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Human Medicines Development and Evaluation

CHMP Safety Working Party's response to the PDCO regarding aluminium hydroxide contained in allergen products

Question 1

Given that the frequency of dosing differs strongly from the vaccines the PDCO would like to know whether the vaccine guideline (EMEA/CHMP/VEG/134716/2004 "Guideline on adjuvants in vaccines for human use") is applicable and covers also potential risks associated with such a long-term repeated administration of Aluminium Hydroxide and potential accumulation in target organs?

Or, should the safety assessment rather be based on the yearly cumulative contamination and which would be the maximum tolerable values in that case?

Response:

According to the scope of the "Guideline on adjuvants in vaccines for human use", "the principles of this guideline should also be applicable to quality and non-clinical aspects of 'therapeutic vaccines' (e.g. …allergen specific immunotherapy …)". Thus, the Guideline is applicable also for allergen specific immunotherapy products. However, its main focus is the evaluation of new adjuvants and "the applicability of this guideline to established adjuvants (i.e. aluminium hydroxide and aluminium or calcium phosphate) will vary on a case-by-case basis."

The use of aluminium hydroxide as adjuvant in products for specific immunotherapy is established for several decades and is regulated in the European Pharmacopoeia. In the general monograph "Allergen Products" (Ph. Eur. 01/2010:1063) the Al content is restricted to 1.25 mg per human dose and manufacturers of allergen products comply with this maximum amount of Al. Up to now, the spontaneous surveillance system of adverse events in pharmacovigilance and clinical studies have not revealed safety concerns regarding the aluminium in allergen immunotherapy apart from well-known local reactions (granuloma etc.).

Thus, additional non-clinical safety studies in accordance with the "Guideline on adjuvants in vaccines for human use" are not considered useful to address the special risk resulting from long-term repeated administration.

Concerning the second part of the question see response to question 2a.

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Question 2

Given that these types of products are administered s.c. as 4- or 6-weekly injections over a period of up to 4 years and each injection contains about 0.5mg Aluminium Hydroxide,

a) Does the SWP consider the administered doses of Aluminium Hydroxide contained in these Allergens acceptable without raising specific concerns?

b) If not, what are the concerns and what data is required from the applicants in order to address them?

c) Does the SWP consider that short- or long-term safety monitoring is necessary and if so which parameters need to be included (length, specific safety endpoints,..)?

Response:

2.a) From a toxicological point of view, two safety concerns have to be distinguished when Al exposure from allergens is addressed: (i) acute toxicity arising from possibly toxic Al plasma levels and (ii) chronic toxicity arising from the contribution to the Al "body burden" based on the assumption that Al is retained to a certain extent in the organism. Acute systemic toxicity of Al mainly consists of neurotoxicity, osteomalacia and anemia.

Concerning acute toxicity, Al exposure from allergens can be compared with safe exposure levels from other Al sources.

The primary aluminium source for man is food [i]. Al intake by food varies widely between different regions in Europe, the range is reported to be 0.2-1.5 mg/kg per week for adults and 0.7 – 2.3 mg/kg per week for children (18 months to 13 y) [ii]. A tolerable weekly intake (TWI) level of 1 mg/kg per week for Al by diet was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2006 [iii] and by the European food safety authority (EFSA) 2008 [2].

For the subcutaneous route a NOEL level of 0.7 mg/kg per day was found for 20 subcutaneous injections in rabbits during postnatal development studies [iv].

Normal plasma levels of Al in man are about 5 µg/L. Critical plasma levels associated with disturbance of cerebral function in patients in long-term dialysis were reported to be about 59 µg/L (Sjögren and Elinder 1992) and about 100 µg/L associated with osteomalacia [v].

Relevant Al sources from pharmaceuticals are antacids. Very high plasma Al levels can be observed. Even in children mean levels of 37 µg/L were measured after consumption of 123 +/- 16 mg/kg per day (mean +/- SEM) of elemental aluminium for an average of 4.7 weeks [vi]. Due to safety concerns there is a warning statement in the SmPC of Al-containing antacids that plasma levels should be kept below 40 µg/L.

Therapy allergen products licensed in Germany contain Aluminium hydroxide in amounts of 0.113 – 1.135 mg/ml, equal to mg per dose during the maintenance therapy of 0.113 – 1.135 mg. However, only one manufacturer uses the high amount of 1.135 mg/ml with a dose of 1 ml per administration for one of his product lines. Most licensed allergen products in Germany contain lower amounts of Al and the application doses are also lower resulting in 0.113 – 0.6 mg Al per dose. This is also reflected in the Al contents in several allergen products which are on the market in Germany as "Named patient products" (0.18 – 0.8 mg/dose).

