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A Web site–based reporting system for monitoring home treatment during oral immunotherapy for food allergy

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ABSTRACT

Background: Reactions during the home treatment phase of oral immunotherapy (OIT) are not uncommon. An ongoing accurate reporting of home treatment outcomes is crucial for the safety and success of OIT. Previous reports have shown that as few as 20% of patients are truly compliant with paper-based diaries. **Objective:** To develop a Web site–based electronic reporting system (web-RS) for monitoring home treatment during OIT for food allergy.

Methods: A web-RS was developed and incorporated a thorough questionnaire querying for pertinent data including the dose(s) consumed, occurrence and details of adverse reactions, treatment(s), and relevant potential exacerbating factors. All patients enrolled in milk, peanut, or egg OIT programs for at least 4 weeks from November 2012 through January 2014 were introduced to web-RS ($n = 157$). Successful reporting through web-RS was defined by consecutive reporting during the first home treatment phase (24 days) after its introduction. Comparisons were made with a previous group of OIT-treated patients ($n = 100$) who reported by E-mail.

Results: Successful reporting was achieved by 142 of 157 patients (90.44%) in contrast to a 75% success rate with E-mail ($P = .0009$). The odds for successful reporting using web-RS were 3.1 (95% confidence interval 1.6–6.3) times higher compared with using E-mail. Mild reactions were reported more frequently with web-RS ($P = .0032$). Patient reports were constantly available in real time for medical staff review. No complaints regarding web-RS feasibility were reported. One risk factor for failure to use web-RS was a patient's prior successful OIT experience without using web-RS ($P = .012$).

Conclusion: A web-RS can be a powerful tool for improving OIT safety by achieving a high level of patient cooperation in reporting home treatment results.

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Introduction

Food allergy is common, affecting nearly 5% of adults and 8% of children, and its prevalence is growing.¹ The severity of an allergic reaction is not predictable, and it can be evoked by exposure to minimal amounts of an offensive food.² The current standard treatment of strict avoidance of the allergen and the constant carrying of an epinephrine auto-injector³ has its limitations, because incidental exposures are not uncommon⁴ and patients might not carry or correctly administer the epinephrine auto-injector.^{5,6} In addition, quality-of-life issues are not addressed.^{7–9}

An alternative approach currently being investigated is oral immunotherapy (OIT; for review, see Jones et al¹⁰). OIT is based on the gradual and controlled exposure of the patient to the allergenic protein, inducing a state of desensitization. The efficacy of OIT has been demonstrated in placebo-controlled, double-blinded trials,^{11–28} and although controversial,^{29,30} it has been conducted in some clinical practices.³¹ Almost all OIT clinical trials and practices have included a home treatment phase, in which patients consume daily, planned doses of the target protein at their home.^{11–28} Reactions during the home treatment phase are not uncommon. Although most reactions are mild to moderate, severe reactions requiring epinephrine treatment have been reported in 6.7% to 23% of patients.^{14,32} These reactions raise concern regarding the safety and risk-to-benefit ratio of OIT programs.^{33–37}

The duration of a single period during the home treatment phase in most published clinical OIT trials is 2 weeks,^{11,15–20,22–27} although it varies in others.^{12,13} Critical to the success and safety

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of an OIT program is true accurate reporting of reactions occurring during the home treatment phase. The reaction history, severity, and treatment required each are factors influencing the need for protocol modification^{12,15,22,28} and potentially aborting a specific patient's OIT treatment.^{33,38} Furthermore, this information could assist in identifying potential triggers predisposing to home reactions, leading to safety improvements of the home maintenance phase.³⁹

In most OIT trials, patients' reports of reactions during the home treatment phase relied on a paper-based log diary completed by the patients. There are 3 major drawbacks to this method of reporting. First, as Stone et al⁴⁰ reported, although 90% of patients in a clinical trial had declared good compliance with the paper-based diaries, only 11%, and up to 20% if looser criteria were applied, were actually truly compliant. Seventy-five percent of patients made unacceptable retrospective reports. Second, paper-based diaries might be missing details and run the risk of paper loss, which could lead to the loss of crucial information. Third, physicians are unaware in real time or at least before the next dose of reactions that occur that would require a necessary change of dosing.

