

COMMENTARY

Real-life cow's milk immunotherapy at 15 years: what do these numbers represent?

Comment on: Cow's milk oral immunotherapy in real-life: up to 15-year follow-up study - doi:10.23822/EurAnnACI.1764-1489.424)

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Key words

Cow's milk allergy; oral immunotherapy; eosinophilic esophagitis; long-term follow-up.

Gaspar and colleagues report a much-needed extension of their group's long-standing experience with cow's milk oral immunotherapy (CM-OIT), now following 33 children for as long as fifteen years (1). Complete desensitization was achieved in the large majority of patients, though maintenance was far from uneventful: four in five children reacted at some point, a third experienced anaphylaxis, and eosinophilic esophagitis (EoE) was newly identified in roughly one in eight. This is a genuinely rare dataset, and the authors deserve credit for keeping families in follow-up this long. A few aspects of the report, however, would benefit from further explanation.

The same Lisbon group published an 8-year follow-up of their CM-OIT program in 2018, in which reactions during maintenance were seen in under half of patients and only 7% discontinued for loss of tolerance (2). Between that report and the present one, the proportion of children with a pre-treatment history of anaphylaxis nearly doubled, from 36% to 67%, as did the reaction rate during maintenance itself. Since both studies draw on the same center and overlapping authorship, it is not clear from the current paper whether these are largely the same patients observed for longer, a partially overlapping group, or a genuinely distinct cohort. That distinction matters: if the two publications substantially share patients, the higher event rate reported here reflects longer observation of the same individuals rather than a newly identified, more severe population, and the two datasets should not be read as independent confirmations of CM-OIT's long-term safety profile.

The EoE finding also deserves a methodological note. Whether these cases were confirmed by endoscopic biopsy or inferred from symptoms changes how the 12% figure should be read, given that esophageal eosinophilia during OIT is not reliably predicted by symptoms alone and can be missed without systematic endoscopic surveillance (3,4).

Finally, the authors' own observation that CM-OIT “should always be performed by allergy experts and only motivated families should be enrolled” is worth sitting with, since it is itself a description of survivorship: a single-center cohort of 33 patients who sustained fifteen years of daily milk intake and regular follow-up is, almost by definition, unrepresentative of the wider population that begins OIT.

Families who discontinued earlier, for whatever reason, fall outside this denominator, and neither the efficacy nor the safety figures drawn from it can be assumed to generalize without a comparator arm.

We would welcome the authors' clarification on cohort overlap with their 2018 report, on how EoE was diagnosed, and on how early discontinuations were accounted for in these estimates. None of this diminishes the value of what remains one of the longest CM-OIT follow-ups published to date.

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Author contributions

Both authors: conceptualization, writing – original draft, writing – review & editing.

Conflict of interests

None declared.

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REPLY

Reply to “Real-life cow’s milk immunotherapy at 15 years: what do these numbers represent?”

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N/A

We thank the authors for their commentary on our original article, “Cow’s milk oral immunotherapy in real-life: up to 15-year follow-up study” (1). We appreciate their highlighting the fact that this is one of the longest follow-up studies of cow’s milk (CM) oral immunotherapy (OIT) published to date.

As requested, we would like to clarify that the present study (1) and the study published in 2018 (2) were not conducted at the same center. Although both centers are located in Lisbon, the two studies were conducted at different hospitals and involved distinct patient cohorts.

The study published in 2018 was conducted at Hospital CUF Descobertas (2) and included 42 children with less severe CM allergy; only 36% had a previous history of CM-induced anaphylaxis. The maximum follow-up duration was 8 years, and 3 patients (7%) discontinued CM-OIT. The present study was conducted at Hospital da Luz Lisboa (1) and included 33 children with more severe CM allergy; 67% had a previous history of CM-induced anaphylaxis and 70% had asthma. The maximum follow-up duration was 15 years, and only 1 patient discontinued CM-OIT, due to eosinophilic esophagitis (EoE) during the build-up phase. There was, however, a partially overlapping group of 10 patients who were followed by two of the authors and had also been included in the 2018 report.

The same protocol was used in both studies. Therefore, the higher incidence of adverse events observed in the present study may reflect both the longer follow-up duration and differences in baseline disease severity between the two cohorts. Nevertheless, the real-life, non-controlled design of the present study limits direct comparison.

In the present study (1), we confirmed that 11 patients (33%) experienced anaphylaxis during the CM-OIT maintenance phase. The longest-lasting cases included one patient who experienced anaphylaxis after accidental ingestion of goat cheese after 11 years of maintenance phase, and another who experienced exercise-induced anaphylaxis after 8 years of maintenance phase. We also confirmed that 4 patients (12%) developed EoE. All four cases were confirmed by esophagogastroduodenoscopy with esophageal biopsies showing at least 15 eosinophils per high-power field (3).

The patient who developed EoE during the build-up phase discontinued CM-OIT. The remaining three patients developed EoE after 10 years, 4 years, and 1 month of maintenance phase, respectively. This last patient reduced the daily CM dose to 20 mL, whereas the other two had transient dose reductions and are currently receiving the full maintenance dose.

Therefore, 31 patients (94%) achieved complete desensitization, 1 achieved partial desensitization, and 1 discontinued CM-OIT during the build-up phase because of EoE. Several recent publications have highlighted the importance of early recognition of oral immunotherapy-induced gastrointestinal and eosinophilic responses (OITIGER), as well as other gastrointestinal and eosinophilic manifestations, which represent challenging adverse events during OIT and may lead to treatment modification or discontinuation (4,5). These findings underscore the need for continued long-term clinical surveillance during CM-OIT, including in patients who have successfully reached and maintained the target dose for several years.

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