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REVIEW ARTICLE

Drug hypersensitivity, in vitro tools, biomarkers, and burden with COVID-19 vaccines

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Abstract

Hypersensitivity reactions to drugs are increasing worldwide. They display a large degree of variability in the immunological mechanisms involved, which impacts both disease severity and the optimal diagnostic procedure. Therefore, drug hypersensitivity diagnosis relies on both in vitro and in vivo assessments, although most of the methods are not well standardized. Moreover, several biomarkers can be used as valuable parameters for precision medicine that provide information on the endotypes, diagnosis, prognosis, and prediction of drug hypersensitivity development, as well on the identification of therapeutic targets and treatment efficacy monitoring. Furthermore, in the last 2 years, the SARS-CoV-2 (severe acute respiratory syndrome-coronavirus) pandemic has had an important impact on health system, leading us to update approaches on how to manage hypersensitivity reactions to drugs used for its treatment and on COVID-19 (Coronavirus disease) vaccines used for its prevention. This article reviews recent advances in these 3 areas regarding drug hypersensitivity: in vitro tools for drug hypersensitivity diagnosis, recently identified biomarkers that could guide clinical decision making and management of hypersensitivity reactions to drugs and vaccines used for COVID-19.

KEYWORDS
biomarkers, COVID-19, hypersensitivity reactions, in vitro test, vaccines

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1 | INTRODUCTION

Hypersensitivity reactions (HSR) to drugs are increasing worldwide and display a constellation of symptoms ranging from urticaria to anaphylaxis or Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).[1] This is a consequence of the array of mechanisms involved. From a clinical point of view, HSR to drugs can be classified into immediate (IHSR, mainly IgE-mediated) and non-immediate (NIHSR, generally mediated by T-cells). Usually, IHSR occur between 1 and 6 h after drug administration, whereas NIHSR appears after 6 or more hours.[1]

The diagnosis of HSR to drugs is therefore very complex and highly dependent on the mechanisms involved. A panel which combines in vitro and in vivo tests is recommended for an accurate endotype diagnosis.[1] Many of these methods are not well standardized and in order to improve their results, recent advances in in vitro tools have incorporated the application of nanoparticles for HSR to drug diagnosis. In addition, prior known cellular tests for IHSR and NIHSR, such as basophil activation test (BAT), lymphocyte transformation test (LTT), enzyme-linked ImmunoSpot (EliSpot), and T-cells clonality have been deeply analysed and tuned up their techniques.[2–6]

Moreover, biomarkers are valuable parameters for precision medicine that provide information on the endotypes, diagnosis, prognosis, and prediction of HSR development, as well on the identification of therapeutic targets and treatment efficacy monitoring.[7] Apart from the in vitro tests mentioned before that help in the determination of previously identified biomarkers, new and promising molecules and mediators have been identified as the biomarkers for specific indications. Genetic variants are associated with reactions to particular drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) or dapsone; and the release of IL-10 in drug-desensitized oncologic patients is considered nowadays a biomarker that translates success.[8–10]

The present review addresses the advances performed during the last two years regarding the in vitro tools for HSR diagnosis and recent identified biomarkers that could guide clinical decision making. Moreover, SARS-CoV-2 (Severe acute respiratory syndrome-coronavirus) pandemic has had an important impact on health system, leading us to update approaches on how to manage HSRs to drugs used for its treatment and on COVID-19 (Coronavirus disease) vaccines used for its prevention.[11–13] (Figure 1).

2 | IN VITRO TOOLS FOR THE DIAGNOSIS OF HSR TO DRUGS. WHAT'S NEW IN THE 2020 DECADE?

In IHSRs, the main in vitro diagnostic methods have been traditionally focused on the detection of specific IgE (sIgE) against the culprit drug,[1] in the last years, some novel applications using nanoparticles have emerged. Moreover, cellular tests, specifically BAT, have been analyzed for IHSR evaluation. For NIHSRs, new data about the role of LTT, EliSpot, and T-cells clonality have arisen. (Table 1).

