REVIEW

OPEN

MicroCrystalline Tyrosine-adsorbed immunotherapy

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Purpose of review
The purpose of this article is to provide an overview of the literature pertaining to the use of MicroCrystalline Tyrosine (MCT) in the immunotherapy with an emphasis on recent developments.

Recent findings
In addition to significant effectiveness and safety profiles, additional aspects of interest such as booster immunotherapy concepts, sustained clinical effects, long-term efficacy and disease-modifying effects are being focused on in the recently published studies. The depot adjuvant MCT also shows potential in promising disease-challenge models such as for malaria and melanoma.

Summary
MCT-adsorbed immunotherapy products have been shown to provide convincing overall safety, tolerability and efficacy outcomes, as well in vulnerable groups such as children and asthmatic patients.

Keywords
allergen immunotherapy, allergoid, MicroCrystalline Tyrosine, MonoPhosphoryl Lipid A

INTRODUCTION

The concept of allergen immunotherapy (AIT) was introduced in 1903 as a form of passive vaccination by Dunbar. Few years later, Noon and Freemen transferred the concept to an active vaccination by 'prophylactic inoculation against hay fever'. Until mid of last century, AIT was considered to be a vaccine, and allergens were considered to be toxins in pollen [1]. Likely with the discovery of IgE, this view changed towards desensitization and tolerance induction. Only recently, the original concept was revitalized driven by the growing understanding of the importance of IgG [2]. The term 'therapeutic vaccines for allergic diseases' was re-introduced by the WHO in 1997 [3] and more recently re-emphasized by others 'Where vaccines and AIT have been seen as different areas historically, AIT are now classified as therapeutic vaccines, leading to an immune modulation, with the aim of preventing and relieving allergic symptoms' [4].

Thus, AIT and prophylactic vaccinations started at the same time and were considered being similar. First critical learnings were shared between both such as modification of toxins to toxoids, respectively, allergens to allergoids or the introduction of adjuvants. Modification of native antigens is well established in vaccination. A Structure of a modified allergoid is shown in Fig. 1. Similarly, in AIT, the majority of subcutaneous AIT (SCIT) formulations are modified, resulting in a superior tolerability profile in children and adults [5,6]. However, traditional concepts of AIT developed towards desensitization and long treatment courses, whereas vaccination leverages on induction of protective humoral immunity by three injections and, if required, booster shots. A larger number of adjuvants have been established in the vaccine field, leading to adjuvant systems harnessing synergistic effects of combining adjuvants [7] or in our days to vector vaccines or mRNA technologies. There is nothing alike in the AIT field [8]: currently, only four adjuvants and one adjuvant system are used in commercially available SCIT formulations [9–11]. One of them being MicroCrystalline Tyrosine (MCT) respectively the adjuvant system of MCT and MonoPhosphoryl Lipid A (MPL).

There exist substantial differences in not only conducting allergen immunotherapy but also assessing AIT trials between the United States and Europe [12,13]. As an example, in Europe, only a limited number of well standardized aeroallergen species are used for AIT, whereas in the United States, a larger number of allergens and mixtures

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KEY POINTS

- MCT is a depot adjuvant used in subcutaneous AIT as a biodegradable alternative to the ubiquitous alum salts.
- Since the introduction of MCT-adsorbed immunotherapy products in the 1970s, a high profile of safety and efficacy was recorded.
- Recent studies investigating additional aspects of interest such as disease-modifying effects tend to show protective effects of MCT-adsorbed AIT against new development of asthma.

are in use. Also, in Europe, ready-to-use, adjuvanted, and modified allergen preparations dominate, whereas in the United States, nearly exclusively aqueous allergen extracts are used. Concerns about the usage of aluminium salts as adjuvants in AIT [14–16] might contribute here.

