



Precision medicine for cow's milk immunotherapy in clinical practice

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Purpose of review

Several novel immunotherapies have recently been reported for the treatment of cow's milk allergy (CMA). However, systematic methods for the selection of immunotherapy in clinical practice have not been investigated. In this review, we have provided suggestions for safe and effective immunotherapy for patients with CMA.

Recent findings

Recent studies on cow's milk immunotherapy, using lower target doses, heated or baked cow's milk, combination treatment with adjuvants, or various routes of immunotherapy, included school-aged children with severe allergies, infants, and patients with mild CMA. These patients were administered various maintenance doses for various time periods. In the selection of immunotherapy, it would be useful to consider the patient's age and CMA severity at baseline: threshold dose, history of cow's milk anaphylaxis, and cow's milk-specific IgE levels.

Summary

Considering the risks and benefits for patients with CMA, appropriate treatment should be selected based on the current evidence. Low-dose oral immunotherapy may be useful in clinical practice for school-aged children with severe CMA. Additional studies are needed to assess the indications for immunotherapy to select appropriate treatments in real-life settings.

Keywords

clinical practice, cow's milk allergy, food allergy, immunotherapy, low dose, precision medicine

INTRODUCTION

Cow's milk allergy (CMA) is a major food allergy with a prevalence of 2–3% [1,2]. It represents the largest social burden regarding food allergies [3]. Approximately 20% of school-aged children experience persistent CMA [4]. High maintenance doses (>120 ml cow's milk) of conventional cow's milk-oral immunotherapies (OITs) administered to children with persistent CMA [5–7] have resulted in severe adverse reactions. Moreover, after desensitization to high-dose cow's milk-OITs, many children discontinued OITs [8–10]. To address the safety and discontinuation concerns, new strategies for immunotherapy have been proposed. These include using lower target doses, heated or baked cow's milk, combination treatment with adjuvants or probiotics, or various routes of immunotherapy. The combination of molecular diagnosis and clinical patient factors may be useful for predicting the outcome of OIT in CMA [11^{••}]. However, precise criteria for selecting treatment for CMA have not been

established in clinical practice. Thus, the targets and objectives of current immunotherapies require careful consideration. We have reviewed recent studies on cow's milk immunotherapy indications, methods, and outcomes to identify the optimal treatment choice for CMA.

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KEY POINTS

- Cow's milk immunotherapies, using conventional methods, low-dose, heated or baked cow's milk, omalizumab, and epicutaneous or sublingual, routes have been recommended as a treatment option for children older than school-age with severe CMA.
- The selection of appropriate treatment for patients with CMA in clinical practice requires assessment of the patient's age and CMA severity, which is defined as the threshold dose, history of cow's milk anaphylaxis and cow's milk-specific IgE level.
- For school-aged children with severe CMA, low-dose oral immunotherapy may be recommended in clinical practice.

INDICATIONS FOR COW'S MILK IMMUNOTHERAPY

Conventional cow's milk-OITs have been prescribed to school-aged and older children with severe CMA [5–7]. Present practice shows that most cow's milk immunotherapies are indicated for school-aged children and patients with severe CMA. Such children would have continued to eliminate CM daily because of anaphylactic CMA. Therefore, immunotherapy is needed to improve the quality of life, and the indications for cow's milk immunotherapy should consider the target age and the severity of CMA.

ORAL IMMUNOTHERAPY METHODS AND OUTCOMES

The following summarizes current cow's milk immunotherapies and other treatment options, focusing on the relationship between treatment methods and outcomes (Table 1).

Low-dose oral immunotherapy

Recently, the efficacy of low-dose OITs for allergy to peanuts, cow's milk, hen's eggs, and wheat has been reported [12–18,19[■],20]. Two studies on low-dose cow's milk-OIT were conducted as follows.

