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Psychosocial mediators of change and Patient Selection Factors in Oral and Epicutaneous Immunotherapy Trials

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Abstract

Research into Health Related Quality of Life (HRQL) in food allergy has helped to raise awareness of patient issues and provided a means of individualized assessment for a patient or parent. Immunotherapy is now a hot topic of research. There is clear movement toward making Oral immunotherapy (OIT), and increasingly Epicutaneous immunotherapy (EPIT) viable treatment options for patients with food allergies. The use of HRQL measures in OIT and EPIT can widen the parameters of benefits & harms of these new treatments and allow for the development and improvement in process and outcome quality indicators.

However, there are particular patient related factors that need to be taken into account to allow immunotherapy to fully realise their potential as a beneficial treatment beyond the research setting, over and beyond safety, tolerability and efficacy boundaries. One of the most important questions in OIT/EPIT relates to understanding what aspects (if any) of HRQL improve for whom, and how and why does this improvement may occur.

This paper examines the association between treatment outcomes and HRQL. A clear understanding of this relationship will facilitate the design of optimally effective interventions & treatments. We suggest methods and designs to better understand the role of HRQL in immunotherapy treatment trials that will enable better modelling of the costs, risks, and benefits of this promising therapy.

Introduction

Food allergy is a major public health concern affecting up to 20 million European citizens, including around 1 in 20 infants, with high costs to public health services (1-4). Ninety percent of food allergy is caused by 8 foods (milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish). Allergy to peanut, tree nut, fish, shellfish, and sesame seed are considered to be life-long in 80-90% of cases, and potentially severe. Reactions can occur upon initial exposure, and from minimal quantities. Symptoms range from mild (itching, swelling, hives, etc.) to more systemic (gastrointestinal, cardiac, respiratory, or multi-system involvement). Allergen avoidance and self-injectable epinephrine is the current standard of treatment for food allergy, but accidental ingestion is common, causing frequent and sometimes life-threatening reactions (10-12). Admission rates for anaphylaxis, a systemic hypersensitivity reaction that can be rapidly fatal, have increased approximately 3-fold between2005 and 2012 (5-9) +new). In the US, prevalence has doubled in 10 years, leading to >300,000 annual hospital visits with estimated costs of $24.8 billion annually (7). Those most at risk of anaphylaxis have IgE-mediated food allergy (approximately 5% to 8% of US children and 2% to 3% of adults). Up to 5.1% of US citizens are estimated to have experienced anaphylaxis and 1% of hospitalizations and 0.1% of emergency department attendances for anaphylaxis have a fatal outcome (7). It is not surprising therefore that health related quality of life (HRQL) has been found to be strongly negatively affected.

Quality of life (QOL) is a broad multidimensional concept that includes subjective evaluations of both positive and negative aspects of life, including multiple life domains such as jobs, housing, and health. HRQL is health-focused and may include physical and mental health perceptions and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status .Environmental aspects may also be assessed including policies and practices that may impact health perception at a population level. Patient reported outcome measures (PROMs) particularly HRQL questionnaires are increasingly being used in medical and health research. HRQL is useful in evaluating new policies, technologies, regulations or clinical practices and for guiding decision making when there is a trade-off between treatment and HRQL (31-34). HRQL measures can be generic or disease specific. The development and increased use of disease specific Health Related Quality of Life (HRQL) measures have ensured that the impact of medical conditions and/or treatments are now being evaluated from the perspective of their impact on the specific patient's everyday life. This construct is consistent with the emphasis on "patient centered care" (health care responsive to the person's wants, needs, and preferences), a principle stressed in the Institute of Medicine reports on quality (35) and in the Australian Commission report on Quality and Safety in Healthcare (36).

