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Milk ladder and oral immunotherapy in IgE-mediated cow's milk allergy

Drabina mleczna i doustna immunoterapia swoista w IgE-zależnej alergii na białka mleka krowiego

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Abstract

IgE-mediated cow's milk allergy is a significant clinical problem. It may be persistent in a large percentage of children. This allergy is associated with restrictive diet, limitations in social activities and anxiety arising from the fear of accidental exposure to the allergen and life-threatening anaphylaxis. Currently, elimination diet and education of the child and their caregivers are the basic approaches in IgE-mediated cow's milk allergy. However, this strategy does not modify the natural course of allergy. The so-called milk ladder and specific immunotherapy with cow's milk, which is still an experimental treatment, are methods allowing for increasing the reactivity threshold. Both treatments are causal and can lead to permanent milk tolerance in the patient. The scheme of dietary expansion in a child with IgE-mediated cow's milk allergy using the milk ladder involves introducing food products containing milk that is processed to a varying degree. This method assumes that patients who can introduce baked dairy products into their diet develop tolerance to increasingly higher doses of allergen over time and, at the same time, less thermally processed products. Oral immunotherapy with cow's milk involves administering the allergen, usually in the form of unprocessed milk, in increasing amounts until the target dose is reached. The article discusses the possibilities of inducing tolerance to cow's milk proteins in IgE-mediated allergy using the milk ladder and oral immunotherapy, along with advantages and limitations of such approaches.

Keywords: food allergy, cow's milk allergy, specific immunotherapy

Streszczenie

IgE-zależna alergia na białka mleka krowiego stanowi istotny problem kliniczny. U znacznego odsetka dzieci może okazać się przetrwała. Alergia ta wiąże się z restrykcyjną dietą, prowadzi do ograniczeń w aktywności społecznej oraz powoduje lęk, wynikający z obawy przed przypadkową ekspozycją na alergen i zagrażającą życiu anafilaksją. Obecnie podstawowym postępowaniem w IgE-zależnej alergii na białka mleka krowiego jest dieta eliminacyjna oraz edukacja dziecka i jego opiekunów w zakresie postępowania w przypadku anafilaksji po przypadkowym spożyciu produktów zawierających mleko krowie. Taka strategia nie modyfikuje jednak naturalnego przebiegu alergii. Metodami pozwalającymi na podniesienie progu tolerancji na białka mleka są tzw. drabina mleczna i swoista immunoterapia mlekiem krowim, będąca jeszcze w fazie badań eksperymentalnych. Obie metody są leczeniem przyczynowym, mogącym doprowadzić u pacjenta do uzyskania trwałej tolerancji mleka. Schemat rozszerzania diety u dziecka z IgE-zależną alergią na białka mleka krowiego z wykorzystaniem drabiny mlecznej polega na wprowadzaniu produktów spożywczych zawierających mleko o różnym stopniu przetworzenia. Metoda ta zakłada, że u pacjentów, u których możliwe jest wprowadzenie do diety wypieków zawierających produkty mleczne, z czasem stwierdza się tolerancję coraz większych dawek alergenu, a jednocześnie mniej przetworzonych termicznie. Doustna immunoterapia mlekiem krowim polega natomiast na podawaniu alergenu, zwykle w postaci mleka nieprzetworzonego, we wzrastających ilościach aż do osiągnięcia dawki docelowej. W artykule omówiono możliwości indukcji tolerancji na białka mleka krowiego w IgE-zależnej alergii z wykorzystaniem drabiny mlecznej oraz immunoterapii doustnej wraz z zaletami i ograniczeniami takiego postępowania.

Słowa kluczowe: alergia pokarmowa, alergia na białka mleka krowiego, immunoterapia swoista

INTRODUCTION

Cow's milk allergy (CMA) represents a significant and constantly growing clinical problem. Pathophysiologically, it is classified as IgE-mediated (IgE-CMA), non-IgE-mediated and mixed allergy. IgE-CMA affects <1% of children <2 years of age. It most often develops in infancy. Although the allergy is usually transient, it may persist beyond the age of 5 years in about 15% of patients[1,2]. Cow's milk proteins are the most common cause of anaphylaxis in children[3]. CMA is a significant burden for patients and their families and is often associated with the need for a restrictive diet, which may result in nutritional deficiencies. It also leads to social life restrictions and anxiety arising from fear of accidental exposure to the allergen and life-threatening anaphylaxis.

