

Brief Report

Evaluation of a Compliance Device in a Subgroup of Adult Patients Receiving Specific Immunotherapy With Grass Allergen Tablets (GRAZAX®) in a Randomized, Open-Label, Controlled Study: An A Priori Subgroup Analysis

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ABSTRACT

Objectives: This a priori subgroup analysis was conducted to assess patients' experience with a compliance device for the administration of sublingual specific immunotherapy for grass pollen-induced rhinoconjunctivitis.

Methods: The present paper reports the results of a subgroup analysis of a multicenter, randomized, controlled, open-label European study in which adults with grass pollen-induced rhinoconjunctivitis received once-daily treatment with grass allergen tablets with or without a device to aid compliance. Treatment was given ~6 to 12 weeks before the grass pollen season, during the season (~8–10 weeks), and for up to 2 weeks after the end of the season. In the subgroup analysis, patients from Germany and the Netherlands who had been randomized to receive the compliance device were asked to complete a brief questionnaire at the final study visit. The questionnaire included 6 items concerning patients' use of the device and whether it helped them remember to take their tablets.

Results: Of the 91 patients from Germany and the Netherlands who were randomized to use the compliance device along with grass allergen tablets, 71 returned the questionnaire. Among responders, 58 of 71 (82%) reported using the device sometimes or always, 50 of 63 (79%) found the device easy to use, 32 of 69 (46%) found that the device made it easier to remember to take tablets, and 43 of 71 (61%) indicated that they would consider using the device again.

Conclusion: Most patients in this subgroup analysis used the compliance device as a medication reminder and rated it easy to use. (*Clin Ther.* 2009;31:321–327) © 2009 Excerpta Medica Inc.

Key words: compliance device, sublingual specific immunotherapy, ALK-Abelló grass allergen tablet, GRAZAX®, rhinoconjunctivitis, patient questionnaire.

INTRODUCTION

Grass pollen is one of the most common causes of respiratory allergy and has been associated with >50% of cases of allergic rhinitis.¹ Although allergy is a chronic condition, specific immunotherapy is the only currently available treatment option that targets the underlying cause of the allergic condition.^{2–4} Thus, it has the potential for long-term efficacy and prevention of the development of new sensitizations and asthma.^{5–15} However, according to the World Health Organization, to realize the maximum benefit of specific immunotherapy, compliance with the regimen must be maintained over 3 to 5 years of treatment.^{4,16}

Grass allergen tablets* (75,000-unit standardized quality *Phleum pratense* allergen extract tablets [75,000 SQ-T]) are a sublingual specific immunotherapy with reported efficacy and a favorable tolera-

*Trademark: GRAZAX® (ALK-Abelló A/S, Hørsholm, Denmark).

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bility profile in the treatment of adult patients with grass pollen-induced rhinoconjunctivitis (with or without mild to moderate asthma).^{17–22} In interim results from a 3-year study, grass allergen tablets were associated with sustained efficacy and progressive immunologic changes over 2 years of continuous treatment.²³ Grass allergen tablets, which are approved under the European Mutual Recognition Procedure, are the first widely available specific immunotherapy for home administration, providing wider access to the benefits of immunotherapy.^{17,18,21} However, along with the advantage of home administration comes a need to promote compliance to ensure that patients receive the greatest benefit from a 3-year course of treatment. Compliance with the grass allergen tablet regimen during the clinical development program was >90%,¹⁸ a level of compliance that would not be expected in actual practice, without the regular monitoring that takes place during a controlled study.

In an uncontrolled situation, poor compliance may be intentional (eg, lack of motivation, failure to appreciate the importance of compliance) or unintentional (eg, forgetfulness). Therefore, specialized reminder devices and patient education have been proposed as tools to aid compliance. The present paper reports the results of a subgroup analysis investigating the use of an automated compliance device in adult patients with allergic rhinoconjunctivitis receiving sublingual grass allergen tablet therapy. Patients' experience of the usefulness and ease of use of the device was examined based on their responses to a questionnaire. The compliance, efficacy, and safety/tolerability results in the full study cohort will be reported in a future publication.

PATIENTS AND METHODS

In brief, the overall study was a multicenter, randomized, open-label, controlled, parallel-group trial conducted from February 2006 to November 2006 in accordance with the principles of the Declaration of Helsinki²⁴ and the International Conference on Harmonisation Good Clinical Practice guidelines.²⁵ The study and patient consent process were approved by the appropriate institutional review board or ethics committee at each center. All patients provided written informed consent before entering the trial.

