions

DL 5 mg or placebo were administered orally in identical tablets each morning within 1 h after awakening. The study consisted of two periods: The Run-in Period lasted 4–14 days. If subjects had sufficient symptoms (≥ 30) for 4 days, they were randomized to DL 5 mg OD or placebo for 14 days. Visits occurred at day 1 (baseline visit) and 15 (Final visit). No rescue medication was allowed during the trial.

Objectives

The aim of the present study was to assess the efficacy and safety of DL in patients suffering from IAR as defined by ARIA. This multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group Phase IV study of DL 5 mg (OD in the morning) was conducted at 60 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 per-protocol reflective T5SS in the intent-to-treat population. RQLQ (10) was a key secondary outcome measure. Instantaneous T5SS, individual symptom scores, VAS levels (30, 31), subject's assessment of response were secondary endpoints, and WPAI-AS (12, 13) were used as exploratory outcome measures.

Outcomes

Symptoms 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 subject daily diaries in the morning and evening. Each sign/symptom was scored 0–3 (none = 0–3 = severe) twice daily, in the morning (AM) within 1 h of awakening and prior to dosing (reflective) and in the evening (PM), ~12 h later. In both the AM and PM, 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 visual analogue scale (VAS) assessment. The 24-h reflective VAS rating was recorded in subject daily diaries each morning within 1 h of awakening and prior to dosing (AM) at the baseline Visit and for each treatment day. Scores range from not at all bothersome (0 mm) to very bothersome (100 mm) (30, 31).

Subject's evaluation of therapeutic response to treatment. The subject's response to treatment was assessed by the subject alone

at the Final Visit (day 15). Evaluation included the entire time period since the start of treatment (baseline) up to and including the Final Visit compared to baseline. The assessment was scored as follows in a 5-point scale: Complete Relief, Marked Relief, Moderate Relief, Slight Relief, or No Relief.

The Rhinoconjunctivitis Quality-of-Life Questionnaire-Standardized Version (RQLQ-S) (10), 28 questions, was completed by the subject at the baseline and Final Visits only in countries where the questionnaire has been translated into the native language and in subjects ≥18 years of age.

Interference with sleep and daily activities. At the Run-in Visit, during the Run-in Period (days –4 to –1), and continuing through the Final Visit (day 15), subjects recorded in their daily diaries (at the same times 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 daily activities caused by allergic rhinitis symptoms during that day (except day 15).

Work productivity questionnaire. At the baseline Visit and through the Final Visit, the allergic rhinitis specific Work Productivity and Activity Impairment questionnaire (WPAI-AS) was completed by the subjects (12, 13) (online repository).

Study drug compliance with study drug was assessed by comparing the number of tablets dispensed at the baseline Visit with the number returned at the final Visit. Subjects were considered non-compliant if they had taken $<80\%$ or more than 120% of drugs.

Adverse events. Adverse events were recorded at each visit on the case report form (CRF) and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (32).

Sample size. A sample size of approximately 540 subjects (270 on DL 5 mg, 270 on placebo) was calculated to provide at least 90% power to detect a 1.0 point treatment difference in change from baseline reflective T5SS averaged over days 1–15, with a 5% two-sided level of significance and an assumed standard deviation of 3.5. A 1.0 treatment difference is a 12.5% improvement over placebo, assuming a baseline score of 8.0 points.

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

Statistical analysis. The two-way analysis of variance (ANOVA) model with treatment and side effects was used to examine treatment differences of T5SS, RQLQ, individual diary symptoms, interference with sleep and daily activities, the VAS assessment and WPAI-AS. The Mantel–Haenzel test was used for the subject's 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 was statistically significant. Therefore the overall α of 5% is 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 subjects were included in the analysis (intent-to-treat principle). However, subjects with a missing evaluation at a given visit or time point, including subjects without a baseline score for a given change-from-baseline evaluation, were excluded from the analysis for that evaluation. This exclusion was applied to analyses at each visit and diary interval. If any of the individual symptom scores were missing for a subject, the corresponding T5SS was also considered missing on a given day. For the analyses where AM or PM diary data were to be averaged for each day, if an AM or PM diary reading was missing on any given day, the average for that day was equal to the non-missing value. Interval averages were the mean of all non-missing values within that interval (e.g. baseline and days 1–15).