Patients with IgE-CMA usually develop mild-to-severe symptoms within minutes after consuming cow's milk. Mild-to-moderate IgE-CMA usually manifests with cutaneous (pruritus, urticaria, erythema, angioedema), gastrointestinal (abdominal pain, vomiting, diarrhoea) and/or respiratory symptoms (acute rhinitis, wheezing). Severe IgE-CMA can cause anaphylaxis with severe circulatory and/or respiratory symptoms[4,5].

The diagnosis of IgE-CMA is based on a thorough medical history, physical examination and laboratory tests. Attention should be paid to the relationship between symptoms and consumption of milk and other milk-containing food products, including non-obvious sources of allergens (e.g. cold cuts, sauces). Among laboratory investigations, skin prick tests (SPT) may be helpful. However, a positive SPT only suggests an allergy (it is evidence of sensitisation rather than its causative role in causing clinical symptoms). Determination of allergen-specific IgE (sIgE) against cow's milk extract or its individual proteins is another useful test. Oral food challenge (OFC) is needed to establish the final diagnosis of CMA[6].

Elimination diet and education of the patient and their family on proper management in case of anaphylaxis (epinephrine) following accidental intake of cow's milk-containing products is currently the basic management in IgE-CMA. However, such a strategy does not modify the natural course of allergy. The so-called milk ladder and specific immunotherapy (SIT) with cow's milk, which is still in the research phase, are methods intended to raise the tolerance threshold for milk proteins. Both treatment methods are causal and can lead to desensitisation or even permanent milk tolerance in the patient. The term "desensitisation" (temporary tolerance) refers to a process to increase the threshold exposure to a food allergen. Maintaining desensitisation requires constant intake of the allergen. Permanent tolerance, on the other hand, is the absence of symptoms after ingestion of the food even after periods of avoidance.

This paper discusses the possibilities of inducing tolerance to cow's milk proteins in IgE-CMA using the milk ladder and presents the available data on oral immunotherapy (OIT) along with the advantages and limitations of such an approach, based on the current state of knowledge.

MILK LADDER

Cow's milk contains two main protein fractions that cause hypersensitivity: casein and whey (including alpha-lactalbumin, beta-lactoglobulin, bovine serum albumin and immunoglobulins). Casein is highly thermostable, retaining its structure even after 90 minutes at >90°C. High levels of sIgE against casein correlate with a positive OFC reaction[7]. Whey proteins, on the other hand, are thermolabile. Long-term thermal processing (e.g. in the baking process) changes the structure and stability of milk allergens, affecting their sensitising potential. This is mainly due to the destruction of antigenic determinants that bind to IgE antibodies[8].

It is estimated that approximately 70% of IgE-CMA patients who experience symptoms after raw milk consumption tolerate milk that has undergone prolonged heat treatment[9,10].

The first reports on the use of milk-containing baked products to induce tolerance to milk allergens appeared in 2008. It was at that time that Nowak-Węgrzyn et al. showed that patients with IgE-mediated milk allergy who tolerated baked milk acquired tolerance to reintroduced milk more rapidly[10]. Subsequent studies confirmed the efficacy and safety of this approach. Most adverse events were mild and did not require epinephrine[11]. Based on the collected evidence, a diet expansion programme known as the milk ladder was developed, which involves gradual introduction of milk-containing food products with various degrees of processing[12–14]. This method assumes that patients who can introduce baked dairy products into their diet develop tolerance of increasingly larger doses of less thermally processed allergens (e.g. cheese, yoghurt) over time (Fig. 1).

Achieving tolerance is much more challenging in the case of IgE-CMA with rapid and severe reactions after consuming even small amounts of milk. Ball et al. were the first to publish a retrospective study on the use of the milk ladder in patients with IgE-CMA. The patients were initially given trace amounts of heat-treated milk in the form of biscuits. After achieving tolerance, the servings were increased and their thermal processing was gradually reduced. Achieving tolerance to pasteurised milk was the endpoint. The results were very encouraging, with only 8 out of 86 patients failing to achieve tolerance to unprocessed milk, and no serious adverse effects[15]. Since the diet was expanded in a home setting, children who did not tolerate even trace amounts of baked milk, those with a history of adverse respiratory and/or cardiovascular reactions, patients with SPT >8 mm, and children diagnosed with asthma were excluded from the study.