Study investigators enrolled patients at 39 allergy clinics and general practices in Austria, Denmark, Germany, Sweden, and the Netherlands. Eligible pa-

tients were aged 18 to 65 years, had a clinical history of grass pollen-induced allergic rhinoconjunctivitis (with or without asthma) requiring treatment during the grass pollen season, and had a positive skin-prick test to *P pratense*. Exclusion criteria included symptoms of and/or treatment for upper respiratory tract infection, acute sinusitis, acute otitis media, or other relevant infectious conditions at randomization; a clinical history of severe asthma or anaphylaxis; previous treatment with allergen immunotherapy; and previous immunosuppressive treatment. Female patients of childbearing potential had to have a negative pregnancy test result and agree to use an appropriate method of contraception during the study.

All enrolled patients received treatment with grass allergen tablets (75,000 SQ-T *P pratense* allergen extract tablets) taken once daily for ~6 to 12 weeks before the 2006 grass pollen season, during the season (~8–10 weeks), and for up to 2 weeks after the end of the season. The start and end of the grass pollen season were determined based on the judgment of the investigator at each study center. At screening, eligible patients were randomized 1:1 to receive grass allergen tablets with or without a compliance device. Those randomized to receive the compliance device were provided with instructions for its use. Those randomized to receive the tablets without the compliance device constituted the control group. Allocation to the study groups was determined using a block-randomization procedure at each site, with a randomization list generated by ALK-Abelló Biometrics Medical Writing.

The compliance device (MEMOZAX® [covered by national and regional patent applications based on WO 2007/082543 A1], ALK-Abelló A/S, Hørsholm, Denmark) used in this study was specifically designed to store and dispense the grass allergen tablets, remind patients to take their medication, and keep a record of compliance over the previous 7 days (Figure 1).

Study visits were scheduled to take place at screening/randomization (visit 1), ~2 weeks before the anticipated start of the grass pollen season (visit 2), and ~2 weeks after the end of the season (visit 3).

Study Assessment

This subgroup analysis was conducted to evaluate patients' experience with the compliance device. Because this end point was added as a protocol amendment late in the course of the study, it could be implemented only in patients from Germany and the