One possibility of risk assessment is to compare the cumulative amounts resulting from a 6-weekly immunotherapy using an allergen with different contents of Al/dose to the amount of Al from food which is considered to be safe throughout lifetime (1 mg/kg per week, see above). A relevant

comparison must take into account the bioavailability of Al from the different application routes in order to compare only systemically available amounts of Al from both sources: Average oral bioavailability of Al from diet is reported to be 0.1 – 0.3 % (literature data range from 0.05 to 0.5 %, highly variable dependent on the pH or the presence of ions, most likely 0.1-0.3 %; see review by Yokel and McNamara 2001 [1]). It is unknown whether oral bioavailability of Al is age-related.

Absorption after subcutaneous administration is theoretically 100 % but the rate of absorption is expected to be very low due the insolubility of the Al salts used as adjuvants. However, there are no data on Al concentrations in plasma or urine after s.c. or i.m. application of Al-hydroxide in humans which would allow to estimate absorption rates.

Plasma half-life of Al is reported to be about 4 h. Due to the presumably slow absorption of Al from injected allergen product adsorbed to aluminium hydroxide, the application should be similar to a sustained-release drug depot. Thus, a steady state plasma level should be reached when the daily absorbed amounts stay constant.

Based on these assumptions, a calculation of systemically available cumulative amounts of Al after one year from daily dietary intake compared to that from 6-weekly immunotherapy with allergens containing different Al amounts (corresponding to 8 allergen doses) was done for adults (Table 1) and for a child weighing 20 kg (mean body weight of a 5year old child which is the lowest age indicated for immunotherapy with these products) (Table 2).

Table 1 Comparison of cumulative Al doses in adults

Exposition	Dose Al	Dose for an adult 65 kg	Dose interval	Absorption %	Cumulative absorbed dose/year[a]
Allergen	1.14 mg s.c.	1.14 mg	6 weeks	100	9.12 mg
Allergen	0.5 mg s.c.	0.5 mg	6 weeks	100	4 mg
Allergen	0.15 mg s.c.	0.15 mg	6 weeks	100	1.2 mg
Safe oral dietary intake (TWI [b])	1 mg/kg p.o.	65 mg	1 week	0.1 – 0.3[c]	3.3 – 10.1 mg
Real dietary intake (EU[d])	0.2-1.5 mg/kg p.o.	13 – 98.5 mg	1 week	0.1 – 0.3[c]	0.7 – 15.4 mg

[a] corresponding to 8 allergen doses

[b] tolerable weekly intake established by JEFCA 2006 and EFSA 2008 (see text)

[c] Yokel and McNamara 2001 [1].

[d] data from EFSA (http://www.efsa.europa.eu/en/press/news/afc080715.htm)

Table 1 shows that in adults, allergen therapy with an intermediate Al amount per dose (0.5 mg) leads to a cumulative absorbed dose after one year which is comparable to the lowest level resulting from oral intake of safe levels of food over the same time interval. Assuming linear pharmacokinetics and constant daily absorption, Al plasma levels should be proportional to the daily/cumulative absorbed dose. And the amounts from both sources should be additive during the years of immunotherapy.

Therefore, it might be deduced that during immunotherapy with 0.5 mg Al/dose, steady state aluminium plasma levels would maximally rise to about 2fold of the lowest level expected after dietary

intake of safe amounts according to TWI. Immunotherapy using products with the highest amount of Al (1.14 mg/dose) results in a cumulative absorbed dose which is 3-times of the lowest level resulting from oral intake of safe levels of food. This might lead to a 3fold increase in plasma levels during the period of immunotherapy

The results are in accordance with the calculations done by Yokel and McNamara [1]: They calculated daily absorbed amounts of Al by allergy immunotherapy (0.1-0.6 µg/kg; based on maintenance injections for 3.5 years to an 65 kg adult) which were in the magnitude of the amount daily absorbed by food (0.08-0.5 µg/kg; based on 65 kg adult).

Table2 Comparison of cumulative Al doses in children

Exposition	Dose Al	Dose for a child 20 kg	Dose interval	Absorption %	Cumulative absorbed dose/year[a]
Allergen	1.14 mg s.c.	1.14 mg	6 weeks	100	9.12 mg
Allergen	0.5 mg s.c.	0.5 mg	6 weeks	100	4 mg
Allergen	0.15 mg s.c.	0.15 mg	6 weeks	100	1.2 mg
Safe oral dietary intake (TWI [b])	1 mg/kg p.o.	20 mg	1 week	0.1 – 0.3[c]	1.0 – 3.1 mg
Real dietary intake (EU[d])	0.7 – 2.3 mg/kg p.o.	14 – 46 mg	1 week	0.1 – 0.3[c]	0.73 – 7.2 mg

[a] corresponding to 8 allergen doses

[b] tolerable weekly intake established by JEFCA 2006 and EFSA 2008 (see text)

[c] Yokel and McNamara 2001[1] data from EFSA (http://www.efsa.europa.eu/en/press/news/afc080715.htm)

Table 2 shows that the calculations are slightly different for a child, since intake by food is BW-related and the allergen dose is not: Analogous to the considerations above for the adults, steady state aluminium plasma levels could rise to about 4fold or 9fold, respectively, of the lowest Al level expected after dietary intake of safe amounts according to TWI. However, both cumulative amounts are still in the range of highest intake levels from food observed in the EU in this age group.