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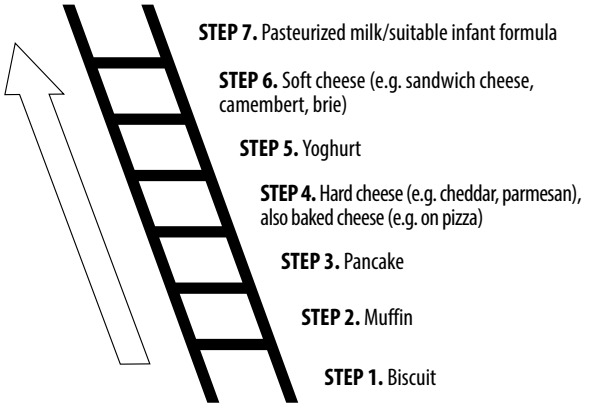

Fig. 1. An example of milk ladder

Although the 2023 World Allergy Organization (WAO) guidelines allow the use of the milk ladder approach in IgE-CMA, no detailed regimen has been developed. Authors emphasise that in the milk ladder, cooked or baked milk products should be introduced in small quantities, and gradually and slowly increased after tolerance is achieved. No time range for completing the milk ladder or the length of its individual stages have been established. It is also important to adjust the dietary expansion scheme to an individual patient[16].

It should be appreciated that although allergenic properties of milk are reduced during thermal treatment, they are not fully eliminated. Patients with CMA may also experience severe allergic reactions after consuming milk that has undergone long-term heat treatment[10]. According to WAO guidelines, patients with IgE-CMA who do not tolerate either fresh or baked milk should avoid it in any form, even highly processed[17].

ORAL IMMUNOTHERAPY IN COW'S MILK ALLERGY

Four forms of specific immunotherapy are currently studied for use in food allergy: OIT, sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and subcutaneous immunotherapy (SCIT).

Despite the lack of a single established regimen, OIT is considered to be the best-studied and most effective immunotherapy for CMA[18].

OIT involves administering the allergen in increasing amounts until the target dose is reached in CMA patients[19]. The protocols proposed by individual researchers suggest the use of unprocessed milk. OIT usually includes three stages: initial dose escalation, updosing or buildup phase, and maintenance phase (Fig. 2).

The goal of OIT is to induce desensitisation to a specific amount of allergen, which reduces the risk of severe reactions after accidental ingestion of milk-containing products. Once the target dose is reached, the patient usually needs to continue regular intake of allergen to maintain desensitisation[20].

OIT should be considered in patients with IgE-CMA, in whom allergen avoidance strategy is ineffective, unachievable or negatively affects quality of life (QoL). Before commencing immunotherapy, it should be confirmed that the allergy is IgE-mediated by performing SPT or serum sIgE measurement. OFC should also be performed to establish the baseline allergen tolerance threshold[19].