2.1 | Novel in vitro immunoassays based on nanoparticles

The development of diagnostic methods for allergic diseases based on nanoparticles has attracted great attention in recent years, hoping that they could improve test sensitivity thanks to their physicochemical properties (such as their larger surface area compared with larger solid supports).[14] In the case of HSR to drugs, nanoparticles are used as a supporting structure decorated with the culprit drug or the suspected drug-derived antigenic determinant. In this way, these nanoparticles mimic the carrier protein-drug hapten complex, which is then used as the solid phase in immunoassays or as the stimulatory component in cell-based in vitro tests (Figure 2A). Some recent works highlight the potential impact of this strategy.[2,15]

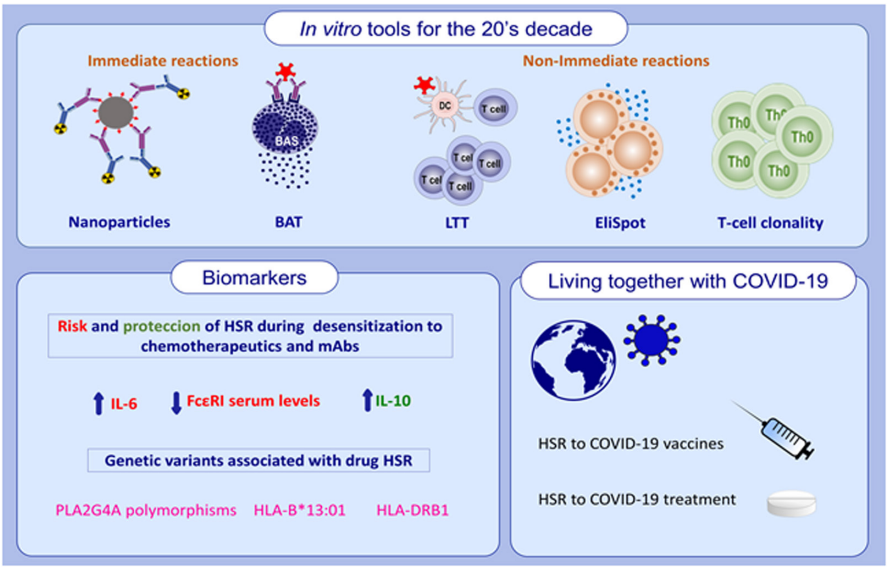
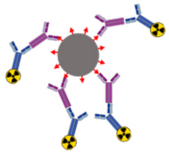
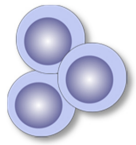
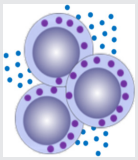
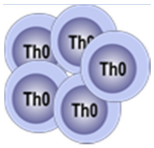


FIGURE 1 Global compilation of the three sections revised last time: (i) In vitro tools for the diagnosis of HSR to drugs, (ii) Biomarkers in HSR to drugs, and (iii) COVID-19 pandemic. BAT, basophil activation test; HSR, hypersensitivity reactions; LTT, lymphocyte transformation test