For diary evaluations, several impact analyses were performed to assess the influence of early discontinuations such as looking at complete subjects only, last observation carried forward (LOCF) and substitution of worst-case values.

Results

Participant flow and number analyzed

Six hundred and sixty-six subjects were screened and 547 subjects were randomized and valid for inclusion in the safety protocol. A total of 262 subjects treated by DL and 256 subjects treated by placebo completed the study. The disposition of study subjects is shown in Fig. 1.

Baseline data

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

Patient compliance

Only four subjects in the DL group and three in the placebo group were not compliant and were therefore excluded from the analysis.

Outcomes and estimation

An assumed difference of 1.0 unit between treatments for the primary efficacy variable was used to calculate the sample size. The observed difference was 0.9 with a standard deviation smaller than assumed.

Table 2 represents the intent-to-treat analysis. There was a 37.7% change in the primary end point (T5SS reflective) in the DL group and a 27.8% change in the placebo group ($P < 0.001$). The secondary outcome (RQLQ) was significantly improved in the DL group by comparison to the placebo group. All RQLQ dimensions but sleep were significantly improved in the DL group by comparison to placebo. All secondary and exploratory outcomes were also significantly improved by DL. The efficacy of DL was found for both instantaneous and reflective symptoms.

When individual symptoms were assessed, all nasal symptoms including nasal congestion were significantly

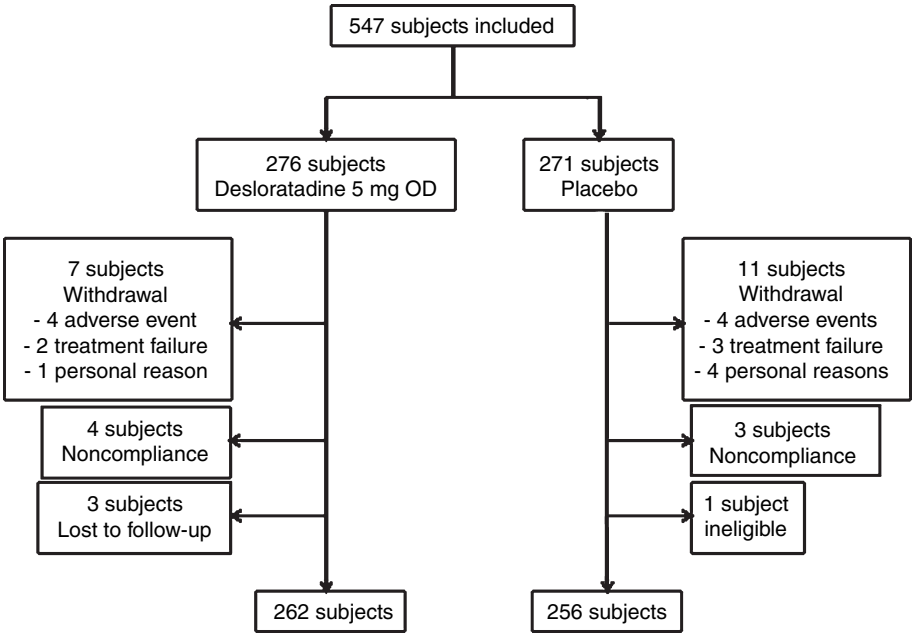

Figure 1. Disposition of subjects.

Table 1. Demographic data

	DL 5 mg	Placebo	*P*-value
N	276	271	
Sex (% males)	44	39	NS
Age (years, mean ± SD)	33.8 ± 12.0	34.6 ± 12.8	NS
Asthma (%)	16.7	17.0	NS

improved in the DL group by comparison with placebo, but to a lesser extent for the single ocular symptom measured (reflective eye itching, $P < 0.047$, and instantaneous eye itching, $P < 0.023$).

