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Food-induced Immediate Response of the Esophagus – a newly identified Syndrome in Patients with Eosinophilic Esophagitis

Short title: FIRE in EoE

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List Allergy: eosinophils, epidemiology, esophagitis, food allergy

ABSTRACT

Background: Dysphagia is the main symptom of adult EoE. We describe a novel syndrome, referred to as “Food-induced Immediate Response of the Esophagus” (FIRE), observed in EoE patients.

Methods: FIRE is an unpleasant/painful sensation, unrelated to dysphagia, occurring immediately after esophageal contact with specific foods. EoE experts were surveyed to estimate the prevalence of FIRE, characterize symptoms and identify food triggers. We also surveyed a large group of EoE patients enrolled in the Swiss EoE Cohort Study (SEECs) for FIRE

Results: Response rates were 82% (47/57) for the expert- and 65% (239/368) for the patient-survey, respectively. Almost 90% of EoE experts had observed the FIRE symptom-complex in their patients. Forty percent of EoE patients reported experiencing FIRE, more commonly in patients who developed EoE symptoms at a younger age (mean age of 46.4 vs. 54.1 years without FIRE; $p < 0.01$) and in those with high allergic comorbidity. FIRE symptoms included narrowing, burning, choking and pressure in the esophagus appearing within 5 minutes of ingesting a provoking food that lasted less than 2 hours. Symptom severity rated a median 7 points on a visual analogue scale from 1-10. Fresh fruits/vegetables and wine were the most frequent triggers. Endoscopic food removal was significantly more commonly reported in male patients with vs. without FIRE (44.3% vs. 27.6%; $p = 0.03$).

Conclusions: FIRE is a novel syndrome frequently reported in EoE patients, characterized by an intense, unpleasant/painful sensation occurring rapidly and reproducibly in 40% of surveyed EoE patients after esophageal contact with specific foods.

1 INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease, defined clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. (1, 2) The clinical portion of this definition relies purely on patient reported outcomes (PROs), whereas the histological portion involves the quantitative determination of eosinophilic infiltration which serves as a biological marker, although pathological findings in addition to tissue eosinophilia are important. The inclusion of PRO's in the disease definition, and the fact that dysphagia is often an undisclosed complaint, illustrate the importance of physician awareness of this disease in order to avoid unnecessary diagnostic delay.

The main function of the esophagus is the transport of nutrients from the oral cavity to the stomach. Based on functional studies, in particular high resolution manometry (HRM), we know that this voluntarily initiated act lasts only a few seconds under healthy conditions. Solid food dysphagia up to food impaction is the hallmark-symptom in adults with EoE. Thus, EoE patients are often asymptomatic except when they ingest solid food. In children the spectrum of symptoms is broader including food refusal in addition to chest and/or abdominal pain, likely due to the inability of children to precisely articulate complaints. (3–5)

Over the past few years our increasing clinical experience identified EoE patients reporting symptoms that were different than manifestations of altered esophageal transport, such as dysphagia and food impaction. Patients reported a previously undescribed esophageal symptom complex consisting of discomfort occurring exclusively and rapidly after esophageal contact with specific foods, such as certain fruits or nuts. Due to the intense and often frightening symptoms patients typically have avoided any further exposures to the inciting food(s). Although, the descriptions had several features in common with Food Pollen Allergy Syndrome (FPAS; formerly referred to as Oral Allergy Syndrome [OAS]), the site of symptoms was unequivocally the esophagus and retrosternal region rather than the oropharynx, clearly separating these patients' reports from FPAS. (6–8) Of note, most patients also explicitly distinguished this symptomatology from either solid food dysphagia or reflux symptoms.

The purposes of this study were 1) to evaluate amongst a large group of EoE-experts in Europe and the USA whether such a phenomenon was independently observed in individual clinical practices across physicians; 2) to characterize this novel EoE-related symptom-complex using the perspective of physicians; 3) to receive a comprehensive description of this syndrome from the perspective of a large number of EoE patients; and 4) to roughly estimate the prevalence of this syndrome among the EoE population.