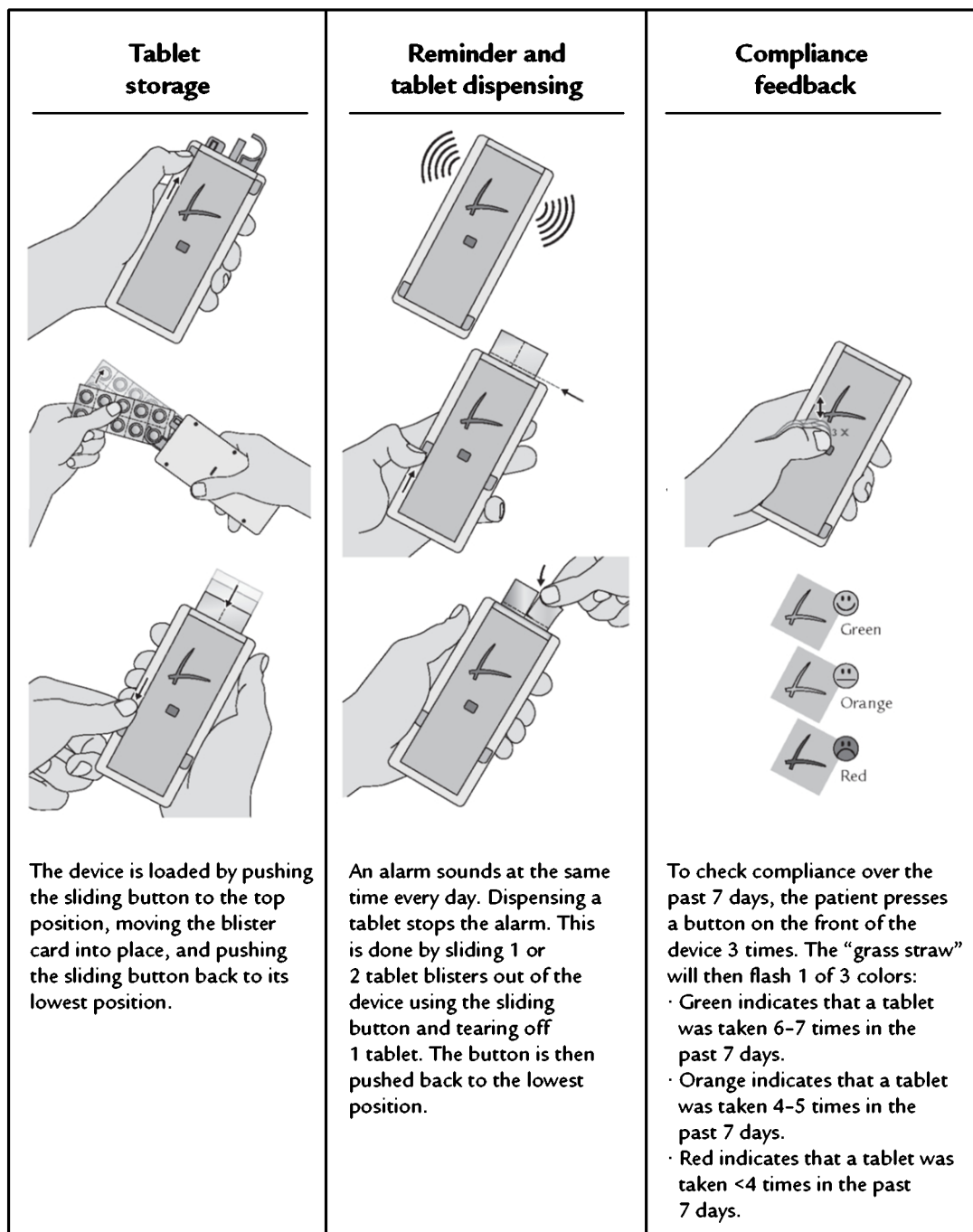


Figure 1. Automated device to aid compliance with grass allergen tablet therapy. Adapted with permission. © 2006, ALK-Abelló A/S, Hørsholm, Denmark.

Netherlands. At visit 3, patients from these countries who had been randomized to receive the compliance device were asked to complete a 6-item questionnaire on their experience with the device. The questions included whether patients used the device, whether the device made it easier to remember to take tablets, ease of use, ease of loading, ease of following the instructions, and any technical difficulties encountered (Table).

Analysis of the questionnaire was descriptive, with the responses calculated as percentages based on the actual number of completed responses for each question. The rate of treatment compliance was calculated for those patients who completed the questionnaire and had a drug record from visit 1 to visit 3 using

the following formula: $100 \times \text{tablets used/number of treatment days}$.

RESULTS

Overall, 91 patients from Germany and The Netherlands were randomized to receive the compliance device along with grass allergen tablets (52/105 from Germany, 39/74 from the Netherlands). Of these, 71 returned the questionnaire (47 from Germany, 24 from the Netherlands), although not all respondents completed all questions. More women than men returned the questionnaire (47 [66%] vs 24 [34%], respectively). The mean (SD) age of respondents was 33.8 (11.7) years (range, 17–63 years), and the mean rate of treatment compliance over the course of the

Table. Patient questionnaire regarding the compliance device (MEMOZAX®, ALK-Abelló A/S, Hørsholm, Denmark).

1. Have you used your MEMOZAX® to remind you to take your tablets?
 - a. Yes, as recommended
 - b. Yes, but only sometimes
 - c. No, I didn't use it
2. Has MEMOZAX® made it easier for you to remember to take your tablets once daily as prescribed?
 - a. Yes, much easier
 - b. Yes, easier
 - c. It had no impact
 - d. No, it was even more difficult
3. Was the compliance feedback from MEMOZAX® indicated by the green, orange, or red light a motivation for you to take your tablets once daily as prescribed?
 - a. Yes, it was highly motivating
 - b. Yes, it was motivating
 - c. It had no impact
 - d. No, it was de-motivating
4. How has MEMOZAX® worked in general?
 - a. Was the device easy to use? Yes/No
 - b. Was the device easy to load with the blister? Yes/No
 - c. Did the device work without any technical problems? Yes/No
 - d. Were the patient instructions easy to follow? Yes/No
 - e. Were my expectations satisfied? Yes/No
 - f. Anything else
5. How or what could improve MEMOZAX® in the future?
6. Would you use MEMOZAX® in the future?
 - a. Yes
 - b. Yes, but it needs improvement
 - c. No
 - d. Maybe

study in the 70 responders with a drug record for each visit was 95%.

Fifty-eight of 71 patients (82%) reported using the compliance device sometimes or always (as recommended), and 32 of 69 (46%) reported that the compliance device made it easier or much easier to remember to take their tablets (Figure 2). The majority of patients stated that the compliance device was easy to use (50/63 [79%]) and easy to load (43/59 [73%]), and that the instructions were easy to follow (51/57 [89%]). Twenty-eight of 57 patients (49%) reported that the device worked without technical difficulties. Problems noted by device users were that the device was too large (8/57 [14%]), that the timer adjustment was inconvenient (16/57 [28%]), and that the blister card stuck on occasion (8/57 [14%]).