The efficacy of DL was significant at day 1 and continued throughout the study. However, the maximum effect was observed after one week of treatment for the primary outcome measure (Fig. 2A). For VAS, a significant difference was also demonstrated at day 1 and continued throughout the study (Fig. 2B). The changes in PAI-AS are presented in Fig. S1.

Adverse events

Table 3 presents the adverse events occurring in more than 1% of subjects in any group. 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. Four adverse events in each group led to the discontinuation of the treatment. There were no abnormal laboratory and vital signs listed.

Discussion

In the present study, we found that DL is a safe and effective treatment of IAR as defined by ARIA (1). This is the first study to use the ARIA criteria on IAR. 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 (8). Other accepted outcomes were used including RQLQ and WPAI-AS. Assessment of symptom severity by VAS was also used as a secondary outcome measure. Interestingly, all the primary, secondary and exploratory outcomes showed a significant difference when compared with placebo.

The patients were well characterized according to ARIA, and, for the first time, IAR has been studied. Other studies were claimed to have been carried out in IAR (8, 33), but the selection of the subjects was not in accordance with ARIA. Very few drop outs were observed in the study and the compliance to the treatment was excellent. The number of centers was very high and this could have induced an heterogeneity of the study possibly related to a smaller difference between placebo and DL. The significance of the results despite this heterogeneity is in favor of the importance of the results.

Desloratadine was effective over a 24 h period as already shown. Improvements in daily diary symptom

Table 2. Primary, secondary and exploratory outcome variables (intent-to-treat analysis)

	DL 5 mg		Placebo		
	Baseline LS mean ± SEM	Days 1–15 LS mean ± SEM	Baseline LS mean ± SEM	Days 1–15 LS mean ± SEM	*P*-value
AM/PM T5SS reflective	8.71 ± 0.15	−3.19 ± 0.22	8.49 ± 0.15	−2.29 ± 0.22	<0.001
RQLQ total score (at endpoint)	2.96 ± 0.08	−1.10 ± 0.10	2.80 ± 0.08	−0.73 ± 0.10	<0.001
AM/PM T5SS instantaneous	8.30 ± 0.17	−2.86 ± 0.20	8.17 ± 0.17	−1.90 ± 0.20	<0.001
AM/PM rhinorrhea reflective	1.81 ± 0.04	−0.58 ± 0.05	1.75 ± 0.04	−0.38 ± 0.05	<0.001
AM/PM Nasal congestion reflective	1.96 ± 0.04	−0.56 ± 0.05	1.87 ± 0.04	−0.43 ± 0.05	0.013
AM/PM sneezing reflective	1.65 ± 0.04	−0.64 ± 0.05	1.61 ± 0.04	−0.42 ± 0.05	<0.011
AM/PM Nasal itching reflective	1.71 ± 0.04	−0.67 ± 0.05	1.65 ± 0.04	−0.43 ± 0.05	<0.001
AM/PM Eye itching reflective	1.38 ± 0.06	−0.58 ± 0.05	1.45 ± 0.06	−0.46 ± 0.05	0.047
AM/PM rhinorrhea instantaneous	1.76 ± 0.05	−0.54 ± 0.05	1.72 ± 0.05	−0.33 ± 0.05	<0.001
AM/PM Nasal congestion instantaneous	1.94 ± 0.05	−0.52 ± 0.05	1.87 ± 0.05	−0.39 ± 0.05	0.009
AM/PM sneezing instantaneous	1.56 ± 0.05	−0.59 ± 0.05	1.51 ± 0.05	−0.36 ± 0.05	<0.001
AM/PM Nasal itching instantaneous	1.65 ± 0.05	−0.63 ± 0.05	1.61 ± 0.05	−0.37 ± 0.05	<0.001
AM/PM eye itching instantaneous	1.38 ± 0.06	−0.58 ± 0.05	1.46 ± 0.06	−0.45 ± 0.05	0.023
Sleep interference	1.37 ± 0.06	−0.39 ± 0.05	1.38 ± 0.06	−0.27 ± 0.05	0.039
Activity interference	1.72 ± 0.05	−0.60 ± 0.06	1.66 ± 0.05	−0.40 ± 0.06	<0.001
Symptom severity reflective (VAS)	57.4 ± 1.36	−17.2 ± 1.50	56.76 ± 1.35	−10.9 ± 1.49	<0.001
Subject's evaluation of response	NA	3.24 ± 0.10	NA	3.66 ± 0.10	<0.001
WPAI-AS Overall work impairment	46.38 ± 2.35	−15.0 ± 2.78	41.37 ± 2.27	−5.7 ± 2.69	0.002
Activity impairment	48.24 ± 1.85	−15.3 ± 2.20	46.04 ± 1.87	−9.2 ± 2.22	0.007