For children more than 5 years of age with a threshold dose of 3 ml or less cow's milk, low-dose OIT for CMA was administered with a fixed maintenance dose of 3 ml cow's milk for 3 years [18]. In the OIT group, most participants (27/33 children) had a history of anaphylaxis. Compared with the control group, the rate of children who passed the 25 ml oral food challenge (OFC) after 2 weeks of complete cow's milk avoidance [25 ml short-term unresponsiveness (STU)] in the OIT group was significantly

higher after 3 years (61%, $P=0.002$). During the 3 years, the rate of severe adverse reactions at home was 0.005% [18]. A randomized controlled trial (RCT) comparing low-dose and high-dose OIT in children aged 5–15 years [19[■]] reported a baseline threshold dose of 1.5 ml in the low-dose OIT group. After 1 year, the median final threshold doses were 10 and 20 ml in the low-dose and high-dose groups, respectively ($P=0.76$). The frequency of severe adverse reactions during maintenance phase was significantly lower in the low-dose OIT group than in the high-dose OIT group ($P=0.018$) [19[■]].

Compared with conventional OIT, low-dose OIT is recommended for school-aged children with severe CMA to increase the threshold dose relatively safely. However, the present evidence does not suggest that tolerance to high doses of cow's milk has been achieved.

Heated or baked cow's milk-oral immunotherapy

Heating decreases cow's milk antigen levels due to conformational changes in the cow's milk epitope that induce allergic reactions in patients with CMA. Three studies on heated or baked cow's milk-OIT have been reported.

A 2015 study by Goldberg *et al.* [21], involving baked cow's milk, included 15 children who failed cow's milk-OIT. At baseline, most patients experienced anaphylaxis and had a threshold cow's milk protein (CMP) dose of 15 mg. One year after OIT, only 21% were desensitized to the CMP maintenance dose of 1.3 g and 20% required intramuscular adrenaline [21]. Amat *et al.* [22] randomized CMA children to receive heated cow's milk or raw cow's milk and prescribed OIT with a maintenance CMP dose of 2720 mg. At baseline in the heated cow's milk group, the threshold CMP dose was 34 mg. In the heated cow's milk and raw cow's milk groups, the desensitized doses were 700 and 1200 mg after 10–18 months ($P=0.24$), 30 and 22% experienced severe adverse reactions ($P=0.73$), and 13 and 11% were administered intramuscular adrenaline ($P>0.99$), respectively [21]. In Japan, Nagakura *et al.* [23[■]] prescribed an RCT of low-dose OIT with a maintenance dose of 3 ml. Before OIT, 59% reacted with cow's milk (<0.75 ml) in the heated cow's milk group. In the heated cow's milk and unheated cow's milk groups, 18 and 31% achieved 25 ml STU after 1 year, respectively ($P=0.42$). The rates of moderate-to-severe reactions and respiratory symptoms were significantly lower in the heated cow's milk group than in the unheated cow's milk group ($P=0.002$ and $P<0.001$, respectively). Significantly, the β -lactoglobulin sIgG₄ level at 1 year significantly