For these reasons, electronic-based patient reporting methods have been developed and investigated.⁴¹ For example, in the study by Stone et al,⁴⁰ a 94% compliance rate by patients was achieved using an electronic diary. Electronic-based reporting methods also are efficient methods for gathering and analyzing data; therefore, its use has become widespread during the past decade.⁴² A Web site–based electronic reporting system (web-RS) offers additional advantages, because patients insert the desired information directly to the server, preventing unnecessary staff labor (information input) and potential data input errors.⁴² A web-RS has recently been found reliable for monitoring childhood asthma control at home.⁴³

An OIT program for milk, peanut, and hen's egg has been active since April 2010 at the Assaf-Harofeh Medical Center in Beer Yaakov, Israel. Initially, patients were requested to keep a paper-based diary and to report daily the results of their home treatment by E-mail.⁴⁴ In the present study, the authors developed a reliable web-RS to improve the safety and monitoring of the home treatment phase of their OIT program.

Methods

Study Participants

Patients (>4 years old) with IgE-mediated cow's milk, peanut, and hen's egg allergy were enrolled in an OIT program at the food allergy referral center in the Allergy and Immunology Unit of the Assaf-Harofeh Medical Center. All patients enrolled in the OIT program from November 2012 through January 2014 were introduced to web-RS for the reporting of results of their home treatment periods. The details of their performance were reviewed and analyzed in February 2014. Comparisons were made to a previous group of patients on OIT from the program (n = 100) who used an identical protocol but reported by E-mail. These patients were enrolled from July 2011 through February 2012.

OIT Protocol

The treatment protocol was identical for all 3 treated food allergies and has been previously described.⁴⁴ Briefly, the maximal tolerated dose was determined over a 3- to 4-day period followed by a home maintenance treatment period, which for the first 3 rounds lasted 24 days. No dose escalations were performed outside the hospital clinic. Informed parental or patient (>18 years old) written consent for OIT treatment was obtained from all

participants. Committee approval was obtained for the publication of patient data according to the Declaration of Helsinki.

Computer Software

Computer software services were purchased from Smix Systems (Jerusalem, Israel), which included personalized specialized Web site creation and system maintenance, protected health information security, and online and telephone availability for technical support. Data security was achieved by https (based on the SSL/TLS protocol), providing authentication of the Web site and the associated Web server while communicating over the computer network. Web site entrance required the usage of multi-symbol passwords to ensure high security. Patients were required to have daily Internet access to use web-RS, which was a prerequisite for registration and communication with staff regarding scheduling of visits.

Web-RS Use Protocol

Demographic data and medical details for each patient, including the allergen being treated, starting dose, and blood eosinophil levels, were supplied by the physician in a registration task form of web-RS (eFig 1) during the first round of induction. This information created individual patients' files in the Web site. An automated notification was sent to each new patient's E-mail from the Web site, which included the patient's personal log-on password to the web-RS. Patients received a detailed explanation about the web-RS operation and had to practice using the program before the beginning of home treatment. Seventeen patients (11%) were introduced to the reporting system approximately 1 month after their treatment had started.

After finishing their daily doses during the home treatment phase, patients filled in and sent their reporting questionnaires through web-RS to the Web site once a day. The content of the questionnaire was derived from the paper-based questionnaire that was submitted monthly in conjunction with the initial daily E-mail reporting system used in the first years of the OIT program. For this publication, the questionnaire was translated from Hebrew into English and vice versa by 2 different laypeople for validation of the translation. In its widest view, the web-RS questionnaire occupied a single screen, the equivalent of 1 sheet of paper. Recording of the information was easily performed by clicking specific choices with the keyboard. At every stage, any missing information required to complete the report prevented its submission to web-RS. Reporting the details of an allergic reaction was first performed by choosing from a fixed list for the involvement of the skin, ocular, nasal, digestive, or respiratory systems, similar to classifications used in other OIT clinical trials.^{15–17,24,25} Further details of the reaction and the timing to the dose were required and filled in the provided free text spaces. A reaction was defined as severe if it was treated with intramuscular epinephrine or required the patient to visit an emergency department. Reporting the treatments or medications used, before dose consumption or later for treatment of the reaction, also consisted of 2 steps. Confirmation of an administered treatment was performed by selecting a checkbox and then the treatment details were described in a text box. The questionnaire ended with a text box for optional comments in the event patients wanted to provide additional details.

A copy of every report was automatically sent to the program's E-mail address and was accessible to all treating physicians. An automatic heading ("reaction") was placed on E-mails with a report of a positive allergic reaction. Direct access to the Web site file of the patient was available and its access required password insertion. Daily review of all reports and E-mails was performed by the medical team and a telephone consultant was available at all times for potential urgent medical or technical problems.

