

## Appendix 4: Narrative summaries of clinical evidence per set of recommendations

### Recommendations on patient-centered care

Four studies in which parents completed the FAQLQ-PF questionnaire (a validated HRQoL instrument in food allergy) regarding the HRQoL of their allergic child both at baseline and after the build-up phase reported statistically and clinically significant improvements in the Total score,<sup>1,89,91,92</sup> with the greatest improvements in the Food Anxiety domain.<sup>89,91</sup> Two of them had randomized<sup>89</sup> or non-randomized<sup>91</sup> control groups, in which HRQoL did not change significantly.<sup>89,91</sup> The RCT observed that 77% of OIT patients reported clinically significant improvement in the Total score three months after completion of double-blind treatment compared to 34% of patients that had been randomized to placebo (P=significant),<sup>89</sup> with achieving sustained unresponsiveness significantly associated with larger QoL improvements.<sup>89</sup> FAQLQ-PF data for 66 patients from one Canadian OIT clinic also showed significant improvements upon completion of OIT (data on file). In contrast, in one double-blind peanut OIT RCT there were no statistically significant changes in FAQLQ-PF scores in the OIT arm, although there were numerical improvements.<sup>2</sup>

Two of the FAQLQ studies included self-reported data from a small number of children and teenagers (N=17 and 46);<sup>2,92</sup> these reported significant improvements from baseline in the Total score and in most of its sub-domains.

One open-label RCT<sup>90</sup> used the generic Pediatric Quality of Life Inventory Version 4.0 questionnaire. The mean total score improved significantly from baseline to year 2 in the OIT group in both the children and their parents, with no significant changes in the control group; differences in the changes were statistically significant for the parents only.

In a longitudinal study following 175 children, the mean FAQLQ-PF scores improved from baseline through mid-up-dosing to reaching maintenance and further at 6 months into maintenance, with the greatest improvements seen during maintenance.<sup>91</sup> In this cohort, a subset

of patients reported deterioration in QoL during mid-up-dosing with a return to baseline levels upon reaching maintenance.<sup>91</sup> Having a history of anaphylactic reactions and worse food-allergy related QoL at baseline was associated with larger QoL improvements.<sup>91</sup> The type of food allergy treated (peanut, egg, milk) was not significant, but having multiple food allergies (in the context of single-food OIT) was associated with less positive QoL outcomes.<sup>91</sup>

## Recommendations on eligible food allergens and clinical outcomes that can be achieved by OIT

A majority of patients undergoing OIT tolerate a higher amount of all food allergens at the end of the build-up phase (*at least partial desensitization*: peanut: 73-90% [<sup>31</sup>see note under Figure 1],<sup>9,56</sup> chicken's egg: 82%,<sup>30</sup> cow's milk: 78-89%,<sup>14,15,29</sup> hazelnut: 65%,<sup>27</sup> sesame: 100%<sup>28</sup>), a significantly higher proportion compared to control patients in all controlled studies (Figure 1). (Note: For peanuts, an increase in the eliciting dose from less than 100 mg to 300 mg peanut protein was estimated to provide an at least 95% reduction of the risk of an allergic reaction stemming from exposure to traces of peanut in packaged foods.<sup>93,94</sup>) Many patients can tolerate a full serving (*complete desensitization*: chicken's egg: 45-84%,<sup>20,30</sup> cow's milk: 60-71%,<sup>13-15</sup> wheat: 52-64%,<sup>24,25</sup> walnut: 89%,<sup>26</sup> sesame: 88%<sup>28</sup>) or a cumulative dose of at least 1 g peanut protein (4.2 peanuts) (56-78%) (Figure 1).<sup>8,31</sup> A sizable proportion of patients continue consuming the food allergen regularly in the longer term (*continued consumption*: peanut: 35-78%,<sup>7,61</sup> chicken's egg: 58-70%,<sup>60,62</sup> wheat: 39%,<sup>25</sup> walnut: 70%,<sup>26</sup> hazelnut: 65%,<sup>27</sup> sesame: 88%<sup>28</sup>) and a variable proportion can maintain tolerance to the allergen after a period of food avoidance (*sustained unresponsiveness*: peanut: 13-74%<sup>4,8</sup> chicken's egg: 35-44%<sup>29,63</sup> cow's milk: 21%,<sup>67</sup> wheat: 13%<sup>67</sup>), but the amount of available data for this outcome is limited.