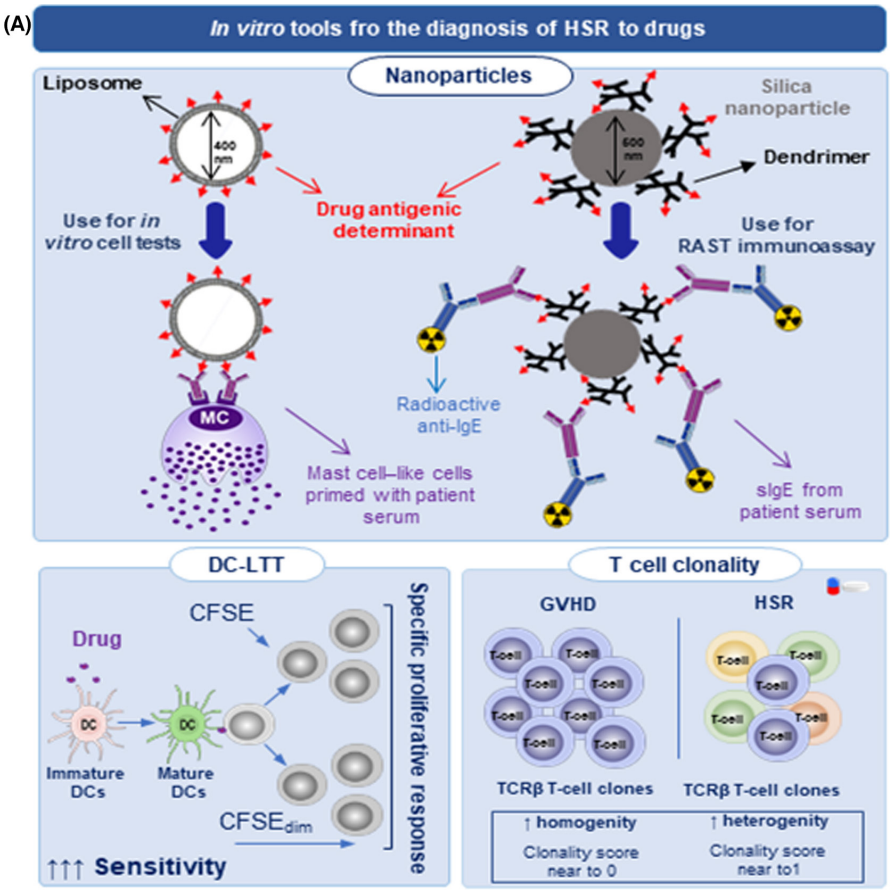
TABLE 1 Novelties in cellular in vitro assays for HSR

Assay	Drug/Disease	Innovation	Ref.
Immediate reactions			
 Nanoparticles	Chemotherapeutic agents	Nanoliposomes-allergen platform for detection of platinum drug allergies	2
	Betalactam antibiotics	Dendrimeric antigen-silica particle composites as nano-based platforms for specific recognition of IgE	15
 BAT	ICM	Complementary in vitro tool with high sensitivity and specificity	17,18
	Antibiotics	Increase in the sensitivity rate up to 83.3% and 66.7%	3,19,20
	Betalactam antibiotics	Together with immunoassays, it has shown greater sensitivity (25.07%) in penicillin allergy diagnosis	21
	Anti-tumor IgE therapeutic	Helps predict patient safety in new treatments	22
Non-immediate reactions			
 LTT	SCARs	Dendritic cells inclusion and proliferative response of effector cells assessment improve LTT sensitivity	23
	Betalactam antibiotics	LTT demonstrated the T-cell involvement in HSR in children	4
	Antiepileptics	LTT can be helpful for drug causality evaluation after recovery in patients with SJS/TEN after taking multiple medications	24,25
 EliSpot	Antibiotics	Improve diagnosis in severe phenotypes and identify culprit antibiotics	26,27
	Anticoagulants	IFNy-realizing cells confirmed the culprit drug	28
	SCARs	Drug-induced IFNy producing cells confirmed the culprit drug	29
	Dapsone hypersensitivity syndrome	Mediator release combination helps in the diagnosis	5
 T-cell clonality	GVHD	Capacity to distinguish HSR from graft-versus-host disease	30

Abbreviations: BAT, basophil activation test; EliSpot, Enzyme Linked ImmunoSpot; GVHD, graft-versus-host disease; HSR, hypersensitivity reaction; ICM, iodinated contrast media; LTT, lymphocyte transformation test; Ref, references; SCARs, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Thus, liposomes containing either an oxaliplatin-lipid or a carboplatin-lipid have been developed for diagnosing platin salts hypersensitivity.[2] These liposomes had a diameter of 400 nm, and the drug was attached to one of the lipids in the formulation, which constituted 5% (molar percentage) of the total lipid content. To prepare the drug-grafted lipid, a lipid containing a short peptide (HWHDHYHLHS) in the polar head was used. This peptide was used to link the drugs, as it is rich in histidines, which are platinum-reactive nucleophilic residues. The platin drug-linked liposomes were used to trigger degranulation in mast cell-like cells primed with sera from allergic patients, observing an inverse correlation between the concentration needed to observe an in vitro cell response and the severity of the patient's reaction. Liposome size was shown to have an effect on the degranulation percentage in this setup, selecting 400 nm liposomes as the optimal formulation compared with 200 nm liposomes which had also been prepared and evaluated.