LS Means, SEM (standard error of the LS means) are obtained from an ANOVA model with treatment and site effects; NA, not applicable.

ratings were corroborated by VAS data, which improved by 31% with DL and by 17% in the placebo group from day 1 to 15. Symptoms were significantly improved by DL on day 1 and over the course of the 15-day study. Although greater reductions from baseline in subjects treated with DL were observed from Week 1 to 2 for all five symptoms, it is possible that the intermittent nature of IAR resulted in some attenuation of treatment differences between the two groups over time. The impact of DL on ocular pruritus was the least robust among all of the symptoms. The placebo scores continued to fall because of the nature of the disease (intermittent) and it was very important to confirm that after 2 weeks, the treatment effect was still significant. This has an important clinical implication. On the other hand, interestingly, VAS levels were falling less than total symptom scores.

The symptoms of AR can cause considerable morbidity in physical and emotional comfort and functional capacity. Subjects rated symptom severity over the previous 24 h using a 100-mm VAS. The mean baseline VAS ratings were 57.4 in the DL group and 56.7 in the placebo group. These results show that most patients were in the moderate-severe category (30). At the end of the study, subjects in the DL group showed a significantly greater improvement in VAS rating compared with placebo. In ACCEPT-1, the mean total RQLQ-S score at baseline was 2.96 in the DL group and 2.80 in the placebo group (maximum score 6.0). These results confirm the VAS rating and underline that patients presented moderate-severe IAR (13). By study end, the total RQLQ global score was significantly improved.

Disordered sleep associated with allergic rhinitis, a bothersome issue on its own, also induces secondary ramifications on productivity, including next-day fatigue, school absence, and poor task performance (34). In the current study, improvements in sleep scores were significantly greater with DL when compared with placebo, and possibly related to improvements in nasal congestion scores.

The ACCEPT-1 study is also the first study to demonstrate that symptom improvement with DL treatment has an economically relevant impact on the productivity of subjects with IAR. Improvement in work/school productivity and daily activity as measured by the WPAI-AS was significantly greater with DL than with placebo. Other studies have found an effect on work productivity (35) but there was no objective assessment. Desloratadine treatment significantly reduced the work absenteeism and presenteeism associated with symptoms of AR. In the United States, AR has been estimated to be responsible for ~2 million school days missed and 3.5 million workdays lost annually (36). In a survey of American employees, AR symptoms were responsible for an average of 3.6 missed workdays/year and contributed to decreased productivity for 2.3 h/workday when symptoms were present (37).