2 METHODS

2.1 Definitions and Design of the Study

Increasing clinical recognition of atypical symptoms in EoE patients led to a face to face meeting on May 7, 2017 of pediatric and adult gastroenterologists and allergists. Participants reached a consensus to perform a survey involving physicians experienced in the treatment of EoE patients and patients affected with EoE, to assess the phenomenon “food-induced immediate response of the esophagus” (FIRE) from the experts’ and patients’ perspective. Physicians experienced clinically and scientifically in the field of EoE were considered as EoE experts.

Clinical experiences of the group were gathered and consensus opinion identified that FIRE was defined as:

1. symptoms of an unpleasant or painful retrosternal sensation,
2. symptoms occurring immediately and reproducibly after contact of the esophageal surface with a particular food or drink,
3. symptoms appearing separately from and unrelated to the well-characterized swallowing difficulties (i.e. dysphagia or food impaction) in EoE.

Exclusionary symptoms included a delayed passage or even interruption of the swallowing process specifically occurring when swallowing solid, dry or fibrous foods (i.e. typical solid food dysphagia), and any symptoms consistent with gastroesophageal reflux disease were deliberately not included in the reporting of FIRE.

2.2 Physicians’ Survey

The investigators developed a physician-oriented questionnaire with the purpose of determining 1) whether other providers who cared for EoE patients encountered FIRE in their EoE patients and 2) to obtain detailed information regarding the frequency, timing, clinical manifestation and triggers of these reactions. In addition, defined patient characteristics were recorded. (*physicians’ questionnaire*, S-Table 1). This questionnaire was distributed to EoE-experts in Europe and the USA, selected by the group of authors based on previous scientific and clinical contributions and recognized expertise in the field.

2.3 Patients' Survey

Results of the physician survey were discussed by the investigators at a second face to face meeting on June 4, 2018. In order to gain more clarity regarding the initial findings, a patient survey was developed that assessed the following items: 1) whether patients experienced immediate reactions in their esophagus upon ingestion of specific foods or beverages and 2) comprehensive descriptions of their reactions including the triggering food categories. Patients were informed that they should disregard the well-known EoE-associated solid food dysphagia and symptoms of gastroesophageal reflux disease (*patients' questionnaire, S-Table 2*).

The questionnaires were distributed among all patients, that had previously given their written informed consent for inclusion into the Swiss EoE Cohort Study (SEECs) and who were treated at the Swiss EoE Clinics in Zurich and Olten, Switzerland. In total 368 patients with previously confirmed diagnosis of EoE according to established criteria [4] were invited to participate either via mail or in the outpatient clinics by a sub-group of authors (PS, LB, TG and AS). The study was supported by the Swiss National Science Foundation (SNF Grant 32473B_160115) and was approved by the local ethics committee (EKNZ 2015-388). All data were anonymized.

2.4 Statistical Analyses

All collected data were anonymized and entered into a database. Results of quantitative data are presented as median plus interquartile ranges (IQR) and range for non-normally distributed data or mean $\pm$ SD and range for data with normal distribution, whereas categorical data are summarized as the percentage of the group total. The Mann-Whitney test Chi-Square test and t-test were used to analyze potential differences between groups for nonparametric and parametric quantitative data, respectively, and for difference among categorical variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using Prism (version 7, GraphPad Software, La Jolla, CA, USA).

3 RESULTS

3.1 Physicians' Survey

The survey was sent to 57 physicians and 47 responded (response rate 82.5%), consisting of 25 gastroenterologists, 21 allergists and one epidemiologist, all of whom were familiar with EoE. Physicians treated adult, pediatric or both patient groups (40.4%, 38.3% and 21.3%, respectively). Almost 90% of these EoE-experts declared that a Food-induced Immediate Response of the Esophagus (FIRE) at least “may” exist in patients with EoE according to a Likert scale from 1-5, with “may exist” (3), “is likely to exist” (4) and “absolutely does exist” (5) in 30.4%, 30.4% and 26.1%, respectively. In contrast, only a minority stated that FIRE is “unlikely to exist” (2; 8.7%) or “absolutely does not exist” (1; 4.4%). The majority of experts estimated the prevalence of FIRE symptoms in the EoE population between <5% and 20%. (*Figure 1*).