On the contrary, silica nanoparticles decorated with betalactam (BL) antigenic determinants were reported for their use as a solid phase in immunoassays (radioallergosorbent test [RAST]) for the detection of BLs-sIgE in sera from patients by[15] improving the sensitivity and specificity compared with the conventional RAST using poly-L-lysine as carrier molecule. These silica nanoparticles had a diameter around 500 nm, and a Generation 2 Poly(amidoamine) (PAMAM G2) dendrimer was first grafted to the surface of the silica nanoparticles (forming amide bonds between amino groups in the dendrimer and carboxylic acid groups on the silica surface). In a second step, the BLs was covalently bound to amino groups present in the dendrimer, through reaction



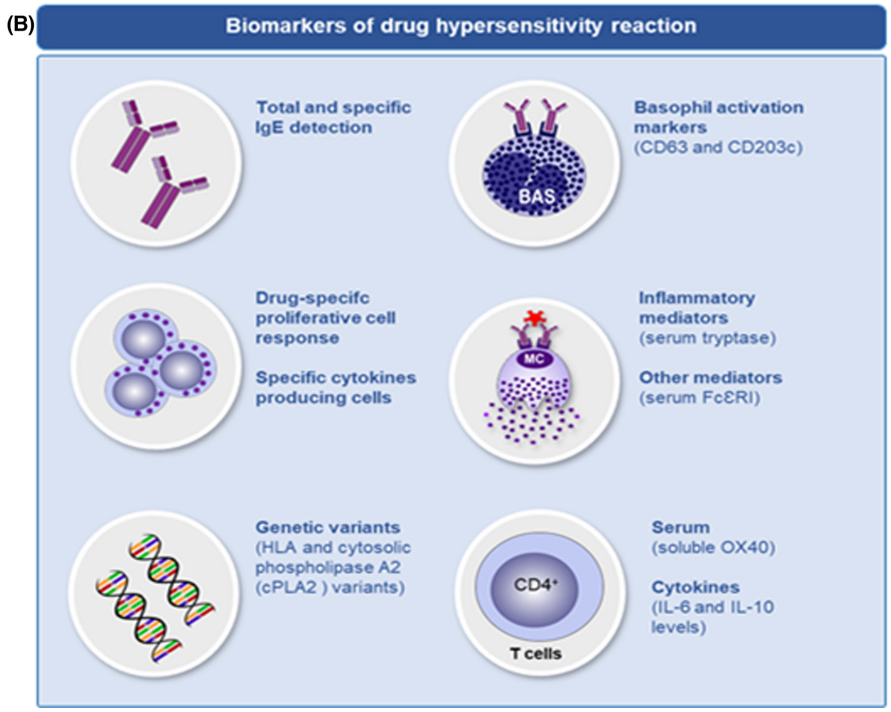


FIGURE 2 In vitro tools for the diagnosis of HSR to drugs. (A) Representation of the novel in vitro immunoassays based on nanoparticles. Liposomes and silica nanoparticles decorated with antigenic determinants, the most used immunoassays for the diagnosis of HSRs, and scheme of the lymphocyte transformation test using dendritic cells (DC-LTT) like drug presenting cells and of the proliferative response[23] together with the schematic representation of the results based on the in vitro tool of T-cell clonity.[30] (B) Biomarkers in HSR to drugs. Biomarkers based on in vitro tests, total and specific IgE level, analysis of activation markers on basophils after stimulation with the specific drug, the proliferative response of effector cells and the measurement of specific cytokine levels by effector cells. In addition, the genetic variant can be also used as potential biomarkers, together with the analysis of soluble biomolecules in serum. CFSE, carboxyfluorescein diacetate N-succinimidylester probe; GVHD; graft-versus-host disease; HSR, Hypersensitivity reactions

that resulted in the opened BL-ring. Thus, the dendrimer grafted onto the silica surface would act as a mimic the conformation of the carrier protein to which the hapten (the BL) is linked, enabling efficient recognition by sIgE. On the contrary, the 500 nm silica support allows the interaction of the allergen-dendrimer conjugate with the sample while also enabling the successful removal by centrifugation for processing and quantification of the sIgE in patient serum.

