

Dysphagia and health-related quality of life in patients with eosinophilic esophagitis: a long-term follow-up

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Abstract Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated disease, with dysphagia as the main symptom. The aim of this study was to survey symptoms and health-related quality of life in adult patients with EoE at least 1 year after diagnosis and a 2-month course of topical corticosteroids. Forty-seven consecutive patients [79 % males, mean age 49 years (range 18–90 years)] were evaluated using three different questionnaires at three different occasions: the Watson Dysphagia Scale (WDS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Oesophageal Module 18 (EORTC QLQ-OES18) and the Short Form-36 (SF-36). The median time from diagnosis to the long-term follow-up was 23 months (range 12–34 months). The WDS scores and the EORTC QLQ-OES18 Dysphagia and Eating scale scores were improved after 2 months of treatment ($p = 0.00007$, $p = 0.01$, $p = 0.004$, respectively), as were the long-term follow-up scores ($p = 0.01$, $p = 0.03$, $p = 0.005$, respectively), relative to the scores at diagnosis. In addition, the EORTC QLQ-OES18 Choking scores were improved after the steroid course ($p = 0.003$) but not after the long-term follow-up. No significant differences were detected with respect to the SF-36 scores. In summary, EoE seems to be associated with a substantial burden of symptoms that

improve significantly after treatment. A partial remission persists more than 1 year after diagnosis and the discontinuation of medication. The WDS and the EORTC QLQ-OES18 appear to be sensitive instruments appropriate for surveillance in these patients.

Keywords Eosinophilic esophagitis · Dysphagia · Quality of life · Follow-up · Questionnaires

Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-mediated disease that affects health-related quality of life (HRQL) in both children and adults. The main symptom in adults is dysphagia, a symptom that may lead the patient to the otolaryngologist, and complications include food bolus impaction, esophageal strictures and perforation [1]. Several treatment strategies have been implemented over the years including esophageal dilatation, anti-allergic medication, proton-pump inhibitors, allergen elimination diet and corticosteroids [2–10]. Dilatation offers symptomatic relief for some patients but does not influence the underlying inflammatory process and is related to severe side effects including esophageal perforation and bleedings [3, 11]. Antibody-treatment against IL-5 resulted in a significant reduction of intraepithelial esophageal eosinophils in a small, double-blind, randomized, placebo-controlled trial in children and adolescents, but no improvements in symptoms or HRQL were observed [4]. The potential mechanism of PPI in an immune-driven disease like EoE is difficult to determine; however, recently, an augmentative effect on eotaxin-3 levels has been demonstrated [5, 6]. Allergen elimination diet, which for several years has been used among children, has lately been reported to exhibit

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beneficial effects in adults as well [7, 8]. However, this treatment requires a major effort from the patient through the exclusion of common groceries, e.g., eggs, cow's milk, soy, wheat, seafood and peanuts.

Currently, the first choice of treatment in adults is topical corticosteroids, applied orally as an aerosol and then swallowed. Studies have reported promising results in decreasing symptoms and decreasing the number of eosinophils in the mucosa of the esophagus; however, randomized controlled trials are scarce [2, 9, 10]. Moreover, Helou et al. reported in a 3-year follow-up study that the disorder requires a repetitive treatment in order to suppress the symptoms, whereas Straumann et al. found long-term low-dose treatment to be effective [12, 13].

Much remains unknown about the natural history of EoE and the optimal handling of these patients and the few long-term studies that exists thus far have largely focused on dysphagia relief and histological findings [12]. In the present study, we followed a cohort of consecutive patients treated with 2 months of topical corticosteroids to survey their symptoms, HRQL, need for medication and complications for at least 1 year after diagnosis.

Methods

From January 2009 to March 2011, consecutive patients diagnosed with EoE according to consensus recommendations (>15 eosinophils/high power field and symptoms related to esophageal dysfunction) [2] at the NÄL Medical Centre Hospital, a secondary referral hospital on the west coast of Sweden, were invited to participate in the present study. The patients were asked to answer three different questionnaires about their symptoms and HRQL both at diagnosis, after 2-month course of orally applied aerosolized mometasone furoate (50 µg per spray, 4 sprays per dose taken 4 times daily) and at a follow-up at least 1 year after diagnosis. The patients who initially did not answer the questionnaires were reminded by telephone. These first results (at diagnosis and after treatment) have previously been presented in part [14].