Research has shown that food allergy specific measures are valid, reliable and are responsive to important clinical changes (37-47). HRQL measures developed specifically for food allergy are more reliable indicators of the positive and negative impact of disease and treatment than clinical opinion or the measurement of objective symptoms . Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) emphasise that outcome measures selected for a study should be well targeted to the specific patient population, which fundamentally rules out the use of generic PROMs (48-51). Both bodies now consider the most widely used generic PROM, the SF-36, to be unsuitable for making claims about the value of treatments.

Research into HRQL in food allergy has helped to raise awareness of patient issues and provided a means of individualized assessment for a patient or parent. The Food Allergy Quality of Life Questionnaires (FAQLQ) are disease-specific developmentally appropriate measures (53-54) that have been developed to assess HRQL in food allergy for all age groups and parents and are the most frequently used HRQL tools in food allergy research and practice. These include the Parental Burden (PB), Parent Proxy Form (PF), the Child-form (CF), the Teen form (TF) and the Adult form (AF). The questionnaires can be used to measure cross-sectional differences in quality of life between patients at a point in time - or longitudinal changes in HRQL.

Evidence shows that HRQL in food allergy is impacted by a multiplicity of factors including : uncertainty and fear of reactions; food anxiety, and dietary and social restrictions (13-19). HRQL may be moderated by development, age and gender; country, co-morbidity and poly-allergy; mental health and personality, coping style and self-efficacy (20-27). Environmental factors also play a role in perception of HRQL by patients, including health care professional and general population attitudes and beliefs, food and ingredient labelling, legislation and health and industry policy and practices (25-30).

The most significant impairment seen in research on the psychosocial impact of food allergy is the persistent fear of an adverse reaction (13-19). With this in mind, it appears intuitive that a treatment that induces tolerance (or sustained unresponsiveness) would improve the lives and safety of patients, particularly for peanut allergy.

Recent studies have explored the efficacy of immunotherapies such as oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) immunotherapies (54-65). In a systematic review in 2017, the European Academy of Allergy and Clinical Immunology (EAACI) assessed evidence on the effectiveness, safety and cost-effectiveness of Immunotherapy for IgE-mediated Food Allergy

(61). Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated SLIT, and one study evaluated EPIT. The majority of these studies were in children. Twenty-seven studies assessed desensitization, and eight studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR) = 0.16, 95% CI 0.10, 0.26) and suggested, but did not confirm sustained unresponsiveness (RR = 0.29, 95% CI 0.08, 1.13). Only one study reported on disease-specific HRQL, which reported no comparative results between OIT and control group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis, excluding those studies judged to be at high risk of bias, demonstrated the 'robustness of summary estimates of effectiveness and safety of AIT for food allergy'(61). None of the studies reported data on health economic analyses. Between studies, protocols are diverse (food allergens preparation, procedures related to dose escalation, maintenance and OFC . However, desensitization has been achieved and systems underlying immunologic changes after immunotherapy have been shown. In studies of OIT, adverse reactions were usually localized, but severe systemic reactions were observed in certain populations (58; 61-62). Studies of SLIT have demonstrated minimal side effects, but overall efficacy is lower than that seen with OIT (60-63).

It appears, therefore, that there is clear movement toward making Oral immunotherapy (OIT), and more recently EPIT, viable treatment options for patients with food allergies. The use of HRQL measures in OIT and EPIT can widen the parameters of benefits & harms of these new treatments and allow for the development and improvement in process and outcome quality indicators (64).

However, there are particular patient related factors that need to be taken into account to allow OIT and EPIT to fully realise -potential as a beneficial treatment over and above safety, tolerability and efficacy boundaries. One of the most important questions in OIT relates to understanding what aspects (if any) of HRQL, improve for whom, and how and why does this improvement occur. A clear understanding of the relationship between treatment outcomes and HRQL will facilitate the design of optimally effective interventions & treatments. We can then identify critical intervention components that influence behavioural (during and following treatment) and other mediators that impact therapeutic outcomes (64,65). We will also be able to elicit the critical time-points for administration of such measures, which can inform standardisation of treatment protocols.