A

DAILY REPORT

Date dose taken *

Dose amount (mg) *

Did you receive any medications prior to your dose? * ☐ Yes ☒ No

Reaction observed * ☐ Yes ☒ No

General remarks
If you would like to add any additional remarks with regards to your health please do so below

After clicking the submission key ONCE, please wait to receive a submission approval

B

DAILY REPORT

Date dose taken *

Dose amount (mg) *

Did you receive any medication prior to your dose? * ☒ Yes ☐ No

Type of treatment *

Reaction observed * ☒ Yes ☐ No

Describe the allergic reaction and treatment given

Type of reaction * ☐ Respiratory ☐ Digestive ☐ Skin ☐ Other

Describe the reaction *

Please describe the reaction in the text box provided above

After which dose was the reaction observed? * ☐ First ☐ Second

Was treatment given for the reaction? * ☒ Yes ☐ No

Type of treatment given *

Potential predisposing conditions * ☐ Fatigue ☐ Physical activity ☐ Illness
☐ Menstruation ☐ Unknown ☐ Other

General remarks
If you would like to add any additional remarks with regards to your health please do so below

After clicking the submission key ONCE, please wait to receive a submission approval.

Figure 1. Web-RS daily report form for (A) patients reporting no adverse reaction and (B) for those reporting a reaction.

In cases of initial report absence, the program staff contacted the patient by telephone or E-mail. In cases of secondary report absence, an E-mail reminder was sent. At the end of every round increase, the physician in charge updated the patient's file on web-RS regarding current dosage. Successful reporting through web-RS was defined by sending daily reports consecutively through web-RS for at least 24 days, which is the standard home treatment period in the authors' OIT protocol during the first 3 rounds. Those who did not succeed in reporting continually for a 24-day period were defined as reporting failures.

Statistical Analysis

Analysis of demographic and clinical patient characteristics of the web-RS group by reporting status (success vs failure) or method of reporting (E-mail vs web-RS) was made using *t* test or the Wilcoxon 2-sample test for continuous variables and χ^2 tests or Fisher exact tests for categorical data. For the association between method of reporting and reporting status, the odds ratio (the OR) with 95% confidence interval (CI) is presented. Multivariate logistic regression analysis was used to obtain the adjusted OR for group impact. Statistical significance was set at a *P* value less than .05. Statistical

analysis was performed with SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Monitoring of Home Maintenance Treatment by Web-RS

Patients reported through web-RS their daily amount of consumed allergen doses, whether premedication was administered, and whether any reaction was observed (Fig 1A). The questionnaire was modular, composed of a basic short unit used for reporting an uneventful home treatment (Fig 1A) and, when relevant, gradually exposed units for reporting allergic reactions and their treatment (Fig 1B). In the event a reaction occurred, a description of the reaction, therapeutic treatments, and possible predisposing factors, such as fatigue, physical activity, illness, and menstruation, were recorded (Fig 1B).

One hundred sixty-one participants were introduced to web-RS during the period of the study. One hundred nineteen were treated for cow's milk, 32 for peanuts, and 10 for hen's egg. Four patients, 3 with cow's milk protein allergy and 1 with peanut allergy, discontinued OIT treatment after 2 weeks owing to allergic reactions. These patients reported daily and despite receiving individualized changes to their protocol, their reactions continued and their treatment was stopped. Because they did not remain in the program for more than 24 reporting days, they were excluded from analysis.

Compliance to Web-RS

Initial characteristics of the patients who continued beyond the first month (*n* = 157) are presented in Table 1. Of these, 142 (90.44%) succeeded in sending daily reports through web-RS for at least 24 consecutive days (success group). The 15 patients (9.56%) who did not fulfill this condition comprised the "failure group." The longest reporting period on web-RS was 14 months. There was a short period in the beginning of the web-RS operation in which some technical difficulties were experienced in introducing some patients to web-RS. Except for this period, none of the patients in the success and failure groups complained that web-RS was difficult to operate.

To identify risk factors for web-RS reporting failure, patients' data were analyzed for factors that might have influenced their cooperation. Success with web-RS was not influenced by age, sex, or the allergen-specific type of OIT (Table 1). The course of treatment, including the starting dose, occurrence of allergic reactions during home treatment, and the late introduction to web-RS, also had no influence (Table 1). The only significant risk factor for failure was found the existence of a past OIT experience (*P* = .012; Table 1). The past experience could have been a previous successful OIT

Table 1
Characteristics of assigned groups^a

Characteristic	Success, n (%)	Failure, n (%)	<i>P</i> value
Patients	142 (90.44)	15 (9.56)	—
Age (mo)	96.7 ± 60.1 (76.5)	95.2 ± 43.8 (89)	.8321
Boys	74 (52.1)	6 (40.0)	.3721
Milk OIT	103 (72.5)	13 (86.7)	.3568
Egg or peanut OIT	39 (27.5)	2 (13.3)	
Starting dose (mg)	190.5 ± 479 (45)	284.5 ± 398.8 (45)	.2083
Late introduction to web-RS	14 (9.9)	3 (20.0)	.2099
Experienced reactions	107 (75.4)	9 (60.0)	.2212
Past OIT experience	3 (2.1)	3 (20.0)	.0120

Abbreviations: OIT, oral immunotherapy; web-RS, Web site–based electronic reporting system.