Table 1. Summary of recent studies of treatment for cow's milk allergy

Reference	Indication ^a		Methods		Outcome	
	Sample size	Age; median, years (range)	Threshold dose; median (ml)	History of An	CM-sIgE level; median (kUA/l)	Duration
Low-dose OIT						
Yanagida <i>et al.</i> [14]	OIT: 12 Control: 25	OIT: 8.3 (6.7–12.8)	OIT: 1.6 Control: 2.6	OIT: 11/12 (92%)	OIT: 38.2	1 year
Miura <i>et al.</i> [18]	OIT: 33 control: 16	OIT: 8.3 (6.8–8.8)	OIT: 1.5	OIT: 27/33 (82%)	OIT: 31	3 years
Takaoka <i>et al.</i> [19 [†]]	Low: 14 High: 19	Low: 9 (5–12)	Low: 1.5 High: 2	–	Low: 39.6	6 months
Heated or baked CM-OIT						
Goldberg <i>et al.</i> [21]	OIT: 15 (single-arm)	(6.5–12)	15 mg CMP	14/15 (93%)	–	1 year
Amat <i>et al.</i> [22]	BM: 23 RM: 18	BM: 7 (5–10)	BM: 34 mg CMP	Included	BM 14.1 RM 12.4	10–18 months
Nagakura <i>et al.</i> [23 [†]]	HM: 17, UM: 16	HM: 7.6 (5.2–11.2)	HM: 10/17 reacted ≤0.75	HM: 2/17 (12%)	HM 56.0 UM 55.6	1 year
Combined with omalizumab						
Nadeau <i>et al.</i> [24]	OIT: 11	8 (7–17)	<10	Included	50	24 weeks
Wood <i>et al.</i> [25]	Omalizumab-OIT: 28, placebo: 29	Omalizumab: 11.7 (9.5–15)	Omalizumab: 10 mg CMP	Severe An excluded	Omalizumab-OIT 38	28 months
Infant OIT						
Berti <i>et al.</i> [26]	OIT: 68 (single-arm)	7.3 months (3–11 months)	>1	1/68 (1%)	1.8	3.5–16 months

25 ml STU: OIT 4/12, control 0/25 (P=0.007)

In hospitalization and at home, AR: 57.1 and 19.5%. Severe AR, Ad: 0 and 0.03%

25 ml STU: OIT 2/16 Control 20/33 (P=0.002)

In hospitalization and at home, AR: 57 and 20%, severe: 0.6 and 0.005%, Ad: 0.6 and 0.02%

In the low and high-dose groups, severe AR: 0.1 and 0.5% (P=0.018). Ad: 0.03 and 0.3% (P=0.047)

Final threshold doses: low 10 ml, high 20 ml (P=0.76)

Ad: 3/15 (home: 2, induction: 1)

Desensitized to 1.3 g of baked CMP: 3/14 (21%)

In the BM and RM, AR: 12/23 and 11/18 (P=0.57), severe AR: 7/23 and 4/18 (P=0.73), Ad: 3/23 and 2/18 (P=1.0)

Desensitization-dose: BM 0.7 g CMP, RM 1.2 g CMP (P=0.24)

In the HM and UM, AR at home: 8.8 and 9.6% (P=0.01), moderate–severe AR: 0.7 and 1.2% (P=0.002), Ad: 0.02 and 0.02%

In the HM and UM, AR: 1.8%, severe AR: 0.1%, Ad: 2/11

Desensitized to 8 g CMP: 9/11

In omalizumab-OIT and placebo, AR per patients in rush phase: 2.1 and 16.1% (P<0.001), Ad: 0.004 and 0.04% (P=0.05)

Desensitized to 10 g CMP: 24/28 and 20/29 (P=0.18), SU to 10 g CMP: 13/28 and 10/29 (P=0.42)

Desensitized to 150 ml CM: 66/68

Table 1 (Continued)