FIRE was most frequently characterized as burning, painful and narrowing with a sensation of heat and pressure on the chest by physician (*S-Figure 1*). Milk products, wheat, nuts and fruits were considered to be the most frequent offending food products (*S-Figure 2* illustrating whether physicians considered candidate food items as typically FIRE-provoking).

About a third of experts considered certain beverages in addition to solid food to also trigger FIRE in EoE patients (35.5%), while another third did not identify any role of beverages in FIRE (32.3%). Physicians who attributed a role of certain beverages in inducing FIRE symptoms, wine, beer and milk (29.4%, 23.5% and 23.5%, respectively), rated these beverages as rather typical or very typical in inducing FIRE symptoms) (*S-Figure 3*).

The onset of FIRE symptoms after food ingestion ranged from 1 to 60 minutes and 76.7% of patients had onset within 5 minutes. The typical duration of an episode of FIRE ranged from < 10 minutes to 6 hours. The duration was <30 minutes in 72.4% and <2 hours in 96.5% of patients (*Figure 2*).

A majority of 48.3% of EoE-experts felt that typical EoE patients with FIRE did not differ in terms baseline clinical characteristics from their counterparts without FIRE, with however a large fraction of undecided responses (41.4%). In contrast 10.4% thought that patients with vs. those without FIRE differed in terms of one or more epidemiological features. Likewise, 58.1% think of FIRE as a chronic/recurrent/reproducible phenomenon in EoE patients and only 12.9% considered it a temporary phenomenon, resolving over time (29.3% could not decide based on their current clinical experience). While FIRE is felt to be seen more often in patients with active EoE by 35.5%, 22.6% of physicians also considered FIRE a phenomenon independent of EoE activity (S-Figure 4).

3.2 Patient Survey

In total, 239 of 368 patients responded to the questionnaire (response rate 64.9%).

Table 1 provides an overview of baseline characteristics of the patient cohort.

The prevalence of FIRE amongst all patients was 39.7% (95/239) (i.e. positive response to the key question, Nr.6, from our questionnaire, *Supplementary Table 1: "Did you ever experience an unpleasant or even painful sensation in the mouth, throat or esophagus (behind the breastbone), which is different from, and unrelated to, the well-known swallowing difficulties, immediately after the ingestion of a particular food or drink? (We are not referring to the typical EoE symptoms with a slight choking or even blockade in the swallowing process specifically occurring when swallowing solid, dry or fibrous foods)*). There was no significant difference in FIRE prevalence in male vs. female patients (41.7% vs. 35.2%). Of note, patients with FIRE were significantly younger than their counterparts without FIRE (mean age of 46.4 vs. 54.1 years; $p<0.01$). Likewise, we observed a younger age of EoE symptom onset (mean age at symptom onset of 28 vs. 35.6 years, standard deviation 12.6 vs. 15.4 years; $p<0.01$) as well as diagnosis of EoE (mean age at diagnosis of 35.1 vs. 43.3 years, standard deviation 13.9 vs. 14 years, $p<0.01$). Interestingly, the presence of FIRE was associated with a significant increase in diagnostic delay in patients with vs. without FIRE (8.2 vs. 7.5 years, $p<0.01$; Figure 3).

3.2.1 Allergic Diseases and FIRE

The prevalence of allergic diseases was 58.2% (139/239). We observed significantly more allergic diseases in general and allergic rhino-conjunctivitis (ARC) as well as FPAS, in FIRE patients compared to patients without FIRE, (allergies overall 69.2 vs 53.2%, $p=0.02$; ARC 51.6% vs. 33.3%, $p<0.001$; FPAS 26.3% vs. 11.1%, $p<0.01$). In contrast, prevalence of allergic asthma and food allergies was similar in the two groups.