2.2 | Basophil activation test

BAT is a functional assay that measures the degree of basophil activation (CD63 and CD203c) after stimulation with the responsible drugs that interact with sIgE bound to the cell surface.[16] BAT is used as a diagnostic tool in IgE-mediated HSRs and is considered complementary to other diagnostic in vivo approaches, although more studies are required to standardize the protocols and guarantee results reproducibility.[16] Recent studies have been mainly focused on improving these limitations for example for diagnosing severe IHSRs to iodinated contrast media, where BAT has demonstrated a high specificity (100%) and sensitivity (94.1%).[17,18]

Moreover, two studies have demonstrated that BAT can be used as diagnostic tool for IHSRs to different groups of antibiotics, 5-nitroimidazole and cefazolin, showing sensitivity rate up to 83.3%[3] and 66.7%, respectively.[19] In addition, BAT was able to diagnose patients allergic to quinolones, with a higher sensitivity than skin prick test (SPT).[20] Another study has demonstrated that the combination of the results from BAT and immunoassays increases the sensitivity (25.07%) for diagnosing IHSRs to penicillin.[21]

BAT has also been used to predict capacity of new drugs of inducing basophil activation and therefore clinical symptoms. Indeed, the anti-tumor IgE (MOv18) drug has been tested in vitro with results indicating that it did not induce basophil activation in samples from cancer patients.[22]

2.3 | Lymphocyte transformation test

LTT has been widely used to evaluate NIHSRs, with the particular advantage of detecting the different key elements in the immunological response. However, there are some unmet needs regarding the great heterogeneity of NIHSRs, the controversies regarding the best moment for performance, the unavailability of commercial tests, and the low sensitivity and specificity. In this sense, LTT has been modified using dendritic cells (DCs) such as drug presenting cells and the proliferative response analyzed in effector lymphocyte subpopulations (Figure 2A).[23] The results showed that the LTT with DCs (DC-LTT) showed significantly higher sensitivity (61.8%) than the conventional LTT (29.4%). This was confirmed when analyzing each clinical entity including serious cutaneous adverse reactions (SCAR). In fact, this DC-LTT increased the proliferative response when analyzing the involved effector cells, reaching sensitivity rates of up to 68. 4% up to 100% in all the clinical entities. Therefore, the results concluded that the combination of the use of DCs and the evaluation of the involved effector cells proliferation showed greater sensitivity in all the clinical entities including SCAR. These findings indicate that, although more research is needed, DC-LTT DC in vitro test enhances the proliferative response to drugs in NIHRs by DCs and offers us important information about the immunological mechanisms involved for each clinical manifestation in a specific manner. New advances in the DC-LTT in vitro test development, as the identification of specific biomarkers, will help to increase the in vitro diagnosis of NIDHRs.

LTT performance has been poorly evaluated in children. Recently, in a study performed in a group of children with NIHSR to betalactams confirmed by drug provocation test, it was shown an involvement of T-cells in 52.9% of cases.[4] Furthermore, in NIHSRs to antiepileptic drugs, LTT showed a sensitivity and specificity of 58.4% and 95.8%, respectively. Interestingly, 3 out of 4 children with severe reactions to carbamazepine had a positive LTT.[24]

Finally, LTT results demonstrated a good correlation with the algorithm of drug causality for epidermal necrolysis (ALDEN) score, indicating the role of this method for diagnosing severe HSR.[24,25]

