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Vaccination against COVID-19 and allergic risk: considerations for use in general practice

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CONTEXT

Vaccination against COVID-19 started in France on 27 December 2020. It is presently at the center of attention from the standpoint of caregivers, decision-makers and the general population. General practitioners (GPs) are taking action to allow those who wish for vaccination to be effectively vaccinated[1]. They are the main interlocutors of patients for whom they serve as attending physicians and to whose many questions on vaccination they endeavor to respond[2]. While the technology bringing into play mRNA is hardly novel, the recently commercialized vaccines are the first to put it to work. Its arrival not only arouses hope in the fight against the pandemic, but also – on the contrary - raises questions about the risk of occurrence of adverse effects. Anaphylaxis is the most severe form of acute allergic manifestations; it appears immediately after contact of an organism with an allergen, and can be life-threatening. The day after the worldwide launching of vaccination with the BNT162b2 vaccine in the Pfizer/BioNTech program, two cases of anaphylaxis were observed in the United Kingdom. Over the following days, six other cases were reported in the United States[3,4]. In spite of its being exceedingly rare, anaphylaxis is potentially fatal, and the eventuality of post-vaccinal anaphylaxis has been repeatedly emphasized in the media and become a prime cause for concern among a number of patients.

The objective of this work was to offer a synthesis of present-day knowledge on vaccination against COVID-19 in cases where a patient has a history (antecedents) of allergic reactions. Relevant knowledge should prove useful to GPs intent on addressing the questions put forward by patients and their kith and kin in the framework of shared decision-making.

METHOD

A narrative review of the literature was carried out by selecting data pertaining to the care, treatment, and management of patients with allergy history who are to be (or who have been) vaccinated against COVID-19. References in French or English to documents published up until 21 January 2021 were included; no criteria of exclusion were applied. The data bases of summary documents drawn up by the French and international health authorities and the main worldwide learned societies of allergology were consulted. The relevant citations identified in the references of the selected publications were included in the synthesis. Recommendations for management of anaphylaxis were added a posteriori.

RESULTS

The epidemiological data

No anaphylactic reaction was reported in the phase III Pfizer/BioNTech and Moderna trials; that said, persons with known history of allergy to a vaccine component or of severe allergy to any other vaccine had not been included in these trials[4].

As regards the Pfizer/BioNTech vaccine, as of 23 December 2020, out of the first 1,893,360 vaccinations, 21 confirmed cases of anaphylaxis had been reported in the United States, that is to say 11.1 cases among a million vaccinations, and without any death[5,6]. Seventy-one percent of the reactions occurred during the first 15 minutes following injection. Among those 21 patients, 17 had diverse allergy histories, including 7 cases of anaphylaxis, 2 of which were ascribable to a vaccine. In France, as of 14 January 2021, 4 cases/389,000 Pfizer/BioNTech vaccinations had been reported, and the trend was favorable[7]. Incidence of anaphylaxis associated with the Pfizer/ BioNTech vaccine approximates 1/100,,000 vaccinations, which is comparable to the rates observed (from 1/100,000 to 1-5/1,000,000) for other commonly employed vaccines[8,9]. Given its status as the first vaccine derived from a specific technology, it cannot be compared to other mRNA vaccines.

Concerning the mRNA-1273 Moderna vaccine, out of the first 4,041,396 vaccinations, as of 10 January 2021 there had been 10 confirmed cases of anaphylaxis in the United States, that is to say 2.5 cases among a million vaccinations, and without any death[10]. Among these ten patients, nine had allergy histories , including 5 cases of anaphylaxis, none of which were ascribable to a vaccine. Ninety percent of the events occurred during the first 15 minutes following injection. Diverse localized and

Highly probable anaphylaxis if one of the following two criteria is fulfilled

Criteria 1

Abrupt onset (within a few minutes or an hour) of cutaneous reactions (mucous or cutaneo-mucous manifestations): generalized rash, pruritus or flush, edema of the tongue, the lips or the uvula, associated with at least one of the following symptoms:
- respiratory dysfunction (dyspnea, bronchospasm, wheezing, stridor, hypoxemia, decreased peak expiratory flow);
- lowered blood pressure or hemodynamic failure or organ failure (hypotonia, collapse, syncope) ;
- severe gastro-intestinal symptoms (intense abdominal cramps, repeated vomiting).