^aCategorical variables are presented as number (percentage) and continuous variables are presented as mean ± SD (median).

Table 2Comparison of reporting outcomes between web-RS and E-mail^a

	Web-RS, n (%)	E-mail, n (%)	P value
Patient population	157 (100)	100 (100)	—
Successful reporting	142 (90.4)	75 (75)	.0009 ^b
Age (mo)	96.6 ± 58.6 (77)	105.1 ± 53.3 (85.5)	.0366
Boys	80 (51.0)	60 (60)	.1557
Patients reporting reactions	116 (73.9)	63 (63)	.0642
Patients reporting severe reactions	19 (12.1)	20 (20)	.0853
Patients reporting mild reactions only	97 (61.8)	43 (43)	.0032
Milk OIT	116 (73.9)	83 (83)	.0883
Starting dose (mg protein)	199.5 ± 471.7 (45)	222.5 ± 503.8 (45)	.9702

Abbreviations: OIT, oral immunotherapy; web-RS, Web site–based electronic reporting system.

^aCategorical variables are presented as number (percentage) and continuous variables are presented as mean ± SD (median).^bOdds ratio 3.1 (95% confidence interval 1.6–6.3).

treatment (lacking web-RS usage) for a different food for the same patient or a previous OIT treatment of a different family member.

In detailed and individual analysis, 8 patients in the failure group did not report the results of their home treatment in any written form. Another 4 patients in this group sent sporadic E-mails, primarily a temporary response to a reminder. No motivator other than lack of compliance could be identified in these subjects. Two additional patients who failed to report through web-RS faced some technical difficulties at the beginning of web-RS usage. Like other patients in their situation, they were asked to report temporarily (1–2 days) by sending a daily E-mail, but after starting with such reporting, they failed to adjust to the web-RS operation.

In a retrospective analysis, successful reporting through web-RS (90.44%) contrasted to a 75% success rate when reports by E-mail were used ($P = .0009$; Table 2). For patients reporting by web-RS, the odds for successful reporting was 3.1 (95% CI 1.6–6.3) higher compared with patients reporting by E-mail. Because age and reporting by patients who experienced mild reactions only during home treatment also were significantly different between the study groups ($P = .0366$ and $P = .0032$, respectively; Table 2), multivariate logistic regression was used to obtain the adjusted OR for group impact (2.8, 95% CI 1.4–5.7, $P = .0046$). When adjusted for the study groups, age was not significant ($P = .7094$) but reporting by patients who experienced only minor reactions was significant (adjusted OR 2.2, 95% CI 1.07–4.5, $P = .0328$). However, the reporting of severe reactions (requiring epinephrine or visiting an emergency department) was not statistically different between web-RS and E-mail ($P = .085$).

Discussion

The main objective of this study was to develop an electronic Web site–based reporting system to facilitate monitoring of patients while on the home maintenance treatment phases of their OIT programs. The goal was to develop an efficient and user-friendly program to increase the compliance of patient reporting, thus improving the safety of OIT during its home maintenance phase. Using web-RS, 90.44% of patients successfully reported during home therapy. There were no patient complaints regarding use of the system and answering of the questionnaire. Patients who were introduced to web-RS after the initiation of treatment were equally successful in reporting, justifying a late introduction to web-RS, when applicable. Patients who were previously successfully treated in an OIT program could have judged that reporting was not as necessary and thus were less compliant with web-RS.

Before the generation of web-RS, patients were requested to keep a paper-based diary and to report electronically by E-mail.⁴⁴ A

paper-based diary alone has significant methodologic limitations. First, there is no validation that patients are in fact entering their reaction histories on the date on which the reactions occurred, subjecting their reports to recall bias. This has been demonstrated, for example, by the use of paper-based diaries equipped with concealed recorders for compliance assessment during a clinical trial⁴⁰ and in studies estimating home compliance to medication use by electronic monitoring, when drug blood levels or other biologic markers could not be measured.⁴⁵ Second, reaction histories with paper-based diaries were submitted at the monthly visit and thus timely adjustments to the patient's dosing could not be performed.