2.4 | Enzyme linked ImmunoSpot

EliSpot quantifies the number of spot-forming cells that release cytokines, such as IFNy or cytolytic molecules (Granzyme B, GrB) after the patient's PBMCs are stimulated with the suspected drug(s). This represents a new approach to study the effector mechanism and increase the sensitivity of in vitro tests. Recently, two studies reported that patients with NIHSR to antibiotics were positive to the implicated drug on IFNy EliSpot testing,[26,27] improving diagnosis in severe phenotypes and helping on culprit antibiotics identification. Moreover, in another study, warfarin was confirmed as the culprit in SJS with severe liver injury using specific IFN-γ-releasing cells.[28] Likewise, the measurement of IFNγ-releasing cells was key for identifying culprit drugs in a cohort of 27 patients with different clinical phenotypes of severe cutaneous adverse reactions SC.[29] Finally, EliSpot assay using the combined detection of IFNγ-, GrB-, and IL-5- releasing cells showed usefulness for diagnosing dapsone hypersensitivity syndrome.[5]

2.5 | T-cell clonality

Recently, the clonal diversity of T-cell repertoire has been analyzed as novel diagnostic tests to distinguish HSR from graft-versus-host disease (GVHD) (Figure 2A). CDR3 region of the TCR β chain from affected skin tissue was sequenced and a high degree of homogeneity in TCR sequences of T-cell clones in GVHD compared with HSR (to hydroxyurea) was found.[30] The difference in clonal heterogeneity allowed distinguishing GVHD from HSR to drugs, with a clonality cutoff of 0.042, a sensitivity of 60% and a specificity of 71%. In fact, this sensitivity and specificity were comparable with the sensitivity of 59% and the specificity of 76% reported by a clinical symptom of "facial involvement including pinnae," which is used to differentiate acute GVHD from HSR.[6] This indicates the usefulness of this approach for performing a differential diagnosis among entities with similar clinical and histological characteristics, but different management. Currently, important efforts have been made for detailing the antigenic specificity and phenotype of T-cell clones generated

from patients with HSR,[31,32] offering new information about basis immune response for HSR.

3 | BIOMARKERS: RECENT APPROACHES

In order to continue improving the diagnosis of HSRs, new biomarkers need to be identified. The most important diagnostic biomarkers are the detection of sIgE in serum, the over-expression of certain molecules on the cell surface during BAT (mainly CD63 and CD203c) and proliferation or mediator release in other cell-based tests (Figure 2).[7] However, recent developments (Figure 2B) have analyzed the role of other biomarkers in diagnosis, prognosis, or prediction on HSR, and have evaluated the effect of therapeutic approaches.[33,34]

3.1 | Biomarkers in HSR to chemotherapeutics and monoclonal antibodies

The development of HSRs to cancer treatments, such as taxanes, platinum compounds, and biological agents, constitutes a significant problem that could decrease the quality of life and life expectancy.[35] Drug desensitization (DD) treatment by gradual exposure to increasing amounts of the drug is generally considered a safe and effective option that leads to temporary drug tolerance and allows the continuation of the chemotherapy treatment.[36–38] Recent studies have found that after successful DD with platinum-based chemotherapy as well as with other drugs as lenalidomide, dexamethasone, and bleomycin,[8] IL-10 is increased in peripheral blood of patients compared to baseline levels. Despite the efficacy of DD, some patients can undergo breakthrough reactions (BTRs) during desensitization, thus finding a suitable biomarker to identify the risk of BTRs is also of utmost importance. In this sense, the high IL-6 and low serum tryptase levels have been observed in patients undergoing BTRs during DD to chemotherapy.[39] Furthermore, FcεRI serum levels below 2 ng/ml were considered as the biomarkers of those patients with a high risk of experience BTRs during DD.[40] These observations might help identify patients with the risk of BTRs.