Reference	Indication ^a		Methods			Outcome			
	Sample size	Age; median, years (range)	Threshold dose; median (ml)	History of An	CM-sIgE level; median (kUA/l)	Duration	Maintenance dose (ml)	Safety, % = per ingestion doses	Efficacy
EPIT									
Dupont <i>et al.</i> [27]	EPIT: 10; placebo: 8	3.82 ± 2 (10 months–7.8 years)	<10	–	OIT 20.2	3 months	1 mg skimmed CM	Systematic AR: EPIT 24/470, placebo 8/316, An and Ad: 0/18	Mean threshold dose: EPIT 12-fold, placebo 8% increase (<i>P</i> = 0.13)
SLIT									
Keet <i>et al.</i> [33]	SLIT: 10; OIT: 20	SLIT: 8 (6–17)	SLIT: 101 mg CMP	SLIT: 8/10 (80%)	SLIT: 23	1 year	SLIT: 7 mg CMP	In OITs compared with SLIT, multiple AR and respiratory AR were significantly higher (<i>P</i> < 0.001)	Desensitized to 8 g CMP: SLIT 1/10, OIT 14/20, SU to 8 g CMP: SLIT 1/10, OIT 8/20
Combined with probiotics									
Berni Canani <i>et al.</i> [37]	LGG: 27 Control: 28	LGG: 3.9 (2.5–5.2) months	<144	Excluded	–	6 months	–	After passing DBPCFC at 6 months, infants consumed CM daily without symptoms	In the LGG and control group, 144 ml OFC passed: 5/27 and 1/28 in IgE-mediated (<i>P</i> = 0.046), 18/27 and 8/28 in non-IgE-mediated (<i>P</i> = 0.006)
Low-dose OFC									
Okada <i>et al.</i> [39]	3 ml-tolerated: 41, reactive: 40	4.3 (1–12)	12.5 (3–25)	3 ml-tolerant: 21/41 (51%)	3 ml-tolerant: 19.7	1 year	3	In the reactive group at OFC, An: 30/42, Ad: 3/42	25 ml OFC passed: tolerant 45%, reactive 0%

Ad, intramuscular adrenaline; An, anaphylaxis; AR, adverse reaction; BM, baked cow's milk; CMP, cow's milk; CM, cow's milk; OFC, oral food challenge; OIT, oral immunotherapy; RM, raw cow's milk; sIgE, specific IgE; SLIT, sublingual immunotherapy; STU, short-term immunotherapy; HM, heated cow's milk; LGG, *Lactobacillus rhamnosus* GG; OFC, oral food challenge; OIT, oral immunotherapy; RM, raw cow's milk; sIgE, specific IgE; SLIT, sublingual immunotherapy; STU, short-term immunotherapy; SU, sustained unresponsiveness; UM, unheated cow's milk.

^aThe data listed in the indication column represent all data collected at the beginning of each study.

increased from baseline in the unheated cow's milk group ($P < 0.001$), but not in the heated cow's milk group [23].

Therefore, heated cow's milk-OIT is recommended for school-aged children with severe CMA. Furthermore, while heated cow's milk-OIT combined with a low maintenance dose may be safer than conventional OIT, it has a lower efficacy compared with unheated cow's milk-OIT.

Oral immunotherapy combined with omalizumab

To decrease the risks and potentially enhance the efficacy of OIT, adjunctive treatment with omalizumab has been investigated.

A pilot study of cow's milk-OIT combined with omalizumab included children aged 7–17 years with threshold doses less than 10 ml cow's milk and a history of anaphylaxis to cow's milk [24]. OIT with a maintenance dose of 2000 mg CMP was combined with omalizumab for 16 weeks. At 24 weeks, 90% of the patients were desensitized to 7250 mg of CMP. Most adverse reactions were mild, and only one, swelling of the tongue, was severe [24]. A double-blinded trial randomized 57 participants aged 7–32 years who reacted to 10–20 mg CMP to the omalizumab-OIT or placebo group [25]. Omalizumab was discontinued 28 months after OIT initiation. After 32 months, after avoidance of cow's milk for 8 weeks, OFC with 10 g of CMP was performed. Desensitization was observed in 89 and 71% of participants in the omalizumab-OIT and placebo groups ($P = 0.18$), respectively, with sustained unresponsiveness rates to 10 g CMP of 48 and 36% ($P = 0.42$), respectively. The rates of reactions per dose per patients and administration of intramuscular adrenaline were significantly lower in the omalizumab-OIT group than in the placebo group ($P < 0.001$ and $P = 0.05$, respectively) [25].

Therefore, for patients over school-age with severe CMA, combination therapy with omalizumab was safer than conventional OITs, enabling the achievement of sustained unresponsiveness to high-dose cow's milk. However, an increase in the efficacy of OIT has not been reported. The high cost may make it difficult to continue this treatment in clinical practice.