To measure dysphagia and HRQL the following scales and questionnaires were used:

The Watson Dysphagia Scale

The Watson Dysphagia Scale (WDS) provides a score ranging from 0 (no dysphagia) to 45 (severe dysphagia). Nine ranked groceries (from liquids to solid food) are scored according to the presence of dysphagia by the patient on a 3-point Likert scale (1 = always, 0.5 = sometimes, and 0 = never). This score is then multiplied by the factor for each substance (1–9), and the

scores for all substances are summed. The scale has been used in several studies incorporating patients with esophageal dysphagia [15–17].

EORTC QLQ-OES18

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Oesophageal Module 18 (EORTC QLQ-OES18) was originally designed to investigate problems due to esophageal cancer location and treatment. However, because the majority of the questions are not cancer-specific, the questionnaire has been extensively used in different HRQL studies, and its cross-cultural validity and psychometric properties are considered satisfactory [18, 19]. The questionnaire comprises 4 scales (the dysphagia, eating, reflux, and local pain scales) and 6 single questions concerning related symptoms. The scores are calculated according to the EORTC scoring manual. The questions are scored by the patient on a 4-point Likert scale (not at all, sometimes, most of the time, and always), and the 4 points are transformed into scores from 0 to 100, where a high score represents a high level of symptoms/problems.

The Short Form-36

The Short Form-36 (SF-36) questionnaire is a multipurpose, general health survey consisting of 36 questions. The SF-36 yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures. The questionnaire has been used in numerous studies, and its validity is well documented [20]. The patient scores the questions using a 2-, 3-, 5-, or 6-grade Likert scale. The scores are transformed into a score from 0 to 100, where a high score represents a high level of functioning/well-being.

The supplementary questionnaire

At the long-term follow-up, a supplementary, non-validated questionnaire with questions regarding medications and hospital visits was added to the three questionnaires above (Table 1). The patients were able to answer these questions in free text, and the answers were categorized for analysis purposes. Additionally, the medical records of all included patients were surveyed and compared with the latter questionnaire regarding hospital visits and treatment.

Statistics and ethics

The mean, median, standard deviation and range were used for descriptive purposes, and the Wilcoxon matched-pairs

Table 1 Results from the supplementary questionnaire

Question	Answer (% of patients)
“For how long have you had swallowing difficulties?”	<1 year/1–5 years/> 5 years 0/29/71
“How many 2-month courses of corticosteroid-spray treatment due to eosinophilic esophagitis have you had since diagnosis?”	None/one/several 0/57/43
“How many episodes of aggravated swallowing difficulties have you had since diagnosis?”	35/19/47
“How many episodes of food bolus impaction have you had since diagnosis?”	30/2/67
“Have you had treatment with a corticosteroid spray due to eosinophilic esophagitis in the last month?”	Yes/no 20/80
“Have you experienced a seasonal variation in swallowing difficulties since they started?”	4/96

N = 47, compliance >95 %

signed-rank test was used to compare the questionnaire scores at diagnosis, after 2 months of medical treatment and in the long-term follow-up.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Committee at the University of Gothenburg. Informed consent was obtained from each participant before inclusion.

Results

Out of 51 consecutive patients asked to participate in the study, 48 completed the questionnaires. One patient declined participation and two did not answer despite several reminders. Moreover, one patient was excluded due to another concomitant esophageal disease (scleroderma). Consequently 47 patients (92 %) were eligible for analysis (Table 1). Thirty-seven patients were men (79 %), the mean age was 49 years (range 18–90 years) and 32 patients (68 %) had a concurrent allergy. The median time between diagnosis and the long-term follow-up was 23 months (range 12–34 months).

At diagnosis, all patients completed the EORTC QLQ-OES18, six did not complete the WDS and one missed the SF-36 questions of General Health, Vitality and Mental Health. At the 2-month follow-up, four patients did not receive any questionnaires, and two more did not complete the WDS or the EORTC QLQ-OES18. At the long-term follow-up, all patients completed all of the questionnaires.

The WDS scores improved significantly from inclusion to after treatment ($p = 0.00007$) and also from inclusion to the time of the long-term follow-up ($p = 0.01$). Deterioration was, however, observed between the scores after treatment and at the long-term follow-up ($p = 0.04$) (Fig. 1; Table 2).