This review focuses on MCT-adsorbed immunotherapy utilizing modified allergens. MCT is a biodegradable Th1-polarizing depot adjuvant [17▪,18] with a superior safety profile [9]. Favorable physicochemical properties [19] and mode-of-action [18] are well described. The process of absorbing MCT to allergens is a sophisticated and IP-protected (WO12/143732) manufacturing step, probably best described by 'co-precipitation', resulting in the formulation of the allergens within the MCT needle-like structures. This process guarantees a controlled and synchronized release of allergen and adjuvant and assures no free allergen or free adjuvant is within the solution [20]. Combining a well tolerated and biodegradable adjuvant like MCT with allergoids (MCT-adsorbed Allergoids; Allergoid-MCT) allows the convenient delivery of high cumulative dosages throughout a treatment course. The platform of Allergoid-MCT is well established and marketed in numerous countries worldwide, covering a wider range of allergens. Table 1 provides an overview. Whereas Allergoid-MCT is predominantly positioned as a perennial treatment scheme, the introduction of a powerful adjuvant system consisting of MCT and MPL allowed the introduction of ultra-short course preseasonal AIT [Allergoid-(MCT-MPL) Adjuvant System, Pollinex Quattro, PQ]. Table 2 illustrates the availability and allergen spectrum of this product platform. Adopting concepts from vaccination into AIT, such as modification and modern adjuvants, respectively, adjuvant systems revolutionized AIT and will further do so [21]. Also, vaccine concepts like 'booster AIT' could successfully be established within the AIT field using product platforms based on adjuvant systems [22].

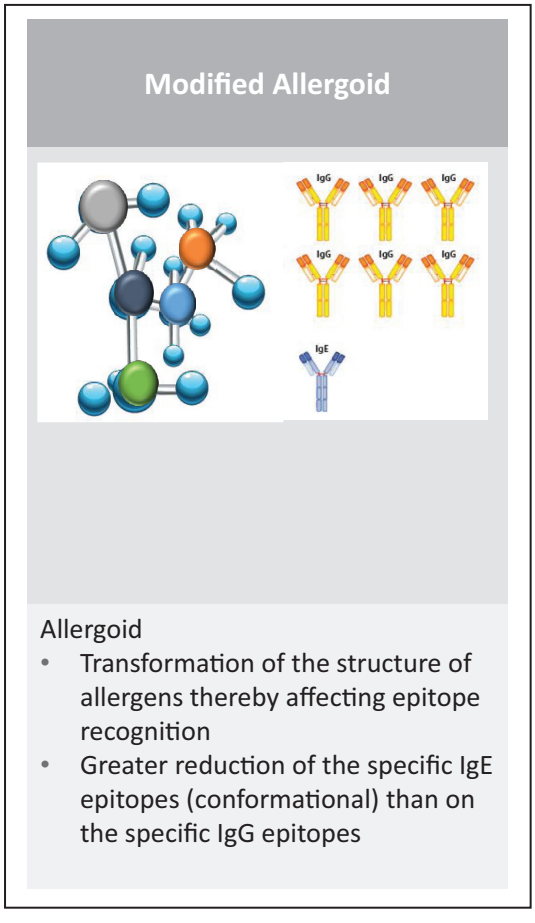


FIGURE 1. Modified Allergoid.

THE ADJUVANT MICROCRYSTALLINE TYROSINE

MCT is the crystalline form of the nonessential amino acid L-tyrosine. Its use as a depot adjuvant in subcutaneous AIT reaches back several decades as the biodegradable alternative to the ubiquitous alum salts [17▪,23]. MCT has an estimated half-life of 48 h at the injection site and is completely cleared from the site within 7 days [18]. The depot effect and the resulting prolonged immune exposure are important for humoral and cellular immune responses [24]. This is especially notable as there has been a discussion on whether alum salts' immunological effects are attributed to their depot function at all [25,26].