This paper will investigate the impact of OIT/EPIT on patient related outcomes in studies that have used HRQL measures. In the Discussion, we will suggest methods and designs to better understand the role of HRQL in trials that will enable better modelling of the costs, risks, and benefits.

The paper does not focus on selection of questionnaires, which requires consideration of several key quality standards, including the development processes, instrument scaling, psychometric properties and cultural translation and adaptation processes. These issues have been discussed elsewhere (52, 53).

Although allergen immunotherapy has been used to treat allergic diseases since the early 1900s (65-66), to date, there is limited patient related outcomes based research into food allergy OIT.

For food allergy, the major forms of immunotherapy are oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Oral immunotherapy (OIT) was first used successfully in 1908 in a child with severe egg-induced anaphylaxis (66, 67). After this, it was not until 1984 that Patriarca et al (68) published results of a successful OIT for milk, egg, fish, and orange allergies. Within the last 12 years, the pace of research into allergen-specific immunotherapies has increased (66).

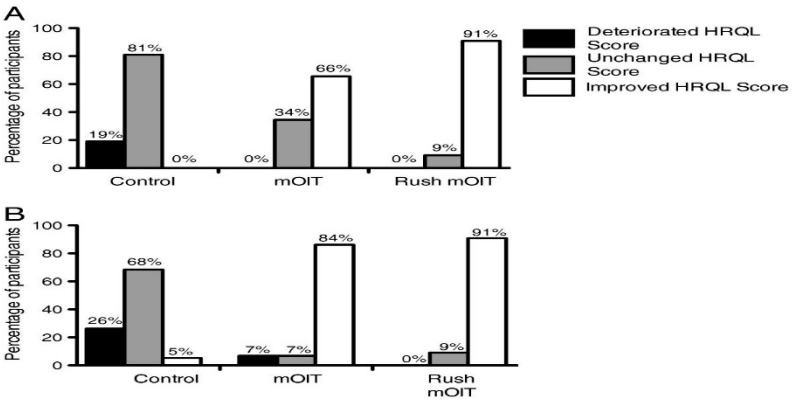
With OIT, the possibility of success must be weighed against risk, for example the annual rate of severe reactions in peanut allergy is 1.6 % (67, 68). In their retrospective study of 5 clinical practices performing peanut OIT in the USA, Wasserman and colleagues (69) reported 95 uses of epinephrine in 352 patients over an average of 1.8 y (annual rate of 22%). However, in the clinical setting severe reactions are anticipated, recognized and treated promptly. Only 3 of the 95 reactions required a second epinephrine and none required more intensive treatment (69). More importantly, it should be noted that from a patient's point-of-view, severe reactions in the context of diagnosis are generally acceptable since food allergy is associated with a decrease in quality of life mainly due to the anxiety of potential reactions and secondary social and nutritional impact (68). The context of "expected" reactions with OIT differs from the uncertain but potential accidental reactions with avoidance. DunnGalvin et al (70) examined factors related to HRQL, that may influence parents' decision to allow their children to participate in research on clinical food allergy. Parents of children with food allergies were offered investigational oral immunotherapy (OIT) in a regular outpatient clinic. Forty parents (group A) declined, and 25 parents (group B) agreed to take part. Both groups agreed to complete the Food Allergy Quality of Life–Parent Form and the Food Allergy Independent Measure. Children were aged between 1 and 12 years (mean: 6.5 years). Groups A and B displayed a similar and typical distribution for gender, age, number of foods, severity and number of symptoms, and socioeconomic variables. Parents who chose to enrol their children in the OIT trial reported a similar impact of food allergy on the HRQL of their children as parents of children who did not volunteer for the study. Participating parents perceived a significantly higher likelihood (odds ratio: 6.8) of their child having a severe reaction and dying if food is ingested. By using this model, the likelihood of taking part in immunotherapy could be predicted accurately in 90% of cases. This study, together with the finding that a food challenge (open or double blind) may be valuable, not only as a diagnostic tool, but as a therapeutic one (14) has implications for the selection, recruitment and management of patients in OIT trials. The results suggest that, irrespective of outcome, a safe context and meaningful information may impact positively on HRQL,

in contrast to the constant fear of accidental reactions and uncertainty of day to day living with food allergy.