Correspondingly, the Dysphagia Scale scores of the EORTC QLQ-OES18 improved from inclusion to after treatment ($p = 0.01$), and the improvement was significant relative to the scores at the long-term follow-up ($p = 0.03$). The same development applied for the Eating Scale scores ($p = 0.004$ and $p = 0.005$, respectively), whereas the Choking scores only improved significantly directly after treatment ($p = 0.003$). No other significant changes were observed at the various measurement points for the other scales and questions, including the SF-36 scale (Table 2).

Based on the results from the supplementary questionnaire enclosed at the long-term follow-up, the majority of the patients reported swallowing difficulties of more than 5 years duration (Table 1). The total number of episodes of aggravated swallowing difficulties for each patient since diagnosis ranged from zero to twelve, and approximately two-thirds of the patients had experienced more than one occurrence of esophageal bolus impaction during the same time period. However, according to the thorough surveillance of medical records, none of these patients were referred to hospital for bolus impaction retrieval. Moreover, none of the patients underwent endoscopic dilatation during the study period and most patients only had the initial 2-month course of topical corticosteroids after the diagnosis. Among the patients who had several courses, the need of 2–3 courses was the most common. Almost none of the patients had experienced seasonal variation in swallowing difficulties.

Discussion

Even though much uncertainty prevails within the field, EoE is known to be a chronic disease that, like most chronic diseases, requires repeated or continuous treatment

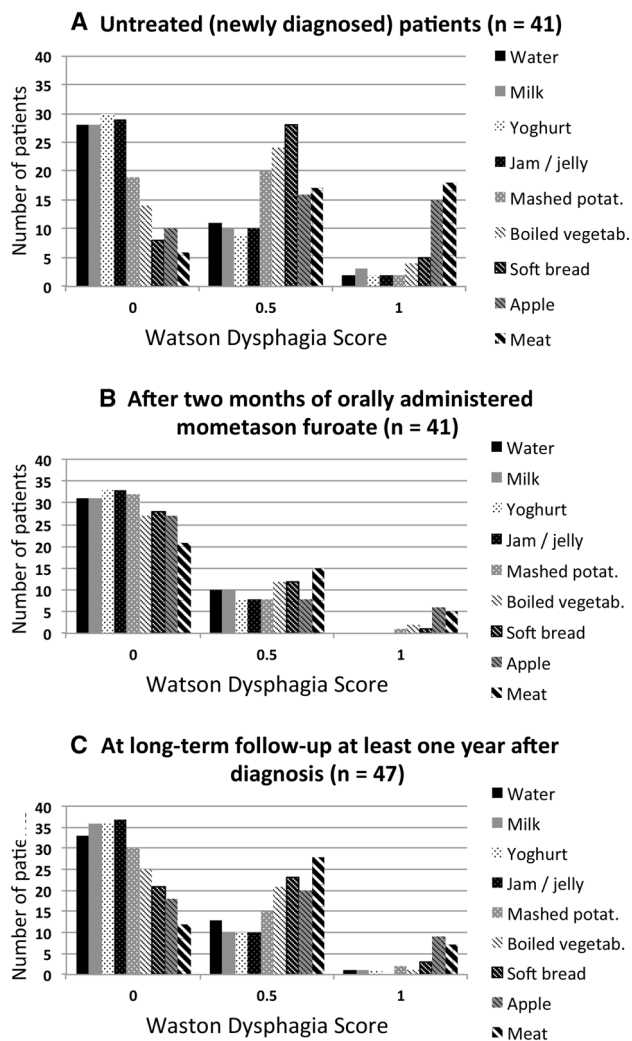


Fig. 1 a–c Assessment of dysphagia in patients with eosinophilic esophagitis using the Watson Dysphagia Scale. Dysphagia for each liquid or solid substance was scored by the patient as follows: 0 = never, 0.5 = sometimes or 1 = always

[1]. However, the present study demonstrated maintained improvement with respect to symptom relief in the majority of patients even 1 year after the initiation of 2-month treatment with mometasone furoate. This finding might be considered a bit unexpected but is actually consistent with the few other follow-up studies that exist and with our own clinical experience thus far. In a study by Helou et al. [12], 32 EoE-patients treated with 6 weeks of orally administered fluticasone were evaluated approximately 3 years later. More than 90 % of the patients reported recurrent symptoms at a mean of 9 months after initial treatment. Moreover, only 69 % of the patients required repeated corticosteroid treatment during the follow-up. A fairly low response rate (63 %) and the lack of HRQL assessment were, however, limitations in that study [12]. In another prospective study, 97 % of the patients ($n = 30$) experienced persistent dysphagia after a mean

follow-up time of 11.5 years. However, the latter patients were untreated, and the grade of dysphagia was evaluated using a structured interview [21].

