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Vaccination during concurrent subcutaneous immunotherapy: safety of simultaneous application

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Key words

Vaccination against infectious diseases; allergen-specific subcutaneous immunotherapy; IgE-mediated allergy, simultaneous application

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Summary

Background. *During subcutaneous immunotherapy (SCIT), injections should be separated from vaccinations against infectious diseases by at least 1 week, because it is assumed that adverse reactions can result from the additional activation of the immune system.* ***Material and Methods.*** *Data of a total of 875 individuals receiving SCIT and/or vaccination in one ENT-practice were included and analyzed retrospectively. 444 individuals had received vaccination against infectious diseases, 336 allergic patients received only SCIT. Moreover, 79 allergic patients had received vaccination and SCIT injections simultaneously on one day in different locations, while 16 patients inadvertently received SCIT injections within up to 4 days after vaccination. Some of the patients were observed for consecutive years receiving several vaccinations parallel to SCIT. Systemic reactions (SRs) during SCIT were classified according to the WAO (World Allergy Organization) grading.* ***Results.*** *Patients exclusively receiving vaccinations did not report any drug-related SR. One SR third grade and two SRs second grade occurred in 3 asthmatic patients exclusively receiving SCIT. The patients simultaneously receiving vaccination and SCIT did not have any SR. This was also the case for the subjects consecutively receiving parallel SCIT and vaccination for up to 5 years.* ***Conclusion.*** *The international guidelines for allergen-specific immunotherapy (SIT) recommend an intermission of at least one week between SCIT and the administration of vaccines. However, these findings demonstrate the possibility to shorten or abolish this interval without increasing the risk of SRs.*

Abbreviations

SCIT - subcutaneous immunotherapy
SR - systemic reaction
WAO - World Allergy Organization
SIT - allergen-specific immunotherapy
WHO - World Health Organization
FDA - Food and Drug Administration
DTP - diphtheria/tetanus/pertussis
EAACI - European Academy of Allergy and Clinical Immunology
MMR - measles/mumps/rubella
TBE - tick-borne encephalitis
ELISA - enzyme-linked immunosorbent assay
RAST - radioallergosorbent assay
SmPC - Summary of Product Characteristics

Introduction

The immune system is a complex interactive network with the capacity of protecting the host from a number of pathogens while keeping either a state of tolerance to self and innocuous non-self antigens or to develop an adaptive immunity against pathogens (1). IgE-mediated allergic diseases are immune tolerance-related and arise as a direct consequence of a dysregulated immune system. The innate and adaptive immune responses to environmental antigens lead to inflammatory reactions with a T-helper-2-type cell and allergen-specific IgE predominance (1).

Currently, allergen-specific immunotherapy remains the only curative approach by administering gradually increasing quan-

tities of an allergen product to an individual with IgE-mediated allergic diseases (2). It induces clinical and immunological tolerance, and thereby improves the quality of life in allergic patients. SIT has long-term efficacy and may prevent either disease progression of rhinitis into asthma and/or the onset of new allergic sensitizations (2).

In general, subcutaneous immunotherapy is started with an up-dosing phase until reaching the maintenance dose. The up-dosing phase may be conducted as conventional 'one injection per week', or alternatively as a clustered or rush regimen (2). In case of a perennial dosage scheme, the injection interval may be spread up to 8 weeks during the maintenance phase, depending on the manufacturers' recommendation. In case of larger intervals, the allergen doses have to be reduced or even SCIT has to be restarted. It is recommended to perform SCIT for 3 to 5 years.

Vaccination is the use of antigenic substances to prevent infectious diseases and/or ameliorate the outcome of infectious- and/or toxin-related diseases. As to the World Health Organization (WHO), "a vaccine is a biological preparation that improves immunity to a particular disease. It typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters."

In the beginning, vaccines like tetanus and diphtheria were administered separately. Having once established the value of each of these, it was proposed combining them, though there was the possibility of interaction between the immune responses (3,4). In the best case, association enriches the immune response which may enhance the protective efficacy. In the worse case, however, a vaccine in association with another displays poorer immunogenicity than the same vaccine administered alone (3). One of the first combination vaccines to be licensed by the Food and Drug Administration (FDA) was diphtheria/tetanus/pertussis (DTP) in the late 1940s (5). Today, the simultaneous vaccination and/or the use of combined vaccines is widely and successfully practiced.

Although SIT is often also called "allergen vaccination" there is a major difference to vaccination against infectious diseases. SIT is usually associated with therapeutic intervention in already sensitized individuals. In contrast, the vaccination against infectious diseases is administered to prevent a disease before its manifestation, and therefore it sensitizes the organism against infectious pathogens (6).