Results from a qualitative study carried out in the US, suggest that OIT/EPIT operates as a buffer against an accidental exposure and is a major motivator for entering a child in peanut allergy therapy (71). Nineteen semi-structured interviews of OIT/EPIT participants were conducted with caregivers. The coded transcripts and main themes show that caregivers of peanut allergic children enrolled in OIT/EPIT phase III trials are motivated by the potential of decreased reaction severity upon exposure, increased time to react to allow for assessment by others, or increased threshold of peanut exposure tolerated. Interestingly, caregivers reported that trial participation decreased their anxiety secondary to experiencing a severe allergic reaction that was promptly treated.

In 2014, Otani and colleagues (72) investigated multiple food allergens oral immunotherapy (mOIT) on FA-specific HRQL in the caregivers of participants with multiple, severe food allergies. Caregiver HRQL was assessed using the Food Allergy Quality of Life – Parental Burden (FAQL-PB) Questionnaire, developed by Cohen (2004). Parents of participants in two single-center Phase I clinical trials receiving mOIT (n = 29) or rush mOIT with anti-IgE (omalizumab) pre-treatment (n = 11) completed the FAQL-PB prior to study intervention and at 2 follow-up time-points (6 months and 18 months). Parents of subjects not receiving OIT (control group, n = 10) completed the FAQL-PB for the same time-points. Caregivers of participants in the mOIT group (n = 29) had a significant improvement in HRQL score at 6-month follow-up (mean 2.5, 95% CI 2.0-30) and 18-month follow-up (mean 1.8, 95% CI 1.4-2.1) compared to baseline ($p < 0.0001$). Caregivers of participants in the rush mOIT group (n = 11) also had a significant improvement in HRQL score at 6-month follow-up (mean 1.7, 95% CI 0.9-2.6) and 18-month follow-up (mean 1.3, 95% CI 0.3-2.4) compared to baseline ($p = 0.001$ and $p = 0.005$, respectively). HRQL worsened significantly ($p < 0.01$) in the control group (n = 10) from baseline (mean 3.6, 95% CI 2.9-4.3) to 6-month follow-up (mean 4.3, 95% CI 3.9-4.8) although at the18-month follow-up , scores were comparable to baseline HRQL . The authors did not find an association between the number of foods or adverse events and the change in HRQL score in either group although they attributed this to a possible lack of power for a sub-group analysis (Figure 1).

Figure 1 : Percentages of participants with deterioration, no change, or improvement in HRQL scores.



Percentages of participants whose HRQL scores deteriorated (change > 0.5), remained unchanged (change between -0.5 and 0.5), or improved (change < -0.5) in the control group, mOIT group, and rush mOIT group at **(A)** 6-month follow-up and **(B)**18-month follow-up.

Although this was a Phase I study and was not placebo-controlled**,** the findings are important in that the efficacy of OIT is typically measured by the ability to tolerate food allergen after discontinuation of therapy (clinical tolerance or sustained unresponsiveness). As in the studies described above, this finding shows that the intervention or treatment itself, in this case desensitization even without discontinuing therapy, provides significant and persistent improvement in caregiver quality of life. This positive impact may have been reinforced by specialist consultation, personalized information and interaction with other children with food allergy during treatment.