In the present study, as much as 67 % of the patients reported several episodes of bolus impaction since diagnosis. However, according to the medical records none of the patients required endoscopic bolus removal why these incidents most likely were transient and self-solved. In addition, more than half of the patients required only one 2-month course of corticosteroid treatment after diagnosis, and among the patients who reported repeated treatment the majority had only taken one, or less common two extra courses. Further, none of the included patients needed treatment with esophageal dilatation. These findings, together with the enhanced scores of the WDS and EORTC QLQ OES-18 scales, underlines the prolonged effect on dysphagia after the initiation of treatment and perhaps also the need of individualized treatment. In a very recent study, Kuchen et al. reported consistent findings in a cohort of 206 patients with a median follow-up time of 5 years in their study, swallowed topical corticosteroids resulted in a reduced risk (OR 0.41) of the occurrence of future esophageal bolus impaction [22]. Whether the reasons for such long-lasting improvement may be pharmacological or merely the consequence of an increased awareness of the disease among the patients, resulting in a modification of eating habits, should be subjected to further investigations. The outcome of the WDS score measurement at the long-term follow-up, however, not only showed a significant improvement compared to inclusion, but also demonstrated a deterioration compared to the time point after the 2-month corticosteroid course. This finding implicates, quite reasonable, a slow but declining effect of the initial treatment over time and also emphasizes the higher ability of WDS to detect minor changes in dysphagia compared to the other scales used in this study. In other words, the WDS scoring of dysphagia for nine ranked groceries by the patient results in a higher sensitivity compared to answering for instance the three questions of the EORTC QLQ-OES18 Dysphagia scale.

As a matter of fact, our findings of the reduced burden of symptoms long after treatment are intricate and shed light on the question regarding the true etiology of the disease. A few studies have emphasized an allergic mechanism; however, the actual allergen or allergens in adults have not to date been identified [23–25]. Straumann et al. reported of increased numbers of T-cells and mast cells as well as increased levels of IL-5 and TNF- α in esophageal epithelial biopsy specimens, supporting the hypothesis of EoE as an allergen-driven disease [26]. Concordantly, mice subjected to epicutaneous antigen sensitization developed EoE via a Th2-dependent pathway in a study by Akei et al. [27]. Moawad et al. demonstrated that the number of cases

Table 2 Results from the Watson Dysphagia Scale (WDS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Oesophageal Module 18 (EORTC QLQ-OES18) and The Short Form-36 (SF-36) questionnaire at the various measurement points

	Inclusion	After treatment	Long-term follow-up	Inclusion vs after treatment	Inclusion vs long-term follow-up	After treatment vs long-term follow-up
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	<i>p</i> value	<i>p</i> value	<i>p</i> value
WDS	18.8 $\pm$ 9.7	9.0 $\pm$ 10.2	13.1 $\pm$ 9.7	0.00007	0.01	0.04
EORTC QLQ-OES18						
Dysphagia Scale	15.5 $\pm$ 19.9	5.4 $\pm$ 9.9	7.3 $\pm$ 13.6	0.01	0.03	ns
Eating Scale	35.1 $\pm$ 29.4	18.3 $\pm$ 24.1	18.8 $\pm$ 24.4	0.004	0.005	ns
Choking	36.1 $\pm$ 34.0	14.6 $\pm$ 21.1	23.3 $\pm$ 26.9	0.003	ns	ns
Saliva	18.4 $\pm$ 30.2	8.1 $\pm$ 20.7	14.1 $\pm$ 29.9	ns	ns	ns
Dry	18.4 $\pm$ 28.5	20.3 $\pm$ 31.5	16.3 $\pm$ 29.0	ns	ns	ns
Taste	12.0 $\pm$ 26.4	5.7 $\pm$ 18.1	2.8 $\pm$ 7.2	ns	ns	ns
Cough	8.5 $\pm$ 17.6	15.4 $\pm$ 28.0	9.2 $\pm$ 18.3	ns	ns	ns
Speak	4.9 $\pm$ 13.8	5.7 $\pm$ 21.0	4.2 $\pm$ 9.9	ns	ns	ns
Reflux Scale	21.6 $\pm$ 24.8	15.6 $\pm$ 18.8	19.7 $\pm$ 23.3	ns	ns	ns
Local pain	17.4 $\pm$ 20.6	10.2 $\pm$ 15.1	10.8 $\pm$ 17.6	ns	ns	ns
SF-36						
Physical functioning	86.8 $\pm$ 20.1	89.0 $\pm$ 16.0	89.0 $\pm$ 19.0	ns	ns	ns
Role-physical	82.0 $\pm$ 35.0	87.0 $\pm$ 27.0	84.0 $\pm$ 27.0	ns	ns	ns
Bodily pain	76.0 $\pm$ 24.0	84.0 $\pm$ 23.0	79.0 $\pm$ 22.0	ns (0.07)	ns	ns
General health	72.0 $\pm$ 24.0	73.0 $\pm$ 23.0	75.0 $\pm$ 21.0	ns	ns	ns
Vitality	67.0 $\pm$ 23.0	67.0 $\pm$ 23.0	65.0 $\pm$ 22.0	ns	ns	ns
Social functioning	82.0 $\pm$ 24.0	90.0 $\pm$ 15.0	90.0 $\pm$ 15.0	ns (0.09)	ns	ns
Role-emotional	82.0 $\pm$ 35.0	85.0 $\pm$ 28.0	85.0 $\pm$ 30.0	ns	ns	ns
Mental health	77.0 $\pm$ 21.0	82.0 $\pm$ 15.0	80.0 $\pm$ 16.0	ns	ns	ns