Criteria 2
Abrupt onset (within a few minutes or an hour) of hypotension or a bronchospasm or laryngeal injury after exposure to a known or highly probable allergen, even in the absence of cutaneous reactions.

Sidebar 1

belated reactions (> 5 days after the 1st dose) have also been reported subsequent to the Moderna vaccine, including erythema, pruritus, edema and local induration[11]. These different delayed reactions, which are in all likelihood T cell-mediated, do not contraindicate vaccinal continuation; by the time of the 2nd dose, they are generally attenuated.

Potential allergen

mRNA vaccines contain lipid nanoparticles that prevent rapid enzymatic degradation of mRNA[12]. In the Pfizer/BioNTech vaccine, these nanoparticles are surface-stabilized by polyethylene glycol (PEG) with a molecular weight of 2 000 g/mol (PEG 2000)[9], which is presently the main suspected allergen with regard to the cases of anaphylaxis observed with the Pfizer/BioNTech vaccine[13-15]. Some exceedingly rare cases of anaphylaxis have also been reported with PEGs presenting different molecular weights[9,16].

PEG is an excipient that is widely used in daily life in a variety of cosmetic and pharmaceutical products; whether in an injectable or orally administered form, it is contained in 30% of medicines. The Moderna vaccine likewise contains PEG 2000, and the viral vector Oxford-AstraZeneca vaccine (chimpanzee adenovirus) contains polysorbate 80[9]. Cross-allergies have been observed involving PEG with a molecular weight of 3350 g/mol (not used in vaccines) and polysorbate 80[9,17]. The degree of cross-reactivity between PEG and polysorbate remains unknown, and the possible clinical repercussions of their interactions have yet to be reported[18].

Synthesis of the recommendations

Taking into account the cases of anaphylaxis that have occurred in the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) rapidly adopted precautionary measures; vaccination is henceforth contraindicated in any person presenting a history of anaphylaxis with regard to a vaccine, a drug or a nutriment[19]. However, the different international learned allergology societies have been highly critical of this decision[9,18-24]. While an active allergy or an allergy history involves up to 30% of the population, prevalence in Europe of anaphylaxis, all causes considered, ranges from only 0.3 to 3%[9,19]. In terms of immunity, the benefit/risk equation for the above-mentioned contraindication appears disadvantageous from a collective as well as an individual standpoint[9,25].

Table 1 presents a synthesis of the French recommendations designed to stratify the risks entailed by vaccination[26]. Table 2 presents a comparison of the degrees of allergy risk reported in six countries (France[26], United States[27], United Kingdom[28,29], Canada[23,30] and Switzerland[31] and Spain[24]).

Past history of allergy or anaphylaxis do not constitute systematic contraindications to vaccination. On the other hand, there exists a consensus on the nature of the high risks justifying absolute contraindication:
- systemic reaction after the 1st dose of a vaccine;
- history of known systemic reaction to a vaccine component;

The recommendation issuers also agree on the fact that a localized reaction to the 1st dose does not contraindicate administration of a 2nd dose.

The differences between the respective recommendations of the different countries are minimal, essentially involving divergences in risk stratification ("moderate" or "low") and as regards more or less lengthy time of observation[32-34]. Switzerland[31] is the one country to recommend anti-H1 premedication in certain cases, while in the United States, premedication is officially prohibited, given that it would supposedly not prevent anaphylaxis occurrence, and that it might in some cases mask initial signs predictive of disease onset[27,30]. As for Great Britain, it is the only country to propose alternative vaccination by ChAdOx1-S of AstraZeneca in the event of elevated risk[29].

The management of post-vaccinal anaphylaxis[35-39]

Anaphylaxis is a clinical diagnosis; in the absence of adapted treatment, it evolves rapidly. Multiple definitions exist in the literature; in view of harmonizing existing practices, in 2020 the World Allergy Organization (WAO) proposed a simplified definition[35] (sidebar 1).

Even though cutaneo-mucous manifestations are quite frequent, they are not always present (15% of cases)[37].