MCT has been shown to have broad adsorption capacity not only with model antigens and allergens but also nanostructures such as Virus Like Particles (VLPs), which is in part attributed to its crystalline structure [20]. This crystalline structure is described as needle-like, with a tendency to form stacks, which results in a high degree of structural order [19]. These structures can aggregate to rods exceeding 5 μm in length. This may play an important role in the safety profile of MCT as seen in Fig. 2, as reuptake and recognition by THP-1 macrophages

Table 1. MicroCrystalline Tyrosine-Allergoid products marketed worldwide

Allergen	Country	Trade name
Grass mix	Netherlands	Pollinex Graspollen
	Italy	M.A.T.A. Graminacee
	Czech Republic, Macedonia, Poland, Slovak Republic, Serbia, United Kingdom	POLLINEX Grasses + Rye
	Germany	TA Gräser top
	Switzerland	Polvac Gräser + Roggen
	Albania, Croatia, Estonia, Latvia, Lithuania	POLLINEX Rye
Birch + alder + hazel	Netherlands	Pollinex Boompollen
	Czech Republic, Macedonia, Poland, Slovak Republic, Serbia, United Kingdom	POLLINEX Tree
	Germany	TA Bäume top
	Switzerland	Polvac Bäume
	Albania, Croatia, Estonia, Latvia, Lithuania	POLLINEX Tree
Ragweed	Canada	POLLINEX-R
Mites	Austria	Acarovac
	Albania, Estonia, Italy, Latvia, Portugal, Spain, United Kingdom	Acarovac Plus
Individual recipe	Germany, Croatia	TA Kräuter top
	Italy	M.A.T.A. Free Dose
	Spain	Polligoid

and thus transport across barriers like the blood–brain barrier are hindered [19].

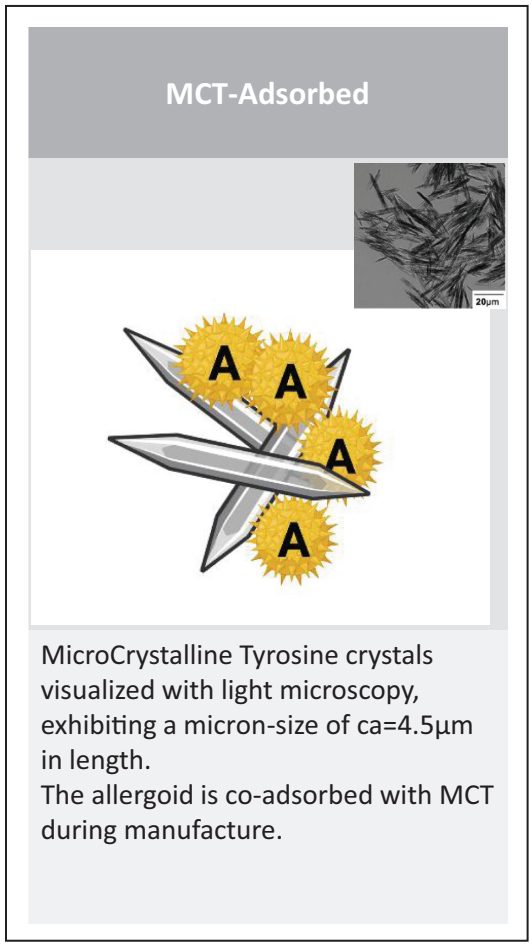
MCT has been described as a depot adjuvant for the first time in 1982 [27]. Since then, its immunological properties have been extensively studied, and compared with alum in head-to-head trials. Alhough most B-cell responses were indeed comparable to alum when experimentally combined with model allergens, MCT triggered notably less IgE, the key mediator of allergic responses. This effect is consistent across several studies [18]. MCT has also been shown to trigger specific T-cell cytokine responses, which in concert makes it a Th 1-biased depot adjuvant, a favorable quality when used for treating allergies. While both, MCT and alum, were found to activate the inflammasome, this activation does not seem to be relevant for generating neither B-cell and T-cell responses nor early inflammatory markers and, therefore, unlikely to affect the immune response needed for the production of antibodies in AIT [18].