diagnosed with EoE is highest in the spring and correlates with grass pollen counts, implying a seasonal variation of the incidence [28]. In contrast to this, almost all participants (96 %) in the present study negated a seasonal variation in swallowing difficulties which do not necessarily facilitate the task to determine the cause of this disease.

A potential limitation of our study is that the patients included were diagnosed according to the consensus recommendations valid at the time, and the recommendations have since been modified [1, 2, 29]. The most important alteration, which one currently must keep in mind when diagnosing patients with EoE, is the introduction of a new ailment called proton-pump inhibitor responsive esophageal eosinophilia (PPI-REE). Patients with the latter condition exhibit eosinophil peak count values that exceed 15/HPF but respond histologically and/or symptomatically well to PPI-treatment. To exclude PPI-REE, patients suspected of having EoE should be put on PPI for at least 2 months and then re-examined with endoscopy and new biopsies [29]. However, whether PPI-REE is really a disease entity of its own or merely a subset of patients with

EoE who respond well to PPI-treatment is a matter of debate and will indisputably be questioned in future studies.

That HRQL was improved by medical treatment in the present study, was not demonstrated by the outcome of the SF-36 questionnaire which might be to general, but by the results of the EORTC QLQ OES-18 Eating Scale. This scale incorporated questions such as “Have you had trouble enjoying your meals?” and “Have you had trouble with eating in front of other people?” The impact of these findings is even more obvious when considering the fact that the mean Eating Scale score before treatment was in the vicinity of those reported in patients with esophageal cancer [19]. HRQL studies in patients with EoE are, however, scarce and will require further exploration. To the best of our knowledge, this study represents the first use of the EORTC QLQ OES-18 questionnaire in an EoE study. The more general SF-36 questionnaire has only been used by one other research team for an EoE study [30]. Taft et al. showed using qualitative interviews that patients with EoE have concerns about impact of eating, dysphagia episodes and available treatments among other things but

also that they felt a relief upon receiving diagnosis [31]. The same authors have also developed a recent adult EoE quality of life questionnaire [32]. The validation demonstrated reliable results but was performed using patients without a confirmed diagnosis, and according to the author the questionnaire should be re-validated with patients diagnosed according to EoE consensus recommendations. Just recently, Schoepfer et al. developed and validated a symptom-based activity index instrument specifically for use in adults with EoE [33].

Conclusions

Managing both patients with various atopic diatheses as well as patients with dysphagia, it is imperative for the otolaryngologist to be updated on EoE since these patients sooner or later will visit the open door clinic. Adult EoE seems to be associated with a substantial burden of symptoms that improve significantly after a 2-month course of topical corticosteroids. A partial remission persists more than 1 year after diagnosis, even though the medication was discontinued. The WDS and the EORTC QLQ-OES18 appear to be sensitive instruments appropriate for the surveillance of symptoms and HRQL in these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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