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Perceived high risk of COVID-19 vaccination: The revealing power of placebo

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Clinical Implication

The use of a placebo as an additional diagnostic step in the allergological workup of suspected hypersensitivity reactions can be of great value. In this study, nearly 1 in 3 patients had symptoms after administration of placebo.

Self-limiting mild adverse events (AEs) after COVID vaccination are common and should not contraindicate revaccination.[1] Unfortunately, these are too often erroneously labeled as hypersensitivity reactions (HRs), precluding revaccination.[2] A patient with a history compatible with an immediate HR to the vaccine should be offered allergological evaluation with the excipients of these vaccines based on the respective type.[3] In contrast, in the diagnostic workup of patients with subjective symptoms or multiple unverified drug hypersensitivities, a placebo-controlled challenge should be considered.[4]

In this prospective cohort study, we assessed the reoccurrence rate (RR) of AEs after vaccination or the occurrence of AEs unrelated to the vaccine in patients unvaccinated for COVID-19. We report data on 69 individuals who attended the outpatient clinic of the Antwerp University Hospital from April 1, 2021, to July 1, 2022, for risk stratification concerning COVID-19 vaccination. Patient characteristics are summarized in Table I. Patients were informed about a 2-step vaccination in which one of the doses (first or second) could be placebo and that the total administered dose would be the recommended dose. Informed consent was obtained from all patients.

All patients were administered a placebo, either as primary diagnostic (n = 52) or after negative skin testing (n = 17). One dose of placebo (NaCl 0.9%, intramuscularly, single blind, volume either 0.3 or 0.5 mL in congruence with the volume of the vaccine) was administered 30 minutes before administration of the vaccine. The main reason for referral was symptoms after previous COVID-19 vaccination (n = 41). In 14 of 41 patients, these symptoms were potentially severe (ie, syncope, desaturation, or involvement of 2 or more organ systems). In none of these patients, an acute tryptase was obtained at the vaccination center. Twenty-eight patients were COVID-19—vaccine naïve, and reasons for referral and details concerning symptomatology are shown in Table I. Seventeen of the 69 patients were offered allergologic evaluation including skin tests (STs) with the concerning excipients or the COVID vaccine based on clinical suspicion. The used excipients were polysorbate 80 (skin prick test [SPT] and intradermal test [IDT] with dilutions of 10^{-5} up to 10^{-1}) and macrogol 4000, 1 mg/mL (SPT with dilutions 10^{-2} and 10^{-1} and IDT with dilutions of 10^{-6} up to 10^{-3}). In 1 patient, a polysorbate 80 allergy was diagnosed. She suffered from a so-called 1-1-1-urticaria (ie, the occurrence of urticaria within *1 hour* of exposure of the *first dose* that lasted less than *1 day*)[5] after administration of Vaxzevria. SPTs with polysorbate were negative for all used concentrations, but an IDT with a dilution of 10^{-5} resulted in a wheal and flare of 10 and 25 mm, respectively. STs with macrogol were negative, and the patient was later vaccinated with Comirnaty uneventfully. In all other patients, allergologic evaluation was negative. All 69 patients were (re)vaccinated in a placebo-controlled manner. In 11 patients previously vaccinated with Spikevax (n = 3), Jcovden (n = 3), or Vaxzevria (n = 5), a switch was made to Comirnaty either because of practical reasons of availability of vaccines in our center (n = 10) or because of confirmed hypersensitivity to polysorbate 80 as described above (n = 1).

Of the 41 patients who reported symptoms after previous dose, 14 reported symptoms after placebo administration and were vaccinated uneventfully afterward. In 6 of these 14 patients (42.86%) with symptoms after placebo, the index reaction was categorized as potentially severe (as explained above). Two of 41 patients had symptoms immediately after re-exposure to Comirnaty despite negative allergological workup: 1 patient experienced dyspnea with urticaria that was considered anaphylaxis, and 1 patient had urticaria immediately after the vaccination. Both did not meet criteria for mast cell activation based on paired tryptase sampling.[6] The first patient with anaphylaxis had no relevant comorbidities, and the second patient had a previous history of chronic urticaria. However, she was asymptomatic without maintenance therapy since several years. Moreover, the close temporal relationship between administration and the vaccine, and the fact that no symptoms were observed after provocation with placebo, a causal relation between the vaccine and the symptoms was confirmed. Neither of them had prior vaccine-related reactions that were beyond the physiological response.

Of the 28 COVID-19—vaccine naïve patients, 5 had symptoms after administration with placebo and were later vaccinated uneventfully without subjective symptoms. In total, 19 of 69 patients (27.54%) experienced symptoms after placebo. Of the 14 patients with potentially severe symptoms on initial presentation, 6 patients (42.86%) had symptoms after placebo. In the group of 27 patients with nonsevere symptoms, 8 patients (29.63%) had symptoms after placebo. Overall, 67 of 69 patients were vaccinated uneventfully without premedication, and the RR of AEs was 1 in 20 (4.88%). Details regarding allergologic evaluation and vaccination are shown in Table II.