The rate of treatment-related AEs was similar between DL and placebo, confirming the results of previous studies that have found DL safe and effective (22, 25). 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

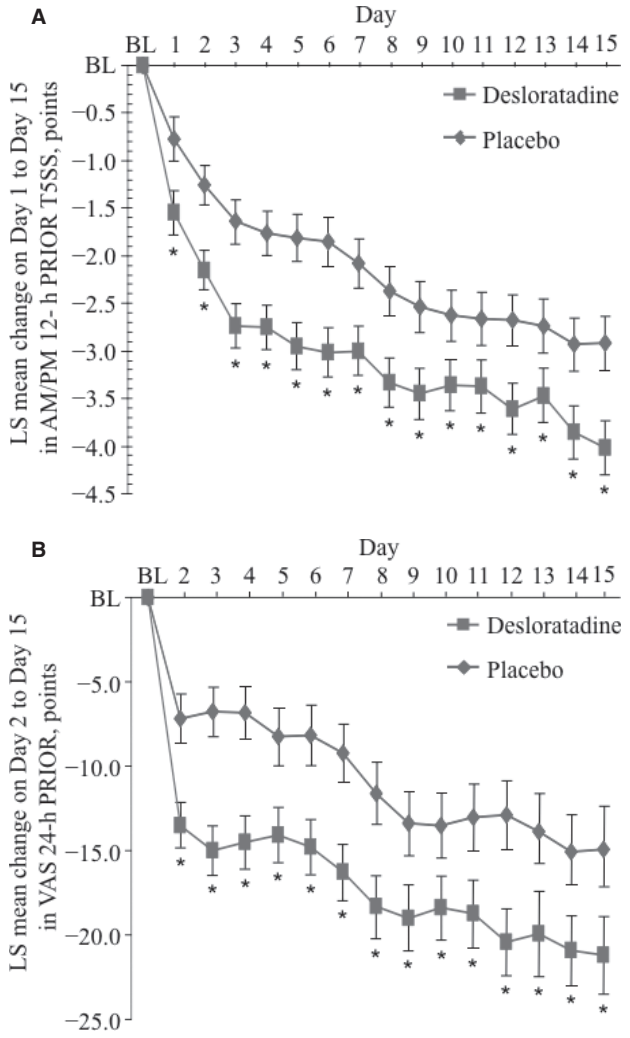

Figure 2. Evolution of reflective T5SS (A) and symptom severiry by VAS (B). LS means obtained from an ANOVA model with treatment and site as a covariate in the model. $*P \leq 0.018$.

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

	DL 5 mg (*N* = 271)	Placebo (*N* = 276)
Report of adverse any event	20 (7.2%)	19 (7.0%)
Adverse event leading to treatment discontinuation	4 (1.4%)	4 (1.5%)
Nausea	2 (0.7%)	3 (1.1%)
Fatigue	3 (1.2%)	0
Thirst	1 (0.4%)	3 (1.1%)
Headache	7 (2.5%)	5 (1.8%)
Sedation/somnolence	3 (1.1%)	1 (0.4%)

penetration of the blood–brain barrier. The results of this study also corroborate these data, with a low incidence of somnolence, similar to that seen with placebo.

Around 30% of patients consulting in primary care and 20% in specialist care (in Europe) present intermittent rhinitis. The present study is important for the following points: (1) Intermittent rhinitis is not identical to seasonal, thus there was a need to determine whether an oral H1-antihistamine was effective in this situation. (2) Although likely, this had to be confirmed. (3) The efficacy of the treatment was significant after 1 day. This was also likely but had to be confirmed. It was totally unknown whether the efficacy of the treatment could be maintained over a 2-week period due to the nature of the disease (intermittent). This is a major finding of the study.

Importantly, this is the first GA^{2}LEN clinical trial. This European network of excellence (26, 27) can therefore be used to perform and enroll well-characterized patients for a large RCT.

Conclusions

This is the first study to demonstrate that a daily antihistamine (desloratadine) can reduce the total symptom burden and individual symptom scores associated with IAR, with a safety profile similar to that of placebo. Improvements were also noted in various measures of QoL and school/work productivity, issues that are of great importance to those patients with allergic rhinitis. This study will have an impact on the ARIA guidelines already translated into 52 languages.

Accept Study Group

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Supporting information

Additional supporting information may be found in the online version of this article.

Figure S1. Percent change from Baseline to Endpoint in Overall work Impairent and Activity Impairent in WPAI-AS.

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