Nevertheless, since SCIT and vaccination for infectious diseases both influence the immune system, there are recommendations to separate the injections. As per the EAACI (European Academy of Allergy and Clinical Immunology) task force paper, "allergen injections should be separated from vaccinations by at least 1 week (2) because it is assumed that adverse reactions can result from the additional activation of the immune system" (7). Many manufacturers recommend interrupting subcutaneous immunotherapy for a total of 3 weeks in case of vaccination. This might be especially difficult during the up-dosing phase, when allergen injections are mainly administered in weekly intervals. Also during the maintenance phase, additional consultations cause inconvenience in patients who already perform a time-consuming SCIT. This raises the question whether it is possible and safe to administer both injections for SCIT and vaccination simultaneously, and if there is an increased risk in a case of simultaneous application. With this retrospective analysis the safety and feasibility of simultaneous SCIT and vaccination should be analyzed.

Material and methods

A total of 875 patients (about 23% children/adolescents up to 18 years of age) receiving SCIT and/or vaccination between 2007 and 2012 in one German otorhinolaryngological medical practice were included and analyzed retrospectively. For demographic data see **table 1**.

Table 1 *- Demographic data.*

Number of patients receiving	
Vaccination	444
SCIT	336
SCIT and vaccination simultaneously (total)	95
thereof intended	79
thereof accidentally	16
Sex	
Male	45%
Female	55%
Age	
Range	3-91 years
thereof children (< 18 years)	23%

444 individuals (age 3 to 91 years) had received at least one vaccination with influenza, pneumococcus, tetanus, tetanus / diphtheria, measles / mumps / rubella (MMR), hepatitis and/or tick-borne encephalitis (TBE).

SCIT was performed in patients with severe IgE-mediated allergic diseases (rhinitis and/or asthma) who showed respective allergen-related symptoms at exposure, a positive skin prick test, existence of specific IgE ≥ class 3 (ELISA, RAST) and a

Table 2 *- Number of patients receiving SCIT and vaccination simultaneously (n = 95).*

Number of patients receiving simultaneously	**Vaccination with**				
SCIT with	**Influenza**	**Pneumococcus**	**TBE**	**Hepatitis**	**Tetanus**
mite	25	3	-	-	-
early blooming trees	56	-	-	3	1
grasses	43	2	2	-	-
cat	2	1	-	1	-
lepidoglyphus	1	-	-	-	-
wasp	2	-	-	-	-
bee	1	-	-	-	-
dog	1	-	-	-	-

Patients receiving at least 2 SCIT preparations and 1 vaccine occur multiple. Patients receiving one SCIT preparation and at least 2 different vaccines occur multiple. Patients receiving 1 SCIT preparation and the same vaccine more than once occur once only. (TBE = tick borne encephalitis)

positive nasal provocation test. A total of 431 allergic patients (age 5 to 73 years) received SCIT. Of these, 336 patients were treated with SCIT only while 79 patients received vaccination and SCIT injections simultaneously on one day at different locations, e.g. into the left and right arm. Every patient was informed about that this procedure is not recommended by the manufacturer or the guidelines. This procedure was performed in all patients who agreed. No patient was excluded because of asthma. Additionally, 16 patients inadvertently received SCIT injections within up to 4 days after vaccination because they had not informed the physician about their previous vaccinations, that were administered in the practice of another physician. All patients were in the maintenance phase of SCIT.

Allergoids as well as unmodified depot preparations (Allergopharma GmbH & Co. KG, Reinbek, Germany; ALK-Abelló, Wedel, Germany) were used for SCIT, predominantly in a perennial application mode. **Table 2** shows the number of patients receiving vaccination and SCIT simultaneously as well as the type of vaccination and the allergen for SCIT.

Independent of the SCIT preparation, there was no dose reduction during the pollen season or when starting a new package. Allergen dose was only reduced in case of interruption of SCIT for more than 10 weeks. Some of the patients were observed for up to 5 consecutive years receiving several vaccinations during SCIT. Systemic reactions (SRs) were evaluated according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (8). Local adverse reactions like swelling, redness and itching were not documented. Patients got the physician's mobile phone number, to call him in case of delayed local or systemic reactions for up to 24 hours after the SCIT injection.

This survey was neither initiated nor sponsored by industry.

Results

Patients exclusively receiving vaccinations did not report any drug-related SR.

3 patients with allergic asthma receiving SCIT only showed one immediate SR each: One SR grade 3 (dyspnoea) and two grade 2 (shortness of breath, asthma) (**table 3**). Due to practice's competency of emergency treatment none of these patients was admitted to hospital and all recovered within 2 hours. No patient called the physician's mobile phone because of delayed local or systemic reactions. The 95 patients receiving SCIT and vaccination either simultaneously or within a maximum period of 4 days did not have any SR (**tables 3 and 4**). This was also the case for a subgroup of 36 of them who consecutively received SCIT and vaccination for up to 5 years. Additionally, none of the patients suffered of delayed SR.