Infant oral immunotherapy

OIT is generally recommended for children over school age. Conversely, in a 2019 study, infants less than 12 months of age with IgE-mediated CMA were targeted for single-arm OIT [26]. Infants less than 3 months of age who reacted to less than 1 ml cow's

milk or who showed severe adverse reactions at the first OFC were excluded. In addition, 40% of the infants were negative for the first OFC, with a cumulative dose of 16 ml cow's milk. One infant experienced anaphylaxis to cow's milk at baseline. The outcome was the rate of infants who reached maintenance doses of 150 ml cow's milk rather than the final OFC. Most infants were able to consume 150 ml of cow's milk at a median time of 5.5 months. At home, 43% of patients experienced adverse reactions, most of which were mild [26].

Infant OIT can be safely prescribed to patients with mild CMA. However, infants who can spontaneously achieve tolerance should not be included. Safety is not guaranteed in infants with severe CMA. Therefore, it seems to be difficult to recommend cow's milk-OIT for infants in everyday settings.

Epicutaneous immunotherapy

A pilot study of epicutaneous immunotherapy (EPIT) has also been performed for CMA [27], in which 19 children aged 3 months to 15 years, who reacted to less than 10 ml cow's milk at the OFC, were randomized to the EPIT and placebo groups. An epicutaneous delivery patch containing 1 mg skimmed cow's milk powder was administered to the EPIT group for 3 months. At the OFC after 3 months, the mean threshold dose increased 12-fold in the EPIT group and by 8% in the placebo group ($P = 0.13$). In the EPIT and placebo groups, 5 and 3% of the patients experienced systematic symptoms, respectively, with no anaphylaxis [27].

The results of this pilot study suggest that cow's milk-EPIT could be recommended as a safe immunotherapy option for children more than 10 months of age with relatively severe CMA. However, the efficacy of cow's milk-EPIT was lower than that of OIT.

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) has been used to treat various food allergies [28–32]. In one study, 30 children were randomized to the SLIT alone or SLIT followed by OIT (OIT-A group or OIT-B group) groups. At baseline in the SLIT group, the median age was 8 years, the threshold CMP dose was 101 mg, and 80% of the children had a history of anaphylaxis to cow's milk [33]. The maintenance CMP doses in the SLIT, OIT-A, and OIT-B groups were 7, 1000, and 2000 mg, respectively. After 1 year, the rates of desensitization to 8000 mg CMP were 10%, 60%, and 80%, and those of achievement of SU to 8000 mg CMP after 6-week avoidance of CM were 10%, 30%, and 50%, respectively. The frequency of adverse reactions in the multisystem, gastrointestinal, and lower respiratory tract

was significantly lower in the SLIT group than in the OIT group ($P \leq 0.01$) [33]. Therefore, for high-risk children over school age, SLIT is a safer method; however, it has a lower efficacy than OITs.

NONIMMUNOTHERAPY TREATMENT

Combined with probiotics

Early life intestinal microbiota may be a target for therapeutic interventions or for the prevention of food allergies [34–36]. One study of infants diagnosed with IgE-mediated (43%) and non-IgE-mediated CMA (57%) had a median baseline age of 3.2 months. They received an extensively hydrolyzed casein formula (EHCF) with *Lactobacillus rhamnosus* GG (LGG) [37]. Patients with a history of anaphylaxis to the cow's milk were excluded. After randomization to the EHCF with LGG or the EHCF group, infants continued their consumption for 6 months and avoided cow's milk consumption. After 12 months, 81 and 54% of infants in the EHCF with LGG and EHCF groups, respectively, passed the double-blind, placebo-controlled food challenge with 144 ml cow's milk. The rate of infants diagnosed with IgE-mediated and non-IgE-mediated CMA were significantly lower in the EHCF with LGG group than in the EHCF group ($P = 0.046$ and 0.006 , respectively) [37]. Therefore, treatments combined with probiotics may be useful for infants with mild CMA. However, the efficacy of this approach has not been investigated in school-aged children with CMA.