MCT's preferred physical association with the TLR4 receptor agonist MPL has been extensively characterized [20]. Immunological synergy has been well documented in allergoid formulations when compared with formulations with only MCT

Table 2. Allergoid-(MCT-MPL) Adjuvant System products marketed worldwide

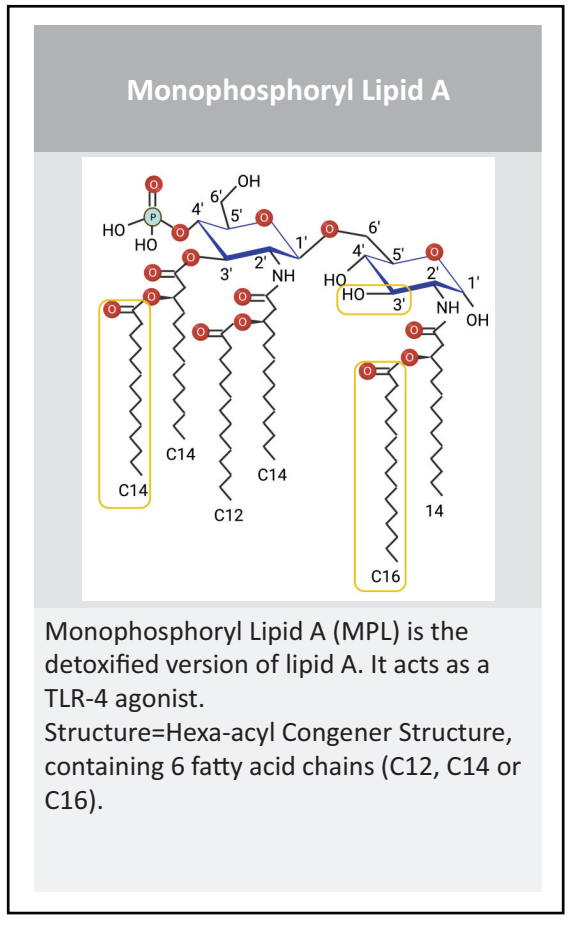
Allergens	Country	Trade name
Grass mix	Austria	POLLINEX Quattro Plus 1,0 ml
Rye[a]	Albania, Germany, Greece,	POLLINEX Quattro
Birch	Portugal, Spain, United Kingdom	
Birch + alder + hazel		
Olive		
Ragweed		
Mugwort		
English plantain		
Parietaria[a]		
Fat Hen[a]		
	Italy	Quattro + mpl adjuvant 1,0 ml

[a]Not available in all markets.



MicroCrystalline Tyrosine crystals visualized with light microscopy, exhibiting a micron-size of ca=4.5µm in length.
The allergoid is co-adsorbed with MCT during manufacture.

FIGURE 2. MCT-Adsorbed.



Monophosphoryl Lipid A (MPL) is the detoxified version of lipid A. It acts as a TLR-4 agonist.
Structure=Hexa-acyl Congener Structure, containing 6 fatty acid chains (C12, C14 or C16).

FIGURE 3. Monophosphoryl Lipid A.

[28,29]. This synergy effect has been used in the PQ platform, allowing the introduction of preseasonal short-course SCIT courses.

Even though MCT has originally been in use primarily for AIT, its depot and immunological characteristics have been explored for other indications: VLPs based on the cucumber mosaic virus plus MCTA (CuMVtt + MCT) has been used in two preclinical malaria challenge model where the combination with MCT improved efficacy significantly compared with alum [30,31]. The structure of MPL is illustrated in Fig. 3. The same platform was used to display T-cell epitopes in an aggressive transplanted melanoma murine model lead to improved antitumor efficacy compared with a formulation without MCT [25]. In an influenua model, MCT was *en par* with alum as a depot adjuvant [32]. MCT's feature to activate T cells seems to be universal.