3.2.2 History of Food Bolus Impaction Requiring Endoscopic Intervention and FIRE

One third of the entire cohort (81/239; 33.9%) reported having suffered from food bolus impaction that had to be removed endoscopically. There was a trend toward a higher percentage of patients in need of endoscopic food bolus removal was higher in patients with vs. without FIRE (40% vs. 29.9%; $p = 0.09$). In contrast, taking only male patients into consideration, we observed a significant association of FIRE with a prior history of endoscopic food bolus removal (44.3% vs. 27.6% in male patients without FIRE, $p = 0.03$; 30.4% vs. 34.8% in female patients, n.s.; S-Figure 4).

3.2.3 Characteristics of FIRE and associated Symptoms

The median intensity of FIRE symptoms on a visual analogue scale (VAS) from 1-10 with 1 as the lowest and 10 as the highest intensity was 7 (IQR, 5-8; range 2-10). The distribution of patient reported FIRE intensity is depicted in *Figure 4*.

Although there was a considerably wide distribution of patient reported FIRE intensity, the majority of patients reported an intensity as high as 8 out of 10, leading to the overall result that 50% of patients reported high intensity scores between 7-10.

The latency, i.e. the interval between ingestion of the FIRE-triggering food or beverage and the onset of symptoms, was less than 5 minutes in the majority of EoE patients experiencing FIRE symptoms (*Figure 5A*). The duration of FIRE symptoms was reported to be shorter than 120 minutes in the majority of patients (*Figure 5B*). The most frequent triggering foods and beverages are depicted in *Figure 6A*. The characteristic features of FIRE most commonly reported by patients were a narrowing and burning sensation with a feeling of pressure and a choking sensation (*Figure 6B*). Anxiety, was also a typical

symptom of FIRE, according to a third of patients. Further, several patients reported the experienced sensation in FIRE as resembling a cramp or prick. These patient-reported characteristics were in line with the results from the free-text question (No. 16), with the aforementioned attributes most frequently mentioned and in addition “panic”, “scraping”, “squeezing” or “itching”.

While the majority of patients did not experience an increase in dysphagia during the few days immediately after experiencing FIRE (68.4%), almost one third (29.5%) had more difficulties swallowing in the subsequent days (don't know / not sure 1.1%).

FIRE was reported to occur only when EoE was active in 28.4% of patients, whereas 38.9% of patients considered FIRE to occur independent of EoE activity (FIRE only when EoE is inactive: 3.2%; don't know / not sure: 28.4%).

Regarding the temporal occurrence of FIRE in relation to the first manifestations of EoE, 31.6%, 24.2% and 15.8% of patients stated, that FIRE had occurred prior, after or simultaneous to the first EoE symptoms, respectively (don't know / not sure: 24.2%). The intensity of FIRE symptoms over time remained roughly stable in 34.7% of patients, while worsening and improvement was reported by 25.3% and 13.7%, respectively (don't know / not sure 13.7%). In 12.7% of patients, FIRE symptoms had completely resolved after a median of 4 years.

4 DISCUSSION

This report describes a newly recognized, clinically defined syndrome associated with EoE. Based on our findings and the esophageal origin of symptoms in these EoE patients, we propose the acronym FIRE: **F**ood-induced **I**mmEDIATE **R**esponse of the **E**sophagus. This syndrome encompasses esophageal symptoms occurring rapidly after contact of the esophageal surface with a specific food. Like Pollen Food Allergy Syndrome (PFAS), FIRE is triggered by fruits and vegetables but FIRE symptoms, like EoE, originate in the esophagus instead of the oro-pharyngeal cavity. In contrast to PFAS, FIRE symptoms include pain as well as those suggestive of esophageal constriction, whereas in PFAS itching represents a prominent symptom. In addition, the patient reported symptoms suggest that FIRE occurs in the absence of the typical symptoms of PFAS. Whether the pathogenesis of FIRE symptoms are represented within the context of EoE or are unrelated is not certain but recognition of this syndrome may provide initial clues toward establishing the diagnosis of EoE.