First-line drug therapies: early adrenalin injection

The one curative treatment for anaphylaxis is adrenalin, but its use is not sufficiently widespread (only 20% of anaphylaxis cases receive the treatment)[37]. Adrenalin is effective with regard to the different symptoms via its adrenergic alpha, beta 1 and beta 2 receptors. It must be administered as early as possible (level IV, grade C)[36]. There is no contraindication to its utilization. The benefits exceed the risks in elderly patients, during pregnancy, and in the event of preexisting cardiac pathologies.

The recommended first-line route of administration consists in intramuscular injection in the anterior surface of the thigh (level I, grade B)[36]. The recommended dosage is 0.01 mg/kg, and the maximum dose is 0.5 mg per injection. Adrenalin auto-injector devices (pre-filled pens) facilitate treatment; their If the symptoms show improvement after 5 minutes, a second adrenalin injection at the same dosage is to be carried out (level V, grade D)[36].

Contrary to the intravenous (IV) route, intramuscular injection is generally well-tolerated.

Second-line drug therapies

In the event of associated bronchoconstriction, inhalation of rapid-action beta2 mimetics (salbutamol) must begin immediately after the adrenalin injection (level V, grade D)[36].

Third-line drug therapies

Corticoids and antihistamines are not considered as emergency treatment for anaphylaxis; in no case should they delay or replace adrenalin administration[36].

As for antihistamines, only oral administration is recommended (level I, grade B)[36]. They have no proven effectiveness against anaphylaxis; on the other hand, they yield some improvement of cutaneous manifestations (level I, grade B)[36]. Intravenous (IV) administration leads to hypotension and is not recommended; nor are first-generation antihistamines, which induce drowsiness.

While (IV or orally administered) corticoids are frequently utilized, their effectiveness against anaphylaxis has never been demonstrated, and at this point in time, they are quite controversial[35]. Moreover, onset of action is slow and belated. Nebulization of high-dose inhaled corticosteroids (budesonide) may be effective against upper airway edema; it is recommended for patients suffering from stridor (level V, grade D)[36].

Allergy manifestations	Advice for vaccination	Duration of observation after vaccination	Measures to take
History of allergic reaction to a vaccine component, particularly PEG, or risk of cross-allergy to polysorbate	Contraindicated in primary care	No vaccination	Contact an allergologist
History of severe immediate reaction (bronchospasm, generalized urticaria, anaphylaxis) to the first injection of a mRNA COVID-19 injection	Contraindicated in primary care	No vaccination	Contact an allergologist
History of severe immediate reaction (bronchospasm, generalized urticaria, anaphylaxis) to a non-COVID vaccine or to an injectable drug	Postponement	Vaccination after expert advice	Contact an allergologist
History of localized immediate reaction to a first injection of a mRNA COVID-19 injection	Normal vaccination	15 minutes	
Drug allergy			
Urticaria, angioedema	Normal vaccination	15 minutes	
Anaphylaxis	Normal vaccination	30 minutes	
Delayed reactions, possibly severe drug eruptions (DRESS, Lyell or Stevens-Johnson syndrome)	Normal vaccination	15 minutes	
Latex allergy			
Urticaria, angioedema, eczema	Normal vaccination	15 minutes	
Anaphylaxis	Normal vaccination	30 minutes	
Allergy to hymenoptera venom			
Urticaria, reaction at the injection site	Normal vaccination	15 minutes	
Anaphylaxis	Normal vaccination	30 minutes	
Food allergy			
Non-severe, oral syndrome, urticaria, eczema	Normal vaccination	15 minutes	
Anaphylaxis	Normal vaccination	30 minutes	
Others			
Rhinitis, conjunctivitis, allergic asthma with regard to airborne allergens	Normal vaccination	15 minutes	
Allergy family history, including anaphylaxis	Normal vaccination	15 minutes	
Contact dermatitis, urticaria or chronic angioedema, bradykinin angioedema	Normal vaccination	15 minutes	
Mastocytosis without history of anaphylactic reaction	Normal vaccination	15 minutes	

Table 1 - The French recommendations[26,34] on COVID-19 vaccination and allergy history

Observation periods

Biphasic anaphylaxis evolution results from a recrudescence of anaphylactic manifestations subsequent to a phase of improvement; they may concern up to 23% of patients[37]. The second phase generally occurs 4 to 12 hours after the first reaction and may be occasioned by delayed administration of adrenalin. The second phase justifies observation in an emergency unit of any patient having presented with an anaphylactic reaction, even in the event of complete symptom resolution. Observation should be maintained for 4 to 12 hours in the event of respiratory symptoms and for 12 to 24 hours in the event of hemodynamic instability (level V, grade D)[36].