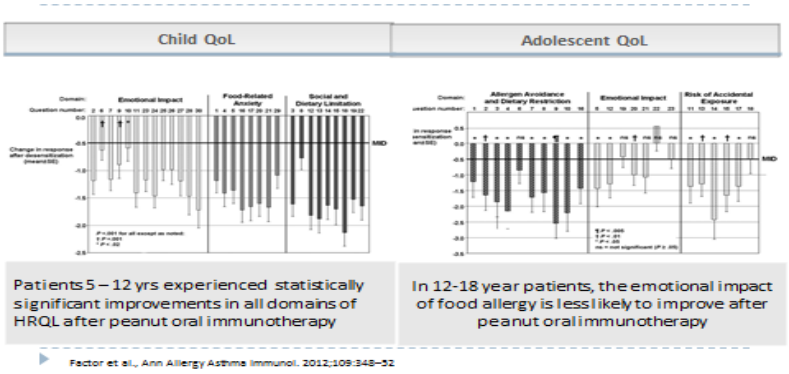
The same authors carried out a follow up study in 2014 with a new population, a larger sample size (n = 57) and a longer follow-up of 24-months (73). Factors associated with worse or improved HQRL scores were examined, including age, asthma, and respiratory allergic reactions during therapy. The same parent answered the FABQL-PB questionnaire at baseline and for 6-month, 12- month, 18- month, and 24-month time points. The authors report that this study lacked power to detect significant differences between some types of food allergens and between quality of allergic reactions (severe, moderate vs. mild). There was no untreated control group. Results showed that caregiver HRQL improved significantly (change < - 0.5, p <0.0001) at each follow-up time point compared to baseline. The percentages of caregivers with improvement in HRQL progressively increased (92% at 24 month-follow-up time point compared to baseline). Results showed more improvement in caregivers of participants older than 10 years or desensitized to more than 4 food allergens (p <0.0001). Caregivers' HRQL scores of 6 subjects treated with cow's milk had a significantly greater improvement (p =0.006) than subjects treated with other food allergens (n =31). This improvement was detected most significantly in the questions regarding the concern about child's nutrition (p <0.001), the need

to spend extra time preparing meals (p <0.001) and to take special precautions before going out of the home with their child (p <0.001).

Caregivers of participants with pre-existing asthma or dose-related respiratory allergic reactions had less improvement in HRQL than those who did not (p <0.01). It is possible that these participants may need more tailored support to ensure optimum outcomes in terms of HRQL.

Another study (74) that investigated the effect of oral immunotherapy to peanut on food-specific quality of life was carried out by Factor and colleagues (2012). One hundred patients (5-18 years of age) were enrolled in an open trial of peanut oral immunotherapy. Parents of children 5 to 12 years old, children 8 to 12 years old, and teenagers completed the FAQLQ-PB,-PF,-CF and -TF before and after peanut oral immunotherapy. Ninety patients (76 children 5-12 years old and 14 adolescents 13-18 years old) achieved the maintenance daily dose of 450 mg of peanut protein. A significant improvement in HRQL was found for patients and parents in all survey domains for patients and parents (allergen avoidance, dietary restriction, risk of accidental exposure, emotional impact, food-related anxiety, and social and dietary limitations) with the exception of the 'emotional impact' domain on the adolescents' survey (Figure 2). This suggests that the psychological impact of food allergy has generalised beyond food allergy itself, as described in quantitative and qualitative research on age differences in HRQL (13,20,23) and that early treatment may be important.

Figure 2 : Differences in HRQL outcomes according to age.



Factor et al., Ann Allergy Asthma Immunol. 2012;109:348–52

The STOP II study examined HRQL as a secondary outcome at study end in a phase 2 randomised controlled crossover trial designed to compare the efficacy of active OIT (using characterised peanut flour; protein doses of 2-800 mg/day) with control (peanut avoidance, the present standard of care (57-58). Randomisation (1:1) was by use of an audited online system; group allocation was not masked. Eligible participants were aged 7-16 years with an immediate hypersensitivity reaction after peanut ingestion, positive skin prick test to peanuts, and positive by double-blind placebo-controlled food challenge (DBPCFC). The primary outcome was desensitisation, defined as negative peanut challenge (1400 mg protein in DBPCFC) at 6 months (first phase). Control participants underwent OIT during the second phase, with subsequent DBPCFC.