In conclusion, the calculations above indicate a theoretical safety concern for the 6-weekly maintenance allergen immunotherapy in children (20 kg) treated with allergen products that contain high Al amounts (> 0.5 mg) per dose.

Regarding "chronic toxicity" (aluminium body burden; discussion on Alzheimer disease etc.) rather long-term cumulative calculations have to be considered: During 3 years of immunotherapy using an allergen containing 0.5 mg Al/dose a cumulative absorbed amount of 12 mg Al can be estimated for both children and adults (see Table 1 and 2). This cumulative dose adds to a life-long (+50y) cumulative amount of 165 - 505 mg absorbed from safe intake by food (TWI) by an adult. Thus, the contribution of immunotherapy to the life-long aluminium body burden is below 10 % if the lowest level of weekly intake is considered and below 2.5% considering the highest weekly intake if the oral absorption rate will be 0.3%. Compared to the real dietary intake, there is no reason for concerns regarding chronic toxicity.

In addition to the theoretical risk estimation above, a safety assessment was made based on adverse events reported in the spontaneous surveillance system of pharmacovigilance and clinical trials. Using the German database, including all spontaneous reports of serious and non-serious cases received from 1988 until 2008, reactions of interests, such as granulomas and potential toxic events caused by aluminium were analysed (Table 3).

A total of 2755 cases where allergen preparations had been administered, including 7638 reactions were analysed. 48 cases with reported reactions of granuloma or induration were identified. 5 reports of necrosis or dystrophy were reported. In 10 cases dyspigmentation occurred. With regard to general toxic reactions, 2 cases of liver function test abnormal, one case each of nephrotic syndrome, proteinuria and encephalopathy were identified during the reporting period of 21 years. Additionally, 12 cases of alopecia or hair loss have been received. A review of neurological events revealed, that in the majority of cases the reactions could be assessed as symptom of systemic or anaphylactic reaction. No cases of anaemia or osteomalacia were reported.

Given the review period of 21 years and the low number of reported events of special interest, the data did indicate no safety concerns regarding allergen immunotherapy apart from well-known local reactions (granuloma etc.).

Table 3 Events of interest from 1988 until 2008, reported from Germany

Reaction	Number of reactions
Application site induration	1
Fat necrosis	1
Granuloma	11
Granuloma NOS	2
Granuloma injection site	1
Granuloma skin	2
Induration	6
Injection site discoloration	3
Injection site gramuloma	3
Injection site induration	10
Injection site infiltration	5
Injection site nodule	3
Injection site pigmentation	1
Necrosis	1
Necrosis injection site	1
Vaccination site induration	1
Liver function tests NOS abnormal	1
Liver function tests raised	1

Encephalopathy	1
Nephrotic syndrome	1
Proteinuria	1
Accelerated hair loss	1
Alopecia	1
Alopecia areata	4
Alopecia totoalis	2
Discoloration skin	2
Hair loss	4
Lipoatrophy	1
Pigmentation	1
Skin discoloration	3
Skin erosion	1
Skin nodule	1
Subcutaneous nodule	2

2.b) As described in 2a) the only concern is that, in children, during the maintenance phase using allergens with high Al content (> 0.5 mg/D) the plasma steady state levels of Al might rise to about 4 – 9-times of the level expected from the lowest safe dietary Al intake.

Simulations of absorbed Al amounts (as in response to Q2a) do not reflect the whole pharmacokinetic picture, since rates of absorption can be much higher than assumed. Then plasma levels might be higher for a short time while the average level is not affected so much. Therefore, in order to answer this question Al plasma level after s.c. administration has to be measured. This should be addressed in pharmacokinetic studies by determining the Al plasma (and urine) concentrations after allergen exposure throughout a dose interval (e.g. before immunotherapy, after the first maintenance dose and after 1 year of exposure). These PK measurements could be included in the long-term-efficacy studies in adults which are already requested.

Until such data are available, is it considered acceptable to use allergen products containing up to 0.5 mg Al per dose in children.

2.c) There has been no safety signal arising from pharmacovigilance. Short- or long-term-safety monitoring (besides routine safety monitoring) is not considered useful at the moment. The theoretical concern of acute Al toxicity can be easily addressed by pharmacokinetic studies (see 2b). These results should be awaited.

On behalf of the Safety Working Party,

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Chairperson

References:

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