Measures to take in cases of anaphylaxis

They are presented in sidebar 2.

DISCUSSION

The level of evidence of the above recommendations for stratification of vaccination risks is low. Available data on anaphylaxis are few and far between, and we have little critical perspective. That said, adverse reaction reporting to the pharmacovigilance system is essential to our understanding of the incidence of these episodes and their impact on patient evolution. Factors other than vaccines such as the local disinfectants (particularly chlorhexidine) utilized prior to vaccination can also be causes of anaphylaxis[30]. Moreover, anxiety may induce anaphylactic reactions; the attention currently given to the risks entailed by vaccination may affect patient behaviors and physician practices, generating a potential overstatement bias[5,30].

While the above recommendations

Measures to take in anaphylaxis cases

1. Diagnosis of anaphylaxis
2. Call emergency: tel. 15 in France
3. Early adrenalin injection (first-line treatment)
4. Second-line treatments:
 a/Position adapted to the patient's condition
- with dyspnea: semi-seated position;
- with consciousness maintained: dorsal recumbency with legs raised;
- with reduced state of consciousness: lateral recovery position
b/ Oxygen therapy with high-concentration mask.
±
c/ Inhalation of rapid action beta2-mimetics (salbutamol).
±
5. Third-line treatments (non-proven effectiveness of anti-h1 and corticoids).
6. Prolonged observation

France SFA-FFA[26] and TRAM group[34] 12/01/2021	USA CDC[27] 06/01/2021	UK MHRA and BSACI[28,29] 30/12/20[20]	Canada CSACI[23] 05/01/2021	Spain SEAIC[24] 04/01/2021	Switzerland SSAI[31] 11/01/2021
CONTRAINDICATION in primary care, refer the patient to a specialized hospital unit (+ in England: possible vaccination with AstraZeneca following reaction to Pfizer or Moderna)					
ATCD of immediate allergic reaction to a vaccine component (PEG or polysorbate, with possible cross-allergy) Systemic reaction after 1st vaccine dose	Anaphylaxis, immediate allergic reaction, whatever the severity, after 1st vaccine dose ATCD of anaphylaxis, or immediate allergic reaction, whatever the severity, to a vaccine component	ATCD of anaphylaxis to multiple drugs or idiopathic anaphylaxis Known allergy to a vaccine component Systemic reaction to the 1st dose Measure to take: propose an alternative with the AstraZeneca vaccine	Anaphylaxis after 1st vaccine dose Anaphylaxis, or immediate allergic reaction, whatever the severity, to a vaccine	ATCD of anaphylaxis after 1st vaccine dose ATCD of anaphylaxis to a vaccine component	Anaphylaxis after 1st vaccine dose Anaphylaxis, or immediate allergic reaction, whatever the severity, to a vaccine component
Moderate risk, vaccination possible in primary care, with mandatory prolonged observation					
ATCD of anaphylaxis to an injectable drug or another vaccine Observation: Request the opinion of an allergology expert ATCD of anaphylaxis to food, to latex, to an identified drug, to hymenoptera venom, idiopathic or mastocytosic Observation: 30 minutes	ATCD of anaphylaxis to an injectable drug or another vaccine ATCD of anaphylaxis to food, to latex, to hymenoptera venom, idiopathic. Measure to take: expert allergology opinion and, if vaccination possible, 30-minute observation Contraindication to anti-H1 premedication	Urticaria or localized cutaneous reaction to the 1st dose Observation: 30 min and emergency material nearby	ATCD of severe anaphylaxis to another vaccine, to a drug, or to some food Observation: no precise duration	Severe allergy to food, latex, venom and airborne allergens ATCD of severe drug allergy ATCD of severe allergy to another vaccine Mastocytosis or mast cell activation syndrome Idiopathic anaphylaxis Observation: 45 min	Mastocytosis Chronic urticaria or mast cell activation Localized urticaria at the site of the 1st dose Measure to take: premedication by anti-H1 (1 cp 60 min before vaccination) and observation: 30 min Measure to take: expert advice and, if vaccination possible, 30-minute observation
Low risk, vaccination possible in primary care					
Allergy to food, latex, venom, airborne allergens Local reaction to first vaccine dose Delayed drug allergy (including severe DRESS and Lyell/ Stevens- Johnson drug eruption) Chronic urticaria, eczema, bradykinin angioedema, mastocytosis Family ATCD, including anaphylaxis	Non-severe allergies to food, latex, drug, venom, airborne allergens Immediate allergy to oral medication Local reaction to a vaccine Mastocytosis Family ATCDs, including anaphylaxis Observation in case of anaphylaxis ATCD: 30 min For other conditions: 15 min	ATCD of anaphylaxis to food, a drug or a clearly identified vaccine, to insect/ hypenoptera venom Observation: 15 min	Non-severe allergies to food, respiratory, to insect/ hymenoptera venom, to a drug Observation: 15-30 min	Non-severe allergy to food, latex, venom and airborne allergens ATCD of drug allergy Local and non-severe reaction to a vaccine or an injectable substance Family ATCD of anaphylaxis Observation: 30 min	Non-severe allergies or anaphylaxis to food, respiratory, insect/ hymenoptera venom Non-severe allergies or anaphylaxis to identified oral, rectal or parenteral drugs Non-identified drugs with purely cutaneous reactions Family ATCD of anaphylaxis Observation: 15 min after the 1st dose, 5 min after the 2nd dose (if 1st dose well-tolerated)