Low-dose oral food challenge

Low-dose OFC is a 'nonimmunotherapy' option for patients with CMA, regardless of the severity of their allergy. In general practice, low-dose OFC has been administered to infants and school-aged children to avoid strict elimination of cow's milk [38,39].

One study was conducted with 83 children aged 1–12 years with CMA who underwent low-dose OFC with 3 ml of heated cow's milk [39]. Among the children who tolerated 3 ml of cow's milk, 50% had a history of anaphylaxis to cow's milk. Children who passed the 3 ml OFC then ingested 3 ml cow's milk at home twice weekly and received 25 ml OFC after 1 year (3 ml-tolerated group). In contrast, children who reacted to the 3 ml OFC completely avoided cow's milk and were administered 3 or 25-ml OFC after 1 year (3 ml-reactive group). After 1 year, 45% of children in the 3 ml-tolerated group were able to consume 25 ml of heated cow's milk. No children in the 3 ml-reactive group passed the 25-ml OFC. In the 3 ml-tolerated group, one child (2%) experienced

anaphylaxis without requiring intramuscular adrenaline after the ingestion of 3 ml cow's milk [39].

Therefore, low-dose OFC is recommended for children more than 1 year of age with a history of anaphylaxis. However, the inclusion criterion for low-dose OIT is 3 mL OFC positivity. Therefore, this treatment is not suitable for patients who are eligible for low-dose OIT.

PRECISION MEDICINE IN COW'S MILK IMMUNOTHERAPY

Age and CMA severity are important clinical factors in determining the appropriate treatment goals for patients (Fig. 1). The importance of each factor, according to the natural history of CMA and the indications for cow's milk immunotherapy, is described as follows.

Age

Although approximately 50–90% of children with childhood-onset CMA acquire tolerance by school age [40,41], high-risk children often have persistent CMA [4,40]. The European Academy of Allergy and Clinical Immunology guidelines recommend cow's milk immunotherapy for children with persistent CMA from 4 years of age [42]. In contrast, OIT was targeted to infants with only mild CMA, some of whom had acquired tolerance [26]. EPIT and low-dose OFC were safely prescribed to patients more than 10 months of age [27,39].

In clinical practice, immunotherapy may be selected as a treatment option for school-aged children, while EPIT or low-dose OFC can be prescribed to infants to increase their cow's milk threshold.

Cow's milk allergy severity

We evaluated CMA severity using the threshold dose of cow's milk, the presence or absence of anaphylaxis history to cow's milk, and the cow's milk-specific IgE (sIgE) level at baseline.

Threshold dose of cow's milk at baseline

Originally, the aim of OIT was to increase the threshold dose (dosage of cow's milk that results in the development of allergic reactions). A study of low-dose OFC reported that patients who reacted to 3 ml cow's milk could not consume 25 ml cow's milk after 1 year [39]. One conventional OIT study showed that patients who failed to achieve desensitization to high-dose cow's milk had a significantly lower threshold dose than those who achieved desensitization [43]. Therefore, patients with a low threshold dose had severe CMA.