Based on multiple clinical observations made by EoE-experienced physicians in the US and in Europe, and based on a comprehensive assessment of its features from expert- and patient-perspectives, we can provide a fairly clear picture of FIRE, identified by the following most important characteristics:

- First, FIRE is characterized by pronounced retrosternal symptoms strictly linked to the ingestion of a specific food or beverage, usually appearing shortly after the exposure with a latency of less than 5 minutes with limited duration, as most patients perceive symptoms for less than 30 minutes.
- Second, despite the rather limited temporal impact of the symptoms, FIRE has a considerably high symptom intensity, graded by at least half of the patients as 7 or more on a 1-10 visual analog scale. Likewise, and in addition to the intensity of the symptoms, the impact on the patient is exemplified by the character of associated symptoms including perceptions of anxiety as well as chest pains or burning sensations in about 30 to 40% of patients. As a consequence, patients usually try to carefully avoid further exposures.

- Third, FIRE appears to be associated with distinctive baseline characteristics of the underlying EoE, in particular a younger age at symptom onset and at diagnosis, a high incidence of co-morbid atopic disease and a high prevalence in men with previous food bolus impaction requiring endoscopic removal.

Our data show that FIRE has a surprisingly high prevalence among adult EoE patients. EoE expert estimates reach 20%, whereas patient reports reach close to 40%. However, it is uncertain whether this syndrome is strictly linked to EoE or if it affects patients without EoE. To date, no corroborative reports have been published.

The detailed clinical description of this phenomenon suggests that under the conditions associated with EoE contact of specific foods with the esophageal surface can rapidly and reproducibly evoke impressive symptoms. Of note, today the mechanisms leading to this phenomenon remain undetermined. It is even possible that more than one mechanism may be involved. The definition of this symptom complex is therefore currently formulated without requiring determination of the pathogenesis. Interestingly, a small study reported an immediate (and also a delayed) response in the esophagus upon the injection of six different allergen extracts in patients with EoE but not in control subjects (9). In addition, some similarities with PFAS and the high co-morbidity with allergic diseases are indicators that, in at least a portion of the patients, an immediate allergic response of the esophageal mucosa likely induces the symptoms of FIRE. A chemical irritation of the inflamed mucosa and the well-known hypersensitivity of the esophagus in EoE (10) are other potential explanations for FIRE in some patients. A more detailed understanding of the pathogenic mechanisms underlying this immediate local reaction has the potential to improve our overall understanding of immune reactions in the esophagus and perhaps the genesis of symptoms in EoE.

Results of several studies treating EoE with protein-free elemental diets have consistently shown that EoE is triggered by food proteins in over 90% of the patients. (11) The identification and elimination of causative foods offers the option of a drug-free treatment. Of note, EoE is not simply an IgE-mediated food allergy. (12, 13) Unfortunately, the search for causative foods is still a challenge, because IgE-based tests

– e.g. skin prick tests, determination of food-specific serum IgEs – do not reliably identify triggering foods in EoE. If and how many patients with FIRE have positive skin tests to the foods that trigger their FIRE remains to be determined. Whether foods and beverages triggering FIRE are causing EoE as well remains to be clarified. Of note, there was only a small overlap between food items associated with EoE with the identified triggers of FIRE, such as for instance with milk, which was however more frequently identified as a FIRE trigger by physicians as opposed to patients. It remains unclear, if triggers of FIRE might sustain or even cause EoE. In this respect, the temporal relationship with FIRE symptoms antecedent to EoE diagnosis in about a third of patients is noteworthy also in view of the discussion of a potential causal relationship of oral immunotherapy in IgE-mediated food allergies and subsequent de novo EoE (14). In case of such a potential relationship of FIRE triggers and EoE, FIRE could aid in identifying foods that should be eliminated from a given patient's diet, although because of the severity of their FIRE symptoms, most patients avidly avoid them anyway.