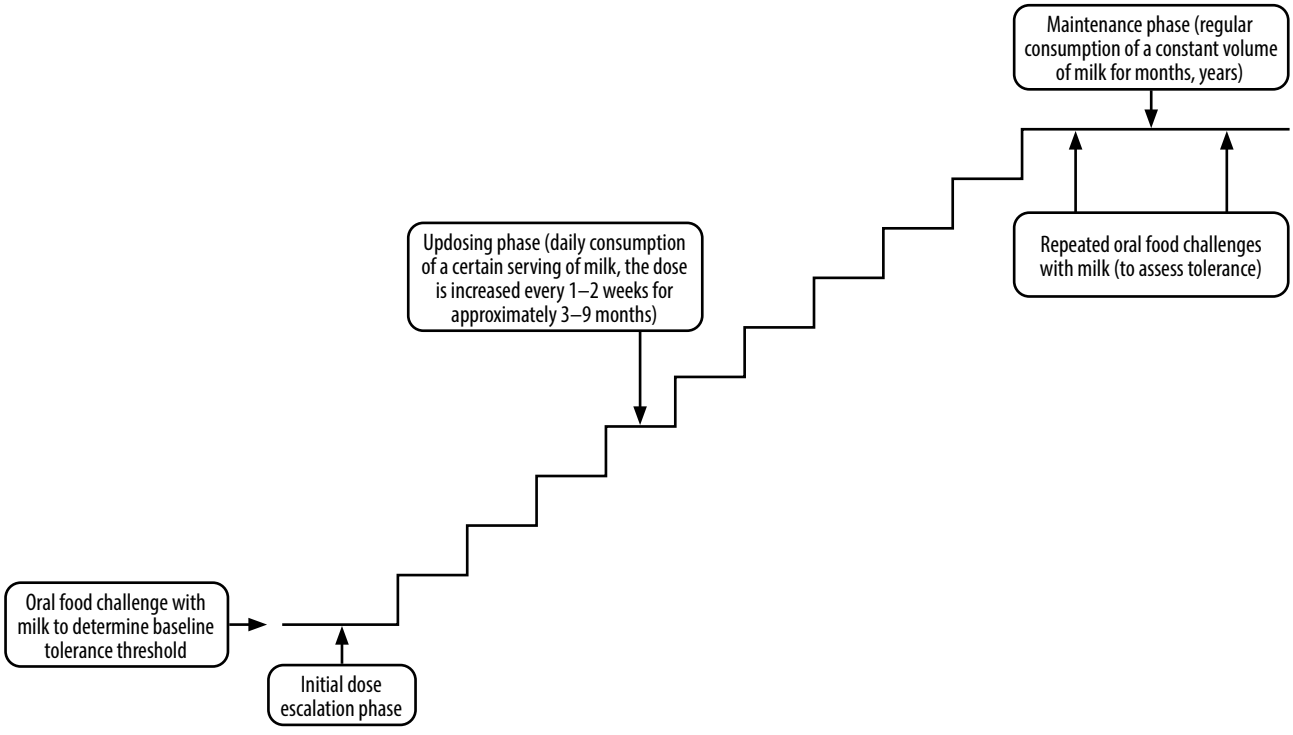

Fig. 2. An exemplary immunotherapy regimen with cow's milk

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Allergen immunotherapy for food allergy (FA-AIT) should only be implemented in experienced centres, with full access to medications and equipment to manage potential complications, including anaphylaxis.

According to the European Academy of Allergy and Clinical Immunology (EAACI), specific immunotherapy can be started at the age of 4–5 years[18]. Although younger children and even infants were also included in clinical trials, it should be remembered that the patient's cooperation is necessary during OIT. The child should be aware enough to report early symptoms of an allergic reaction. It is worth emphasising, however, that the likelihood of developing natural tolerance to cow's milk decreases with child's age.

OIT is a long-term process associated with strict adherence to medical recommendations, hence lack of patient/parental cooperation is the main contraindication. Absolute contraindications further include uncontrolled asthma, active neoplastic process, autoimmune disorders and eosinophilic diseases of the gastrointestinal tract[21].

Efficacy of oral immunotherapy in IgE-mediated cow's milk allergy

In their meta-analysis of 11 studies, Tang et al. showed that over 72% of children (n = 176) undergoing OIT were fully desensitised (tolerated the dose of milk in the protocol) compared with 21.6% of controls (n = 49). Interestingly, when only patients >3 years of age were considered, the percentage of desensitisation in the OIT group was lower (58.7%), while it was 0% in the control group[20]. The above data support the use of OIT in CMA children >3 years of age, in whom the chance of acquiring spontaneous tolerance to cow's milk allergens is close to zero.

Some studies also consider partial desensitisation (tolerance to a larger amount of allergen compared to baseline OFC) [22,23]. The definition of partial desensitisation is not clear. Tang et al. showed in their meta-analysis that a higher percentage of controls achieved partial desensitisation compared to the study group.

Few studies have assessed tolerance after completing immunotherapy (sustained unresponsiveness). According to Salmivesi et al., 23 (82%) and 22 (79%) of 28 children tolerated significant servings of milk 6–12 and 3–3.5 years months after completing OIT, respectively[24]. Meglio et al. reported a rate of 70% at 4.5 years after completing immunotherapy[25].

Risks associated with oral immunotherapy

The vast majority of patients undergoing OIT experience adverse reactions related to milk intake[21]. Although these are usually mild and transient (oral and pharyngeal pruritus, abdominal pain), a significant percentage of children develop anaphylaxis. Nachshon et al. showed that the risk of anaphylaxis in patients undergoing OIT using cow's milk was 30.5% and was higher than in immunotherapy with other foods (chicken egg: 13.3%, peanuts: 16.5%, sesame: 7.8%)[26]. Unlike anaphylaxis after accidental ingestion of cow's milk, parents and patients are informed about and prepared for possible adverse events (AEs) related to OIT by the doctor supervising immunotherapy before commencing OIT. Arasi et al. emphasised the role of written recommendations for parents in preventing anaphylaxis during OIT. The patient should not consume milk on an empty stomach or immediately before physical exercise or sleep, and the allergen dose should be reduced in the case of infection, asthma exacerbation or menstruation. This helps reduce AEs by up to seven times[27].

WAO guidelines suggest omalizumab to reduce serious adverse events (SAEs) during OIT[17]. Omalizumab given during the initial phase of desensitisation reduces the incidence of anaphylaxis and allows more rapid achievement of the maintenance phase, without effect on the percentage of patients reaching this phase[28]. However, due to the low quality of evidence and the high costs of omalizumab therapy, this is not a routine procedure.