Patients undergoing OIT are more likely to experience allergic reactions related to consuming the OIT food allergen dose than patients who are avoiding the food. A majority of OIT patients have at least one allergic reaction, and, based on meta-analyses of milk, egg and peanut OIT trials, 16% to 17% of patients experience systemic or anaphylactic reactions (vs 1.6-2.6% of control

patients),<sup>29,31</sup> which require the use of epinephrine in 8.4% to 12% of patients (vs 0-3.7% of control patients).<sup>30,31</sup> One meta-analysis estimated that peanut OIT approximately doubled the risk of serious adverse events (SAEs) (6.2% vs 3.0% control).<sup>31</sup> Quality assessment of this analysis based on original source publications indicated misclassification of adverse events in some cases, suggesting that the rate of SAEs may be similar between OIT and control groups. Analyses of data from double-blind RCTs of peanut OIT indicate that adverse events related to accidental exposure to the food allergen occur in fewer patients undergoing OIT than in patients receiving placebo.<sup>2,95</sup>

The average rate of discontinuation due to adverse events in peanut OIT RCTs has been estimated at 13% compared to 3.7% of control patients.<sup>31</sup> Discontinuation rates due to adverse events ranged from 0 to 18% across egg<sup>12,17-19,21</sup> and wheat<sup>24</sup> RCTs, sesame<sup>28</sup> and walnut<sup>26</sup> CCTs as well as in peanut<sup>8</sup> and milk<sup>14,15</sup> clinical practice. One exception is a wheat case series, in which an overall of 43% of patients discontinued OIT, 40% of them due to mild or moderate adverse events occurring during the 12-month maintenance.<sup>25</sup>

Many studies across different designs and food allergens report that the occurrence or severity of allergic reactions declines as the treatment progresses from the build-up to the maintenance phase.<sup>2,3,8,9,13,20,25,26,28,32,56</sup>

## Recommendations on who could benefit from OIT (indications)

Most food OIT studies included children and adolescents across wide age ranges. Large case series of milk and peanut OIT, including patients starting from the age of four and up to 27 years, reported no significant association between age and safety outcomes and inconsistent observations regarding efficacy.<sup>7,14-16</sup>

Three studies focused on toddlers and pre-school children (age 1-5 years) (2 peanut<sup>9,68</sup> and 1 milk OIT<sup>11</sup>); they indicate high efficacy (81-90% desensitization,<sup>9,11,68</sup> 78% sustained unresponsiveness,<sup>68</sup> 90% continued consumption<sup>11</sup>) and an excellent safety profile in this age group (0-0.4% had severe reactions). One peanut OIT RCT focused on adolescents (age 12-17 years); it reported a desensitization rate (400 mg peanut protein) of 81% compared to 11% for the

placebo group. A second RCT, performing a sub-group analysis, reported that absolute differences in desensitization rates between OIT and placebo groups were comparable for adolescents and children aged 4 to 11 years (58% [95% CI 40 to 77%] and 66% [95% CI 54% to 78%] respectively).<sup>70,6</sup> The same study also included adults (for a secondary end-point analysis), reporting a desensitization rate of 41% with OIT vs 14.3% with placebo, but the number of patients was small (41 in OIT and 14 in placebo group) and the difference was not statistically significant.<sup>6,70</sup> One small case series of 23 adults receiving OIT reported significant increases in the amount of protein that patients were able to tolerate.<sup>71</sup>

### Recommendations on contra-indications

A history of anaphylactic reactions to the targeted food allergen was generally not an exclusion criterion in OIT studies. Evidence from large case series on whether baseline history of anaphylaxis had an impact on OIT outcomes is inconsistent,<sup>7,8,14,16</sup> but most patients with a history of anaphylaxis were able to achieve at least partial desensitization.<sup>8,14</sup>

Across two reports of OIT clinical practice, there was no correlation between a patient's number of food allergies and the outcomes of single-food OIT.<sup>14</sup> <sup>7</sup> Studies of multi-food OIT targeting patients with multiple food allergies raise no particular safety or efficacy issues in this patient demographic.<sup>22,23,96,97</sup>