The aim of this study was dual: first, to evaluate the RR of presumed AEs after vaccination, and second, to evaluate the rate of AEs unrelated to the vaccine in COVID-19—vaccine naïve patients. A recent meta-analysis stated that 13.65% of individuals experience reoccurrence of non—life-threatening symptoms after a second dose.[7] In our cohort, the RR of AEs was 4.88%. The difference might be explained by the fact that placebo administration enabled us to distinguish the effective reoccurrence of vaccine-induced symptoms from nocebo effect.[8] Actually, after exposure to placebo, almost 28% of patients experienced

TABLE I. Patient characteristics

Characteristic	Value
Demographics	
M/F	8/61
Mean age (range) (y)	52 (18-86)
Relevant clinical history (n = 69)	
Asthma	7
Chronic urticaria	3
Inhalation allergy	4
Reason for referral (n = 69), n (%)	
Anxiety	23 (33)
Multiple anaphylaxis	1 (1)
Refused by vaccination center	4
Suspected hypersensitivity to unrelated drugs	1/4
Suspected hypersensitivity to macrogol	1/4
Anaphylaxis to diclofenac (which contains tromethamine) in clinical history	1/4
Possibly angioedema after unknown vaccine, more than 10 years ago	1/4
Symptoms after first or second dose* (n = 41), n (%)	
Immediate (pre)syncope, hypotension, palpitations	14 (34)
Immediate dyspnea	8 (20)
Immediate dysphagia	2 (5)
Immediate hoarseness	1 (2)
Immediate nausea	2 (5)
Immediate headache	2 (5)
Immediate pruritus	7 (17)
Immediate flushing	1 (2)
Immediate urticaria	4 (8)
Immediate angioedema/sensation of swelling	12 (29)
Urticaria >1 day after vaccination	2 (5)
Unspecified skin rash	4 (8)
Angioedema/sensation of swelling >1 day after vaccination	2 (5)

*Seventeen patients showed signs and symptoms compatible with an immediate hypersensitivity reaction after administration of the vaccine.

TABLE II. Details regarding allergologic evaluation and vaccination

Evaluation and vaccination	Value
Skin testing*	17/69
Polysorbate 80 positive	1/7
Polysorbate 80 negative	6/7
Macrogol negative	12/12
Tromethamine negative	1/1
Administered vaccine (n = 69)	
Comirnaty	57
Jcovden	9
Vaxzevria	3
Symptoms immediately after vaccination	2/69
Anaphylaxis (dyspnea, urticaria)	1/2
Urticaria	1/2
Symptoms after administration of placebo, n (%)	19/69
Subjective feeling of pharyngeal swelling	4 (21)
Generalized malaise	4 (21)
Headache	3 (15)
Pruritus	3 (15)
Thoracal pain	3 (15)
Nausea	4 (21)
Syncope	1 (5)
Palpitations	4 (21)
Symptoms after placebo per referral group	
Anxiety	4/23
Symptoms after first or second dose	14/41
Potential severe symptoms during index reaction	6/14
Multiple anaphylaxis	0/1
Refused by vaccination center	1/4

*Only in patients who showed signs and symptoms compatible with an immediate hypersensitivity reaction within 1 hour of administration of the vaccine.

symptoms (similar to the symptoms that occurred on previous exposure to the vaccine). Placebo-controlled provocation is an important part of drug provocation tests (DPTs) but has not been described before in the context of possible vaccination hypersensitivity. Previous studies on placebo and nocebo effects in DPTs demonstrate that patients with symptoms after exposure, anxiety, and/or depression are prone to nocebo effects.[9] Placebo-controlled DPTs might give rise to some challenges. From a logistical point of view, one must take into account that these protocols are more time-consuming, the placebo should have an identical appearance as the drug, and some drugs can have immediate pharmacological effects that cannot be reproduced by a placebo, compromising blinding. In terms of ethics, it is supposed that in patients who are unaware of a possible placebo administration, one could retrieve the most reliable results. Actually, this is deemed unethical as patients should always be aware of this possibility, ensuring their self-determination and a relationship based on transparency. Therefore, if a systematic use of placebo-controlled DPTs can be debated, the employment of placebo in this study should be contextualized to the need to ensure the widest possible adherence to the vaccine campaign against COVID-19. Adherence was jeopardized from the beginning by an unmotivated perceived high risk.

We conclude that the RR of AEs after COVID-19 vaccination is low. A thorough history and clinical details regarding symptoms and timing are essential for correct risk stratification. The use of placebo is of great value and should be considered in DPTs if appropriate. Patients with a history of symptoms after previous exposure (even in case of potentially severe symptoms) and patients with anxiety or depression might be more prone to experience nocebo effects and thus may benefit from placebo-controlled DPT.

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