EVIDENCE FROM DOUBLE-BLIND PLACEBO-CONTROLLED TRIALS

As Allergoid-MCT has been marketed for decades, many clinical studies including DBPC trials have been conducted since their introduction on the market. A recently published meta-analysis undertaken by Becker *et al.* [33▪] provides an overview about the evidence generated since the 1970s. These data formally fulfil the highest standard for the level of evidence (1A) according to the European Academy of Allergy and Clinical Immunology (EAACI), because they are based on a systematic literature review and meta-analysis [34]. It is focused on MCT-adsorbed pollen allergoids and clearly demonstrates a significant improvement in allergic symptoms and a reduction in the use of antiallergic medication when compared with placebo, together with an excellent safety profile [33▪]. The analysis included, among other randomized controlled trials (RCTs), controlled trials and noncontrolled studies, eight double-blind placebo-controlled trials (DBPCs) with a total of 884 patients with seasonal allergic rhinoconjunctivitis. Those patients also included vulnerable populations such as children and asthmatic patients. The results were unambiguous: for the primary efficacy analysis, there was a significant improvement in the combined symptom and medication score (CSMS) after treatment with

Allergoid-MCT compared with placebo, being similar or even better results than comparable meta-analyses [35–37] in the AIT field mentioned by the authors. Although those DBPC trials were published between 1974 and 1995, they were state-of-the-art when conducted. Evaluating the quality of those trials today, six out of eight trials proved to be sufficient and met the current standard [33▪].

Looking at the PQ platform, when MCT is combined with MPL, the clinical development program is still ongoing [38–40]. Up to 2020, 26 phase I–III clinical trials have been conducted using different allergens and including 4695 patients in total [17▪]. Four DBPC trials conducted with either ragweed [29], grass [41,42] or tree [38] pollen allergoids led to the highest evidence level evaluated by EAACI, proving consistent evidence for the used adjuvant system. Therefore, the PQ platform was rated with grade 1A recommendation in the AIT guidelines for allergic rhinoconjunctivitis [34].

NONCONTROLLED AND NONINTERVENTIONAL STUDIES

Since their inception in the 1970s, more than 100 published studies have been conducted with Allergoid-MCT-based AIT in over 17 000 patients [22,29,33▪,38,41–57,58▪▪,59▪,60▪,61–63,64▪▪,65, 66]. These studies include a wide and heterogeneous variety of allergen extracts (including grass, trees, weeds and mites), product platforms (including Allergoid-MCT and PQ) and study designs (including DBPC trials, biomarker studies, noncontrolled studies, noninterventional studies and investigator-initiated research). Several studies have also enrolled children and adolescents [33▪,51,55,58▪▪,65].

While the majority of published studies are observational trials concentrating on basic effectiveness and safety outcomes, there are several studies focusing on additional aspects of interest.

Booster allergen immunotherapy concepts

A 2017 study [22] has shown the potential to refresh the effect of past successful AIT using a single booster course of PQ.

Sustained clinical effect

Several studies have explored the treatment effect of Allergoid-MCT and PQ over longer treatment time, finding generally improving treatment effects in the second or third year of treatment [46,47,52,55,67,68].

Long-term efficacy and disease-modifying effects

Carry-over effects for several years after treatment completion have been demonstrated in long-term follow-up studies for both Allergoid-MCT and PQ [47,52,55,67], with some studies indicating reduced risk of newly developed asthma [46,69,70▪,71].

Real-world evidence

A recent large-scale retrospective analysis of prescription data in Germany was able to show significant reduction of symptomatic medication use for patients treated with pollen Allergoid-MCT using perennial therapy schedules, as well as confirming protective effects of AIT against new development of asthma [71].

Table 3 gives an overview of published studies for the different Allergoid-MCT products.

Safety data

At present, and since its introduction into AIT in 1970, there are no specific safety concerns known for MCT. It can be anticipated that this fully biodegradable adjuvants will also in future studies not reveal side effects [72]. All available data demonstrate a convincing overall safety and tolerability profile for MCT-adsorbed immunotherapy products: In 43 studies using pollen Allergoid-MCT [33▪], 9 studies using mite Allergoid-MCT [58▪▪, 59▪,60▪,61,62,63,64▪▪,65,66] and 20 studies using PQ [22,29,38,41–57], no treatment-related serious adverse events have been reported.

Table 3. Numbers of studies and patients by product platform and study design

Product	Type	Number of studies	Number of patients
Allergoid-MCT pollen	DBPC	8	884
	CT	18	1077
	NCT	47	4496
Allergoid-MCT mite	DBPC	0	0
	CT	1	30
	NCT	8	819
PQ pollen	DBPC	8	2527
	CT	4	377
	NCT	8	7564
Total		102	17774

CT, controlled trials; DBPC, double-blind placebo-controlled trials; MCT, MicroCrystalline Tyrosine; NCT, non controlled trials.