Desensitisation was recorded for 62% (24 of 39 participants; 95% CI 45-78) in the active group and none of the control group after the first phase (0 of 46; 95% CI 0-9; p<0·001). 84% (95% CI 70-93) of the active group tolerated daily ingestion of 800 mg protein (equivalent to roughly five peanuts). After the second phase, 54% (95% CI 35-72) tolerated 1400 mg challenge (equivalent to roughly ten peanuts) and 91% (79-98) tolerated daily ingestion of 800 mg protein. Side-effects were mild in most participants. Intramuscular adrenaline was used after 0·01% of doses (one participant). Both intervention and control groups showed a similar and clinically meaningful improvement in HRQL in children (FAQLQ-PF) after treatment. A multicenter, randomized, double blind, placebo controlled study, conducted in the USA in 2012 (76) demonstrated that longer duration of therapy led to more successful desensitization (55% at 10 months vs 75% at 22 months), and that sustained unresponsiveness was achievable for a small group (28%). HRQL in children (FAQLQ-PF) was also shown to improve. A

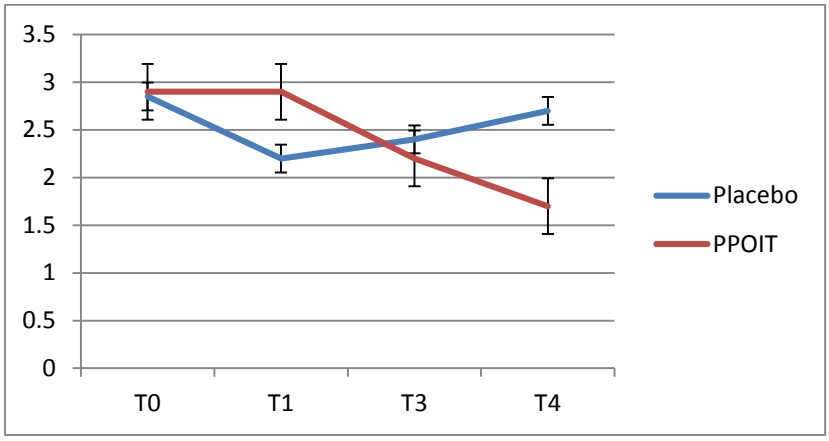
The highest level of sustained unresponsiveness to date as compared with placebo treatment (82% vs 3.6%) was attained by the Probiotic and Peanut Oral Immunotherapy **(**PPOIT) study in a double-blind, placebo-controlled randomized trial. A separate study evaluated the impact of PPOIT on health related quality of life (HRQL) during the course of the trial for both the intervention and control groups (76).

Sixty-two children with peanut allergy, aged between 0 and 10 years at baseline were randomised to receive PPOIT or placebo for 18 months. A double-blind placebo-controlled food challenge (DBPCFC) was performed at 18 months (end-of-treatment, T1) to assess for desensitisation; if this challenge was passed a second DBPCFC was performed 2-6 weeks later to assess for sustained unresponsiveness (T2). Participants who failed the first or second DBPCFC were advised that they remained allergic to peanut and should avoid all peanut in the diet.

Participants who passed both the first and second DBPCFC were informed that they had attained sustained unresponsiveness and were instructed to introduce peanut into the diet and continue intake on a regular basis without specific advice on amount or frequency. The parent study concluded at 3 months after end-of-treatment. In a follow-up study, participants were assessed at 6 months post end-of-treatment by telephone questionnaire and at 12 months post end-of-treatment by clinic visit. The FAQLQ-PF (16-17) and the Food Allergy Independent Measure (26) were administered at: pre-treatment (T0), end-of-treatment (when status of peanut allergy vs tolerance was not yet known, T1); 3-months after end-of-treatment (when status of peanut allergy vs tolerance was known, T3); and 12 months after end-of-treatment (T4).