In contrast, reporting by E-mail enabled the medical staff to have immediate access to reports with a high level of confidence in their reliability. Instructions for further specific treatments of a reaction or protocol modifications were given in response to these E-mail reports. Furthermore, the evaluating physician could access the history of adverse reactions from the E-mails. Documentation also was assisted by patients or providers documenting any urgent phone consultations by E-mail.

Although the E-mail reports were clearly superior to a diary-based system, several limitations remained, giving impetus for the development of the web-RS system. First, in E-mail reporting, incomplete descriptions of the details of a reaction frequently occurred, because the description was solely dependent on the input of the patient or family. In contrast, web-RS enforces a reaction description, including organ system involvement. Furthermore, a detailed description of the reaction must be supplied by the user. Second, a patient's reports were not grouped together unless manually moved into individual folders in a laborious and potentially error-prone process. However, in web-RS, each report is initially placed directly by the patient into the patient's individualized file and the physician can visualize immediately the context of the recent reaction to the patient's clinical course. Third, web-RS significantly increased the compliance in reporting compared with E-mail reports. Approximately 25% of patients failed to report by E-mail on a daily basis during their home treatment phase. Although most severe reactions were reported by E-mail, the awareness of minor reactions during home treatment and the circumstances at which they occurred also can improve the safety of an OIT program. For example, a thorough history of these minor reactions can alert the physician to patient-specific predisposing factors or activities facilitating a reaction. In addition, the recurrence of mild reactions can prompt a protocol change to a lower dose or a delay of an increase at the next induction round.

Although compliance for reporting reached greater than 90% with web-RS, because the initial objectives were to set up and evaluate its ease of use, only minimal effort was applied to increase the compliance rate during the first home treatment period. However, using a Web site–based system provides daily up-to-date

information and early identification of noncompliant patients. Special attention can be paid to patients who are judged to be at higher risk not to report. Immediate correspondence to these patients could be successful in achieving close to a 100% compliance rate for the home treatment phase. For the present analysis, compliance was determined after the first month of treatment. The vast majority of patients in the success group continued to report consistently until the end of their treatment. However, some patients in this group could present with compliance issues as they progress in OIT and might require occasional reminders.

An additional aspect that can be evaluated on a case-by-case basis is the submission of retrospective reaction histories. With web-RS it could be monitored, limited by the used software, blocked, or in certain cases enabled by the medical staff. The authors chose to implement the latter, more flexible option, although it required more effort. However, for other OIT programs, the former options might prove to be more appropriate. There are other expected limitations applying to the elderly,⁴⁶ but these are irrelevant to the OIT target population.

Use of web-RS enables simultaneous home monitoring of large groups of patients on OIT and should prove useful for multicenter clinical trials, including those of OIT with extensively heated foods⁴⁷ and sublingual immunotherapy.⁴⁸ Results from these multicenter clinical trials are currently required for definitive conclusions regarding the safety, efficacy, and optimization of OIT protocols. Moreover, its use potentially decreases manpower needs and, as such, could decrease the overall costs of an OIT program. Further, web-RS is a powerful tool to assist in gathering and analyzing data. This web-RS provides an Excel spreadsheet (Microsoft Corp, Redmond, Washington) that tabulates all data inserted by the patients and physicians. For example, monthly blood eosinophil counts are inserted and followed by the physician during the course of treatment.⁴⁹ Thus, clinical data can be easily analyzed statistically and presented graphically.

Home treatment is an essential part of OIT. Its monitoring is crucial for the success and safety of OIT. A complete and precise daily reporting of home treatment is a cornerstone for the medical assessment of the individual patient and the entire OIT program. The web-RS is a powerful tool for achieving these goals and further significant advancements in food allergy research.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.04.007>.

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Patient information recorded in database

Personal information

First name *

Last name *

E-mail *

Phone number *

Name of phone account holder *

Street address *

City *

Details of treatment

Patient study group *

Patient study # *

Food allergies * ☐Milk ☐Egg ☐Peanuts ☐Nuts ☐Fish ☐Other

Currently treated allergy * ☐Milk ☐Egg ☐Peanuts

Medical history ☐None ☐Asthma ☐Recurrent URI ☐Other

Name of primary allergist

Allergist e-mail

Name of primary pediatrician

Pediatrician e-mail

Treatment starting date

Starting Dose

User ID

eFigure 1. Patient registration task form.