Our work has several strengths and limitations. The confirmation of this newly observed phenomenon by a large group of physicians with significant experience in the field of EoE in several European countries and the USA represents a strength. Further, our findings are based on a comprehensive survey of both EoE-experts and patients affected by EoE. Answers to the questionnaires from physicians and patients were anonymized and most importantly, patients responded to the questions without input from the physicians treating their EoE, which would have invariably introduced the potential of bias or (involuntary) suggestion towards any desired responses. Finally, the high response rates to physician- and patient-questionnaires considerably minimized the risk of response bias.

Certainly, our study has several limitations. We cannot rule out the possibility that physicians and patients participating in the surveys were prone to suggestion due to the simple description of the possibility of such an immediate response upon food ingestion at the beginning of the questionnaire. However, we deliberately designed the introductory wording of the questionnaires to be as short and neutral as possible. Evidently and as applies to every questionnaire study, our investigation remains on a completely descriptive level. Our study did neither objectify endoscopic/histologic disease activity nor

concomitant medication. We also did not perform any longitudinal analyses regarding intensity of FIRE symptoms during induction treatment for EoE. We therefore cannot determine, whether disease activity or lack of response to initiated treatments for EoE impact on FIRE symptoms. According to the limited available information from the questionnaires FIRE does not appear to be strongly related to persistent esophageal inflammation or refractory disease. Physicians' and patients' responses were rather congruent although reflecting some uncertainty, with roughly a third in favor of an association of disease activity and FIRE, whereas the majority of responders were either uncertain or considered FIRE to be a phenomenon independent of disease activity of underlying EoE (the latter reported by almost 40% of patients). By design of the study, the classification of patients' symptoms was not physician based but patient reported. Therefore, we cannot absolutely rule out, that an erroneous overlap with PFAS occurred in a few patients. However, amongst our patients with FIRE, none reported an exclusive localization of symptoms in mouth/tongue and/or throat, i.e. all patients reported symptoms in their esophagus (behind the breastbone) and/or chest and/or upper abdomen. Furthermore, due to the design of this study we cannot determine, whether there are differences in FIRE triggers between the United States or Europe.

In conclusion, this is the first systematic report on FIRE, a novel clinically defined syndrome characterized by an intense, localized, esophagus-attributed sensation, occurring in a large portion of EoE patients rapidly after, and linked to, the ingestion of a specific food or beverage. Despite some similarities, FIRE symptoms are different from symptoms of PFAS. Further investigation of the phenomenon FIRE will ultimately advance our current understanding of the overall pathogenesis of EoE and better define the overlap of EoE with other atopic diseases.

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TABLE

Table 1

Patient number, n	239
Sex, male/female, n (%)	168/71 (70.3%/29.7%)
Current age; years, mean (range, SD)	51 (20-89, 14.4)
Age at symptom onset; years, median (range, IQR)	31 (6-79, 20-44)
Age at diagnosis; years, mean (range, SD)	40.2 (6-85; 14.5)
Diagnostic delay; years, median (range, IQR)	5 (0-52; 1-12)
Presence of allergic diseases, n (%)	139 (58.2%)
History of bolus obstruction, n (%)	81 (33.9%)

Table 1. Demographic and disease-specific characteristics of the EoE patients included in the survey

FIGURE LEGENDS

Figure 1: Estimated Prevalence of FIRE Symptoms within the EoE-Population.

The percentage of EoE-patients affected by FIRE as estimated by EoE experts (percentage of EoE expert physicians on y-axis) is depicted (unsure refers to the answer “I can’t decide this according to my current experience”).

Figure 2: Typical duration of FIRE symptoms and latency.

The estimated typical interval between ingestion of FIRE-triggering agent and occurrence of symptoms (A) and the estimated typical duration of FIRE symptoms (B) as estimated by EoE-experts (percentage of EoE expert physicians on y-axis) are shown (sec. = seconds; min. = minutes; h. = hours).

Figure 3: Age and diagnostic delay in FIRE vs. No-Fire patients. Current age, age at symptom onset and at diagnosis, as well as diagnostic delay according to presence or absence of FIRE are depicted (error bars represent standard deviation).