PPOIT was associated with significant improvement in FAQLQ-PF (F=3.63, p=0.02), with Mean Difference 0.8 at 3 months post-treatment (p=0.05) and 1.3 at 12 months post-treatment (p=0.005), exceeding the 0.5 minimal clinically important difference for FAQLQ-PF. For FAIM, mean difference was 0.5 (p=0.03) at 3 months and 0.4 (p=0.04) at 12 months. In placebo group, post-treatment FAQLQ and FAIM remained unchanged from pre-treatment**.** Improvement in FAQLQ-PF and FAIM scores related specifically to acquisition of sustained unresponsiveness rather than to receiving PPOIT treatment or participation in the trial (Figure 3).

Figure 3 : Mean FAQLQ-PF scores for PPOIT at T0 (pre-treatment); T1 (end-of-treatment); T3 (3 months post end-of-treatment); T4 (12 months post end-of-treatment).



**Lower scores indicate lower burden or better HRQL.* T0: Pre-treatment, T1: end-of-treatment, T3: 3 months post end-of-treatment, T4: 12 months post end-of-treatment.

With regard to the balance between patient benefits and harms, PPOIT treatment did not negatively affect HRQL or key aspects of emotional impact, food anxiety and limitations on social and dietary factors during the treatment phase. Furthermore, HRQL in placebo

participants was not reduced following treatment and was slightly improved during the treatment phase, particularly in the 'food anxiety' subscale. This is likely to stem from supports provided by staff during the trial and reflects the findings of previous research in OIT/EPIT and on food challenges (70-73). Moreover, although improvement in HRQL in the placebo group was transient, there may be some long-term benefit in reframing an individual subject's sense of control over their disease and consequent concerns and anxiety. A further analysis of the longitudinal follow up data (paper in preparation) shows an incremental improvement in HRQL with progressive increase in peanut ingestion in PPOIT group, and a slight continued benefit for Placebo group.

Discussion

Changing the natural course of disease in patients with food allergy is a hot topic of research. Recent research in food allergy treatment has focused on developing safe and effective therapies, and the most active area of research for food allergy involves immunotherapy (66).

Health related quality of life (HRQL) is influenced by physiological, psychological and environmental variables and can be best understood by considering the interactions of factors that cut across multiple levels.

To generate new and generalizable scientific knowledge, it is important to understand an intervention's mechanisms of change, as this understanding can identify critical intervention components that influence behavioural and other mediators that in turn influence the intended therapeutic outcomes.

It is important that the patient perspective is at the centre of new developments in therapy. Therefore evidence-based research aimed at exploring the effects of interventions on outcomes in food allergy are needed, including the influence of patient and parent factors on protocol design. In a systematic review to the earlier EAACI paper on OIT/EPIT for IgE-mediated Food Allergy (77), Dhami and colleagues examined such trials in allergic asthma. The authors recommended greater standardization of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes so as to facilitate evidence syntheses and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Treatment success in all clinical trials, may be defined not only by desensitisation or sustained unresponsiveness but by improved HRQL, on an interaction between the two. Both may depend on tailoring interventions to the characteristics and needs of patients.

Identification of predictors could optimise treatment by helping both implement appropriate, suitable and specific approaches that will benefit patients. The decision to offer any treatment should ideally be carefully matched to a particular patient profile. An example may be the case where a patient or parent has a strong fear of a severe reaction if an allergen is accidentally ingested, and/or believes that there is a high chance that such an event may occur. The ability of OIT treatment to lower thresholds may therefore be very persuasive. Such a patient or parent are also likely to adhere closely to any regimen to ensure that they – or their child- is safe and consequently are less likely to withdraw from the trial. In contrast, if fear is low, impact of food allergy on HRQL is low and confidence in management is high, a potential participant may not

benefit to any great extent. In either case, the severity of past reactions may not be a deciding factor since HRQL is subjective and expectation of a severe reaction may be more damaging to HRQL even if a child has experience no or only mild reactions to date. Furthermore, even the most effective therapy may prove problematic for a patient that has poor management strategies that render it difficult for them to adhere to a complicated treatment regimen and are therefore also more likely to withdraw from a clinical trial.