Table 3 *- Number of patients receiving "SCIT" or "SCIT and vaccination simultaneously" at least once between 2007 and 2012 with systemic reactions (SRs) according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (5).*

	SCIT (n = 336)	**SCIT + vaccination simultaneously (n = 95)**
Patients with SR* grade 1 (n)	-	-
Patients with SR* grade 2 (n)	2	-
Patients with SR* grade 3 (n)	1	-
Patients with SR* grade 4 (n)	-	-

Table 4 *- Number of adults and children receiving inadvertent vaccination and SCIT within a time frame of at maximum 4 days (n = 16). There were no systemic reactions in any patient.*

	Adults	Children
Influenza	4	6
Tetanus / diphtheria	1	1
Pneumococcus	1	-
Measles / mumps / rubella	-	3

Discussion

Vaccination against infectious diseases and allergen-specific immunotherapy both influence the immune-system, however, the underlying immunological mechanisms are different. Vaccinations are administered to healthy people to induce protective immunity by stimulating the body's immune system to recognize the agent as foreign (9). They mediate the induction of high titer antibodies in serum or mucosal surfaces, which confer protection by blocking entry or limiting spread of bacteria, viruses and/or toxins (6).
In contrast, SIT is administered to individuals already suffering from allergic symptoms, to induce specific allergen tolerance by restoring normal immunity (10). Allergen tolerance is the adaption of the immune system characterized by a specific non-inflammatory reactivity to a given allergen, that in other circumstances would likely induce cell-mediated or humoral immunity leading to tissue inflammation and/or IgE production (10). Since both influence the immune system, it is recommended to separate the injections. For example, the EAACI task force paper recommends separating injections for SCIT and vaccinations by at least 1 week (2) because it is assumed that adverse reactions can result from the additional activation of the immune system (7). Many manufacturers recommend interrupting SCIT for a total of up to 3 weeks in case of vaccination, i.e. the interval between the last SCIT injection should be at least one week and SCIT should be continued 1 to 2 weeks after vaccination. Depending on the individual preparation the SCIT dose may also be reduced afterwards. This procedure is less convenient for the patients because it causes additional consultations during SCIT, which itself is time-consuming due to regular visits (up to 4-8 weekly intervals in the maintenance phase during a perennial application dosage scheme) for the recommended 3 to 5 years. Therefore, it would be most convenient if injections for SCIT and vaccination can be administered simultaneously. Moreover, conflicts between patient and doctor and/or medico-legal problems might occur in medical practice, in cases of inadvertent simultaneous and/or contemporary application of vaccination and SCIT. This might be true for real or putative adverse events after simultaneous or contemporary application.
In the present survey on hand, we investigated if there was an increased risk of SRs during simultaneous SCIT and vaccination compared to SCIT or vaccination alone.
There were systemic reactions in 0.7% (3/431) of patients receiving SCIT (with or without simultaneous vaccination) during the 5-years observational period. None of these patients was admitted to hospital and all recovered in the physician's practice within two hours. This is in the lower range of systemic reactions observed in studies performed in the daily practice, with (un-)modified SCIT preparations of different manufacturers showing systemic reaction in 0.8% up to 33% of patients (11-17).
In the trial on hand, no SR was observed in patients receiving vaccination against various infectious diseases. Amongst others, the "German Health Interview and Examination Survey for Children and Adolescents" investigated tolerability of vaccination in children aged 0 to 17 years between May 2003 and May 2006 (18). Data about adverse events during vaccination in 15,958 children and adolescents were evaluable. Parents of 332 (2.1%) children and adolescents reported adverse reactions after one or more vaccinations. Hence, the frequency of adverse events was rather lower than described in the respective Summary of Product Characteristics (SmPC).
In the survey on hand between 2007 and 2012 there was no systemic reaction when SCIT and vaccination were simultaneously administered to 79 subjects in different locations. Additional 16 patients were treated with SCIT and vaccination inadvertently within 4 days, since they had not informed their physician about the preceding vaccination. Since this retrospective evaluation was finished on October 15, 2012, twenty-three additional patients had received SCIT and vaccination simultaneously (17 adults and 3 children receiving SCIT and influenza vaccination, three adults either receiving SCIT and pneumococcus, tetanus / diphtheria or hepatitis A / B vaccination), without any SR confirming safety and feasibility of this procedure. As far as we know there is only one publication about simultaneous SIT and influenza vaccination which was described in 2003 (19). The 43-old woman developed symptoms of multiple sclerosis after SIT (19), but the authors did not offer any evidence of causal relationship and concluded that further studies are needed.
In total, the tolerability in this retrospective study during SCIT and/or vaccination against infectious diseases was slightly better than observed in other studies.

Conclusion

These results indicate that the recommended interval between injections of SCIT and vaccination against infectious diseases might be reduced without increasing the risk of SRs. Further data could be helpful to study the possibility to change the na-

tional and international recommendations respectively and to increase patients' convenience. In an optimum way, future research should focus on collecting data from each specific anti-infectious vaccination, because generalization, when discussing about safety, risks being misleading and dangerous. But until such data are available the present findings give according to the authors' opinion valuable evidences, that the risks of simultaneous vaccination and SCIT are considerably smaller than intended hitherto.

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