Although only 22 of 68 patients (32%) felt that the compliance feedback function of the device made them feel motivated or highly motivated to take their tablets as prescribed, 28 of 54 (52%) felt that the device met their expectations. Most patients (43/71 [61%]) stated that they would consider using the device again, although some commented that it needed refinement.

DISCUSSION

Compliance with a 3- to 5-year treatment regimen is recommended to optimize treatment outcomes of specific immunotherapy.^{4,16} Potential outcomes include symptomatic benefits and improved quality of life. Two placebo-controlled studies of grass allergen tablets reported significant improvements on the Juniper Rhinoconjunctivitis Quality of Life Questionnaire ($P < 0.05$).^{23,26} Furthermore, medical noncompliance has economic implications for society in general, decreasing the cost-effectiveness of health interventions.²⁷ Thus, it is important to promote compliance with immunotherapy, particularly given the shift from physician-administered subcutaneous immunotherapy to self-administered sublingual immunotherapy,^{28,29} and to examine ways of improving patient compliance.

The study reported here employed a questionnaire to assess the use of an automated compliance device in a subgroup of patients with grass pollen-induced rhinoconjunctivitis who were receiving specific immunotherapy with grass allergen tablets. The majority of respondents (82%) reported using the compliance device some or all of the time, and 46% reported that

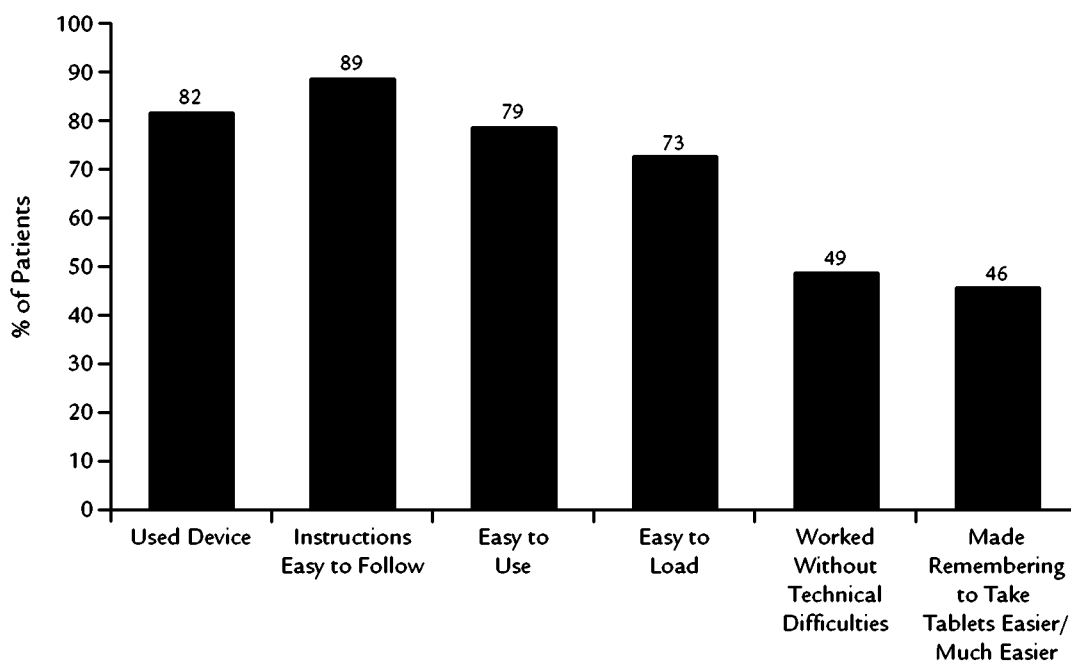


Figure 2. Patient responses to the compliance device questionnaire (N = 71 responders, not all of whom answered all questions).

the device made it easier or much easier to remember to take their tablets.

A limitation of this analysis was that because of practical considerations, only a subgroup of the total study cohort (those from Germany and the Netherlands) could be included, thus reducing the sample size and the ability to generalize the results. Furthermore, the questionnaire was completed at the final study visit, so the results did not take into account the experiences of patients who discontinued the study prematurely (eg, as a result of adverse events). In addition, patients' use of the device and their perception of its usefulness may have been affected by the conduct of the study during the grass pollen season, when symptoms are prominent and are likely to prompt compliance without a reminder device; among responders to the questionnaire, the rate of treatment compliance was high (95%). Thus, the impact of the compliance device requires further study, both in a larger population and outside the grass pollen season.

CONCLUSION

Most patients who returned the compliance device questionnaire reported that they used the device as a reminder to take their medication and found it easy to use.

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