Treatment adherence and patient drop out is a significant problem in all clinical trials, impacting the reliability, validity and interpretation of results. Monitoring HRQL and other patient related constructs, such as management self-efficacy, satisfaction and engagement, can help in this regard. For example, some patients may be unable to maintain a regimen without a strong system of support and prompts and reminders. Distance to a clinical or trial centre may be a problem for others. Side effects may tip the cost/benefit balance, particularly for parents of very young children. Older children and teens may resist following rules and a strict regimen.

Clinical trials provide a tremendous opportunity for more in-depth study of how patient preferences may influence decision-making and the costs, risks, and benefits of oral immunotherapy. Patient reported outcomes are relatively poorly defined to date. In a systematic review in 2017, the European Academy of Allergy and Clinical Immunology (EAACI) assessed evidence on the effectiveness, safety and cost-effectiveness of OIT/EPIT trials for IgE-mediated Food Allergy (77) and found that more data are needed in relation to adults, long term effects, the impact on HRQL and cost-effectiveness.

Timing of measurement is also important. A standardised protocol that incorporates HRQL and other relevant PROMs and agreed definitions of outcomes would allow for the comparison of efficacy of food allergy treatments between centres, trials or countries. To this end, it is vital that patient related outcomes such as improved HRQL, are seen as a primary outcome, and are measured at multiple intervals during the trial duration and beyond. Since HRQL has only been studied in relatively few oral immunotherapy trials to date, primarily looking at caregiver HRQL, it is unclear which factors, measures or subscales are most predictive of short and/or long term treatment outcomes for which type of patient, and which time-points for measurement are most informative.

Data is also needed to determine whether the outcomes of sustained unresponsiveness and desensitization have a different impact on HRQL, ideally through comparing HRQL measures within a randomized trial. If HRQL improves if a patient threshold is raised, even if sustained unresponsiveness is not achieved following treatment, benefit may still accrue for patients.

The creative use of methods and designs (both qualitative and quantitative) to better understand the role of HRQL in immunotherapy treatment trials will enable improved modelling of the costs, risks, and benefits of any treatment. Systematic analysis and modelling of antecedent factors, mediators, and outcomes will be important to boost intervention effects and to maximize the overall benefits of treatment. For example, an increased understanding of the interplay between HRQL and self-efficacy would allow the clinician to select interventions that are appropriate and targeted specifically to that patient. Environmental factors, including community and socioeconomic variables that can enhance or diminish the effect of the treatment on targeted therapeutic outcomes, should also be included in a pathway or care model.

Decision science modelling is another method that could help us understand variations in preferences for treatment, which could affect the health and economic impact of food oral immunotherapy. Assessment of patient/caregiver attribute preference and how this translates to health economic outcomes will provide a basis to understand if strategies used in food allergy can deliver value-based care, which can be applied to the development of future food allergy research. Utility valuations should be derived from responses to disease-specific HRQL instruments, providing more accurate measurement of this construct .

Oral immunotherapy in food allergy is a promising and exciting development that has the potential to change the course of food allergy and hence the course of patient and family everyday lives. OIT is technically not yet FDA approved in the US, however the expectation that there will be an approved use in the US within the next 2 years, gives impetus and imprimatur to the development of novel and innovative ways of examining it's impact on HRQLQ Recognizing the nuanced and diverse role of HRQL in food allergy may constitute an important step in selecting and supporting those patients for whom a therapy is appropriate and who will benefit most from a particular treatment. It can also help us to tailor interventions to the characteristics and needs of patients and to provide targeted supports for patients who would benefit from these treatments, but only with specific care.

In summary, understanding differences and changes in the key patient related factors in immunotherapy studies, using outcome measures such as HRQL, can improve patient communication and adherence, allow for more nuanced outcomes and findings, and ultimately optimise patient outcomes during and following trials and treatment.

Compliance with Ethical Standards

Conflicts of interest.

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