Table 2 - Synthesis of international recommendations on allergy risk management
ATCD : antecedent (past or previous history)

indicate that patients at high risk should be referred to a specialized allergology unit, as of now the feasibility of standardized skin tests for a Covid-19 vaccine remains unknown[9,30]. Even in the event of proven allergy to a vaccine or to one of its components (as is the case with any other vaccine), a habituation protocol is theoretically possible; however, there does not yet exist any clearly established protocol for Covid-19 vaccines[9].

CONCLUSION

The data collected up until now are reassuring; anaphylaxis associated with mRNA vaccines is rare, with rates of occurrence comparable to those associated with other vaccines. Persons with allergy history, even including anaphylaxis (except with regard to the vaccine itself, or one of its components) can safely receive an anti-COVID injection. As of now, the risk/benefit ratio in patients with allergy history favors vaccination.

The information we have endeavored to summarize should help physicians and their patients to make a rational and enlightened choice in the framework of shared decision-making procedures[32-33].

Summary

Context. General practitioners (GPs) work alongside to help provide a COVID-19 vaccination for anyone. They face plenty of questions from concerned patients, such as about vaccine-related anaphylaxis.

Objective. To provide an up-to-date overview to help GPs answer questions about a COVID-19 vaccination in case of history of allergies.

Methods. A narrative literature review was performed until January 21, 2021. Data were collected from French and international authorities guidance and the main international scientific societies of Allergy. The guidelines for the management of anaphylaxis were added a posteriori.

Results. Anaphylactic reactions related to the mRNA COVID-19 vaccine are very rare. A history of allergic reactions or anaphylaxis is generally not a contraindication to the vaccination, except in case of a systemic reaction to the 1st dose of the vaccine or a previous reaction to any of its components. These are absolute ones. People with a local reaction to the 1st dose can receive the 2nd dose.

Conclusion. The up-to-date collected data are reassuring: the rate of anaphylaxis related to the mRNA COVID-19 vaccine is similar to other vaccines. People with history of allergies, including anaphylaxis (except for the COVID-19 vaccine or its components), can receive the vaccine. The benefit of the vaccination in case of history of allergies outweighs the risk. These data will allow GPs and their patients to make an enlightened and more rational choice in the shared decision-making process.

Keywords: SARS-CoV-2; COVID-19; vaccination; allergy; anaphylaxis.

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