There have been reports on eosinophilic esophagitis (EoE) in children undergoing OIT with cow's milk[29]. Symptoms of EoE are nonspecific and often overlap with typical manifestations after milk ingestion (epigastric pain, nausea, vomiting), and therefore oesophageal biopsy is required to confirm the disease. Although the causal relationship between OIT and EoE remains unclear, it is recommended that every patient undergoing food immunotherapy be monitored for this condition.

The impact of oral immunotherapy on the quality of life

There is no doubt that the standard treatment of CMA (allergen avoidance strategy) is associated with a decrease in the QoL of patients. Children on an elimination diet are afraid of accidental ingestion of the allergen and a possible allergic reaction, and the disease significantly limits their diet and affects social contacts[30–32]. However, few publications refer to the impact of OIT on the QoL of children with food allergy and their families. No reliable studies assessing the QoL in children undergoing immunotherapy with cow's milk were found. In their meta-analysis comparing QoL scores over a year in patients undergoing peanut OIT or a restricted diet, Blumchen et al. showed a slight superiority of OIT[33]. Epstein-Rigbi et al. assessed QoL in nearly 200 patients aged 4–12 years and their families before, during, and after immunotherapy with various food products[34]. The researchers used the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) for data collection. QoL scores before OIT and after reaching the maintenance dose improved in many aspects (emotional impact, fear of eating, dietary and social restrictions). Younger age, monovalent food allergy, and poorer baseline QoL were associated with greater improvement in QoL as a result of immunotherapy.

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It should be emphasised, however, that a significant percentage of patients experience temporary deterioration in QoL during dose escalation. The child must regularly consume a previously avoided food product, which sometimes causes unpleasant symptoms (abdominal pain, pharyngeal itching). Furthermore, OIT is associated with additional restrictions in everyday life (e.g. avoiding physical exertion immediately after allergen intake) and regular visits to hospital.

MANAGEMENT OF ANAPHYLAXIS

Developing tolerance using both milk ladder and cow's milk OIT involves intake of an allergen that may cause anaphylaxis. Parents need to be trained in identifying the symptoms of anaphylaxis and should know the procedures to be followed in the event it occurs. Treatment involves immediate intramuscular administration of epinephrine into the anterolateral aspect of the mid-thigh[35]. If there is no clinical improvement after 5–10 minutes, another dose of the drug should be administered. Each patient should be provided with two doses of epinephrine for self-administration (autoinjector) at a dose appropriate for body weight.

In a model scenario, parents receive an individual management plan in the event of anaphylaxis. It contains step-by-step information on what medications and at what doses the child should receive. In addition to epinephrine, which, as emphasised, is the basic medication, antihistamines and oral steroids are used. However, it should be clearly appreciated that these are only adjunct medications in anaphylaxis, and they cannot replace or delay the administration of epinephrine. In the event of any anaphylactic reaction, parents should immediately seek qualified medical help.

CONCLUSIONS

Standard management of IgE-CMA, i.e. avoiding the allergen, is a significant burden for patients and their parents. There is no doubt that the disease significantly reduces the QoL of the whole family. However, there are ways to induce food tolerance in children with IgE-CMA. The use of the so-called milk ladder involves introducing increasingly less processed dairy products into the diet, starting with baked milk products. Unfortunately, no detailed schemes for expanding the diet have been developed. The entire process is largely the responsibility of parents, supported by an allergist. Although the milk ladder is effective and safe, and serious adverse reactions are rarely observed, life-threatening anaphylaxis can develop also after ingesting baked milk. Specific OIT with unprocessed milk, which is still in the research phase, is another method for inducing tolerance to cow's milk. It involves administering gradually increasing servings of allergen according to a detailed protocol prepared by the researcher. OIT should only be performed in experienced centres. It is estimated that over 70% of patients achieve full desensitisation. Unfortunately, the vast majority of patients undergoing OIT experience adverse reactions. Although these are usually mild symptoms, a significant percentage of patients may develop anaphylaxis. Children may also experience temporary deterioration in the quality of life due to the need to regularly consume the allergen and frequent hospital visits.

Good cooperation between children and their parents and the doctor is the key to success (in both milk ladder and OIT). It is important that the family strictly follows the doctor's recommendations. The patient and their caregivers must be aware of the risks associated with inducing milk tolerance and be properly trained to manage anaphylaxis.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study; writing of manuscript: AKB. Collection, recording and/or compilation of data: AKB, ASZ. Analysis and interpretation of data: AKB, ASZ, KG. Critical review of manuscript: ASZ, MK, KG. Final approval of manuscript: AKB, ASZ, MK, KG.

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