Figure 4: Intensity of FIRE symptoms.

The reported intensity of FIRE symptoms according to a Visual analogue Scale (VAS) from 1-10 with the number of patients (y-Axis) is depicted.

Figure 5: Duration and latency of FIRE.

Temporal sequence of FIRE with latency (A) of symptoms and duration (B) upon ingestion of provoking food items.

Figure 6A, B: Pareto chart of most the frequent triggers (A, multiple answers possible) and characteristic features (B, multiple answers possible) of FIRE.

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Patients had to report in a free-text field those foods or beverages they considered to induce FIRE symptoms. Several items not fitting in one of the categories are reported as “miscellaneous”, including mustard, chestnut, meat, chocolate, rice, and bread (A).

Patient were to report from a given selection of characteristic features with multiple selections possible (from 1 – if only one feature - to 12 – if all given features would apply, B). Cumulative frequency of all given answers is depicted by the orange line and represented on the right y-axis.)

CONFLICT OF INTEREST STATEMENT

Dr. Biedermann reports personal fees from Dr. Falk Pharma, personal fees from Vifor AG Switzerland, personal fees from Esocap AG, personal fees from Sanofi-Aventis AG, personal fees from Calypso Biotech AG outside the submitted work. Dr. Holbreich, Dr. Atkins, Dr. Dellon, Dr. de Rooij, Dr. Safroneeva, Dr. Schoepfer, Dr. D. Simon, Dr. HU Simon, Dr. Warners and Dr. Straumann have nothing to disclose. Dr. Chehade reports grants from NIH (R01-AI140133, U54-AI117804), grants from PCORI, grants from APFED/AAAAI, grants and personal fees from Regeneron, grants and personal fees from Shire, grants and personal fees from Allakos, personal fees from Adare , personal fees from Nutricia, personal fees from Medscape, personal fees from Annenberg Center for Health Sciences, outside the submitted work. Dr. Furuta reports other from EnteroTrack, grants from Holoclara, grants from National Institutes of Health, other from Shire/Takeda, outside the submitted work. Dr. Hirano reports personal fees and other from Shire/Takeda, personal fees and other from Regeneron/Sanofi, personal fees and other from Adare, personal fees and other from Allakos, personal fees and other from Receptos/Celgene, personal fees and other from AstraZeneca, personal fees from Gossamer, personal fees from Arena, personal fees from Esocap, personal fees from Lilly, outside the submitted work. Dr. Gonsalves reports personal fees from Allakos Inc, personal fees from Up To Date, outside the submitted work. Dr. Greuter reports grants from Novartis Research Foundation, personal fees from Falk Pharma, grants from Vifor, outside the submitted work. Dr. Katzka reports grants from Shire, outside the submitted work. Dr. Schreiner reports personal fees from Pfizer, personal fees from Takeda, personal fees from Janssen-Cilag, outside the submitted work. Dr. Bredenoord reports grants from Nutricia, grants from Norgine, grants from SST, grants from Bayer, personal fees from Laborie, personal fees from Arena, personal fees from Esocap, personal fees from Medtronic, personal fees from dr Falk Pharma, personal fees from Calypso, personal fees from Reckett Benkiser, personal fees from Regeneron, personal fees from AstraZeneca, other from SST, outside the submitted work.

AUTHOR CONTRIBUTION

AS and MH initiated the study and organized group meetings. All authors participated on group meetings prior to design of physicians' questionnaires. LB, MW, AS and AJB created the physicians' questionnaire, MW and LB performed the analysis. All authors analyzed the physicians' questionnaire and provided critical input for the patients' questionnaire. LB, PS, TG, AS, ES and Asch created the patients' questionnaire. LB analyzed the patient data. LB and AS drafted the manuscript. All authors gave critical feedback at the time of analyzes of the patient data and drafting manuscript. All authors critically read the the manuscript and edited the draft version. All authors approved the final manuscript.

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