Table 4. Adverse reaction rates in postmarketing safety studies

Study	*N*	Product	Percent local	Percent systemic
Drachenberg, 2003	1808	Allergoid-MCT pollen	1.85	0.76
Zielen, 2007	3114	PQ	8.1	0.9
Rosewich, 2010	422	PQ (pediatric)	6.3	0.5
Caminati, 2019	2929	PQ	N/A	2.0[a]
Sala-Kunil, 2020	308	Allergoid-MCT mite	6.5	2.3

MCT, MicroCrystalline Tyrosine.
[a]Study also reports 3.3% nonspecific 'Grade 0' reactions.

Larger scale postmarketing trials report mostly local reactions [48,64▪▪,73]. Systemic reactions reported are few and mostly limited to generalized skin symptoms and/or symptoms of rhinitis and conjunctivitis [48–50,53,57,64▪▪]. Where patient-reported acceptance data is available, data shows over 90% good or very good acceptance and tolerability [48–50,73]. Table 4 summarizes adverse reaction rates in these studies.

Safety data from spontaneous reporting is available for more than 9 million injections (including vulnerable groups such as children and the elderly) since the introduction of MCT-adsorbed immunotherapy products in the 1970s, without identified safety risks or detriments to the risk–benefit ratio of the products [17▪].

MCT as a depot adjuvant has been shown to provide excellent tolerability [27,74]. A recent position paper on adjuvants and formulations in Allergen Immunotherapy by EAACI describes no specific safety concerns for MCT, and does not anticipate future identification of side effects [9].

MPL as the additional immunological adjuvant in PQ has been in clinical use for vaccines since the 1990s [75]. This includes several vaccines marketed by GlaxoSmithKline, such as Cervarix, Fendrix and Shingrix [7]. Studies of its use have found MPL well tolerated for human use [75,76], with mainly transient local reactions noted as common [9].

CONCLUSION

This review focusses on MCT-adsorbed immunotherapy utilizing modified allergens. MCT is a biodegradable Th1-polarizing depot adjuvant with a superior safety profile. Favorable physicochemical properties and mode-of-action are extensively described and synergistic effects of combining with MPL are long proven. Consistently, MCT-adsorbed SCIT products, Allergoid-MCT and PQ are well established product platforms in human use over decades with an exceptional safety and efficacy profile fulfilling 1A grade evidence.

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Conflicts of interest

H.A.S., none. R.M. reports personal fees from Angelini Pharma, personal fees from ALK, grants from ASIT biotech, personal fees from allergopharma, personal fees from Allergy Therapeutics, grants and personal fees from Bencard, grants from Leti, grants, personal fees and nonfinancial support from Lofarma, nonfinancial support from Roxall, grants and personal fees from Stallergenes, grants from Optima, personal fees from Friulchem, personal fees from Hexal, personal fees from Servier, personal fees from Klosterfrau, nonfinancial support from Atmos, personal fees from Bayer, nonfinancial support from Bionorica, personal fees from FAES, personal fees from GSK, personal fees from MSD, personal fees from Johnson&Johnson, personal fees from Meda, personal fees and nonfinancial support from Novartis, nonfinancial support from Otonomy, personal fees from Stada, personal fees from UCB, nonfinancial support from Ferrero, grants from BitopAG, grants from Hulka, personal fees from Nuvo, grants and personal fees from Ursapharm, personal fees from Menarini, personal fees from Mundipharma, personal fees from Pohl-Boskamp, grants from Inmunotek, grants from Cassella-med GmbH & Co. K.G., personal fees from Laboratoire de la Mer, personal fees from Sidroga, grants and personal fees from HAL BV, personal fees from Lek, personal fees from PRO-AdWise, outside the submitted work.

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- ▪ of special interest
- ▪▪ of outstanding interest

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