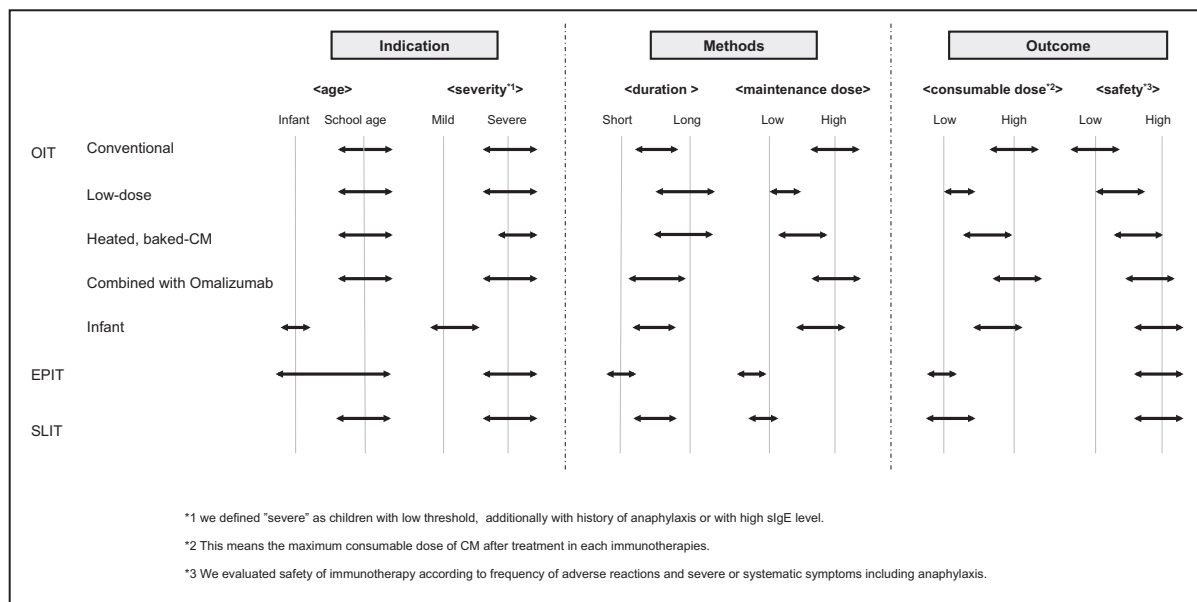


FIGURE 1. Evaluation of recent cow's milk-immunotherapy. Each immunotherapy was charted in terms of indication, methods, and outcome. (*1) We defined 'severe' as children with low threshold, additionally with history of anaphylaxis or with high specific IgE level. (*2) This means the maximum consumable dose of cow's milk after treatment in each immunotherapies. (*3) We evaluated safety of immunotherapy according to frequency of adverse reactions and severe or systematic symptoms including anaphylaxis.

History of anaphylaxis to cow's milk or cow's milk-specific IgE levels at baseline

In observational cohort studies, children with a history of anaphylaxis to cow's milk or high cow's milk-sIgE levels in infancy had persistent CMA at school age [4,40]. In conventional OITs, low cow's milk-sIgE levels before starting OIT have been associated with successful OIT outcomes [44,45]. Therefore, before initiating cow's milk immunotherapy, assessing patient anaphylaxis history to cow's milk or high-sIgE levels to cow's milk may be helpful for evaluating CMA severity.

In clinical practice, after the diagnosis of severe CMA, heated cow's milk-OIT with a low maintenance dose, EPIT, or SLIT can be considered. However, these treatments may not provide sufficient efficacy. Currently, OIT combined with omalizumab for all patients with severe CMA is not reasonable in everyday settings. Therefore, considering its safety and efficacy, low-dose OIT is recommended. Initiating stepwise OFC with low-dose OFC is an appropriate treatment for nonsevere CMA.

CONCLUSION

Current cow's milk immunotherapies struggle to provide both high efficacy and safety for all patients with CMA. Therefore, appropriate treatment selection depends on the age of the child and

severity of the CMA. Considering the benefits and risks of treatment, low-dose OIT may be appropriate for children over school age with severe CMA. EPIT or low-dose OFC could be considered for infants according to the severity of CMA. We anticipate that studies of cow's milk-immunotherapy combined with probiotics targeting children with severe CMA who require treatment will be required. In future clinical practice, individualized immunotherapy for patients with CMA may be prescribed depending on the patient's clinical profile.

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Conflicts of interest

M.E. received fees from DBV Technologies and Mylan to deliver lectures. S.S. received fees from Mylan to deliver lectures. The other authors declare no conflicts of interest.

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