In many RCTs<sup>2-6,10,13,20</sup> and reports of clinical practice,<sup>7,9,14</sup> severe and/or poorly controlled or unstable asthma was an exclusion criterion for OIT. Baseline asthma was associated with an increased risk of adverse reactions in large case series,<sup>8,73,85,87</sup> and asthma exacerbation was recorded as an adverse event in peanut and egg RCTs.<sup>6,20</sup> Nevertheless, most patients with controlled asthma were able to achieve at least partial desensitization.<sup>7,8,15,73</sup>

OIT requires patients (and/or their caregivers) to regularly attend visits, understand and follow instructions regarding administering the treatment at home, and be able to recognize and treat adverse events.<sup>59,98,99</sup>

## Recommendations on personalized protocols

Published OIT protocols vary in terms of food allergen product and preparation, initial dose escalation, build-up starting and target dose, up-dosing frequency, length of build-up phase and maintenance dose and frequency (see Table A1 in Appendix 2).

Most OIT clinical trials and all OIT clinical practice studies used non-pharmaceutical food-based products. There are no head-to-head comparisons between pharmaceutical and food-based products. Meta-analysis of peanut OIT RCTs found that both proprietary and non-proprietary OIT products led to desensitization versus placebo or usual care (non-proprietary: 67% [64/93] vs 7.5% ([4/53]; proprietary: 53% [256/481] vs 2.2% [5/231]).<sup>31</sup>

In terms of data directly comparing different OIT protocols, one egg OIT RCT indicated better efficacy outcomes when weekly up-dosing was combined with small daily dose increments than with weekly up-dosing only.<sup>29</sup> With respect to safety, this approach was associated with higher rates of mild and local reactions but lower rates of moderate to severe reactions.<sup>29</sup> Two small RCTs reported similar efficacy outcomes comparing different target or maintenance doses;<sup>24,68</sup> however, in a clinical practice case series patients appeared to be more likely to continue peanut consumption when the maintenance dose was lowered.<sup>7</sup> Consuming the maintenance dose daily versus every second day was associated with fewer reactions and better adherence in an egg OIT RCT,<sup>21</sup> but in a milk OIT RCT there was no difference in the frequency of adverse events between daily and weekly consumption after one year of maintenance.<sup>100</sup>

With respect to treating multiple food allergies, one non-randomized study (N=40) observed similar rates of reaction per dose with multiple-food OIT (targeting up to 5 foods simultaneously) as compared to single-food OIT, while time to reach 10-fold increase in desensitization threshold was only 3.2 months longer with multi-food OIT as compared to single-food OIT.<sup>22</sup>

## Recommendations for the safe provision of OIT

Clinical studies of OIT report that anaphylactic reactions or reactions requiring the use of epinephrine may occur in the clinic as well as during home dosing. Some studies reporting fewer

reactions at home than in the clinic,<sup>9,14,26,28</sup> while others report more reactions at home.<sup>8,13,56</sup> Note that up-dosing, which is associated with a higher risk of reaction, occurs in the clinic, but the proportion of doses administered at home is usually higher and increases with the duration of treatment. These factors could contribute to the observed differences between studies.

EoE is more prevalent in children with food allergy compared to the general pediatric population (4.7% vs 0.04%) and is particularly associated with milk and egg allergy.<sup>101</sup> Biopsy-confirmed EoE occurred in 0.4% (peanut) to 6.3% (milk) of patients undergoing OIT.<sup>2,5,6,55,66,78,81-83</sup> Recurrent gastro-intestinal symptoms indicative of EoE were reported in 8.2 to 14% of OIT-treated children<sup>8,79</sup> and 1.1%<sup>9</sup> of pre-school children and were managed with dose adjustments.<sup>80</sup>

Three RCTs compared OIT in the presence of omalizumab versus OIT with placebo.<sup>102</sup>

Omalizumab did not improve efficacy outcomes at 28 or 32 months when used for an extended time with a standard slow OIT schedule;<sup>102</sup> however, a short course of omalizumab within an accelerated OIT schedule significantly increased desensitization rates.<sup>97,103</sup> Omalizumab use was also associated with a reduced rate of dosing reactions.<sup>97,102</sup>