3.2 | Genetic variants as biomarkers in HSR to drugs

Several studies have found a correlation between genetic factors and the development of HSR.[41] Human leukocyte antigen (HLA) system variants have been linked to HSRs induced by several drug groups.[42] More recently, the variant HLA-B*13:01 has been highlighted as a diagnostic biomarker for dapsone hypersensitivity syndrome, obtaining a sensitivity of 91.2% and a specificity of 96.2%,[43] whereas the variation in HLA-DRB1 seems to be associated with the development of HSR to drugs as a whole.[9]

Outside the HLA system, genetic variants in cytosolic phospholipase A2 (cPLA2) have been recently associated with HSR to NSAIDs. In particular, some PLA2G4A polymorphisms appear to play a role in NSAIDs-induced acute urticaria/angioedema.[10] It is worth noting that in many cases, differences in the genetic background of different populations hamper finding widely generalizable associations, which hinders the effective translation of these pharmacogenomic biomarkers into the clinic.

3.3 | Other novel biomarkers in HSR to drugs

It has been recently reported that the use of serum soluble OX40 could have significant value as both diagnosis and prognosis biomarker in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS), observing that serum soluble OX40 levels were positively correlated with disease severity.[44] OX40 is mainly expressed on activated $CD4^+$ T cells, and its interaction with its ligand (OX40L) expressed on antigen-presenting cells has been shown to be involved in Th2 differentiation. Moreover, the appearance of DIHS/DRESS is commonly associated with the reactivation of human herpesvirus 6 (HHV6), which is known to use OX40 as a receptor for cellular entry, observing also a positive correlation between OX40 serum level and HHV6 load. This indicates that new immunological elements (soluble OX40) can be a useful diagnostic marker for DIHS/DRESS, reflecting disease severity, as well as, predicting HHV-6 reactivation.[44]

4 | LIVING TOGETHER WITH COVID-19 PANDEMIC

The past two years have been clearly marked by the worldwide pandemic caused by SARS-CoV-2.[45] In order to fight the pandemic and protect people against COVID-19, specific treatment and efficacious vaccines were developed and licensed in a highly accelerated manner.[46] However, HSRs to these compounds have hampered their wide administration.

4.1 | Off-label drugs to treat COVID-19 as HSRs inductor

SARS-CoV-2 causes a wide spectrum of clinical manifestations, ranging from the most common and mild, self-limiting respiratory tract infection, to severe cases complicated by acute respiratory distress syndrome (ARDS) and hyperinflammatory state due to an overproduction of cytokines that leads to thrombo-embolic complications and multiorgan dysfunction syndrome. Unfortunately, at the moment of the pandemic declaration, no specific effective drugs were approved for COVID-19, with off-label drugs being used.[13] Skin manifestations have been associated with COVID-19. A study found skin involvement in 20.4% of patients with COVID-19, erythematous

rash was the main manifestation (77%), followed by widespread urticaria (16%) and chickenpox-like vesicles (5%). It may be related to thrombo-vascular events, typical viral infections, or HSRs to drugs used to treat this disease.[13,47] These HSR are mainly NIHSRs to immunomodulatory drugs (including azithromycin), hydroxychloroquine/chloroquine, and IFNs, but it was not clear if this increased frequency reported was caused by the drug immunogenicity or derived from a greater consumption.[13]

4.2 | Vaccine emergence: Fear after first reactions and recommendations in allergic patients

Vaccine development studies rapidly grew in order to eradicate the SARS-CoV-2 (Figure 3A). The first vaccines approved were the mRNA vaccines by Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and the recombinant adenoviral (AZD1222 or ChAdOx1-S) by Oxford/AstraZeneca.[12] In addition, other novel COVID-19 vaccines have been subsequently authorized or are in different phases of clinicals development.[48–54]

Few days after the vaccination-campaign started, cases of HSRs after receiving the vaccine were reported. This prompted Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom to recommend subjects with history of allergic reactions not to receive the vaccine, and the Centers for Disease Control and Prevention (CDC) to suggest allergic individuals to other vaccines to weigh their benefit–risk of vaccination.[55] However, the understanding of the immunopathology in COVID-19[56] advocates that allergic patients should not generally be excluded from vaccination, and the European Medicines Agency (EMA) and the European Academy of Allergy and Clinical Immunology (EAACI) recommended patients with HSRs to a specific vaccine component or to the first vaccine dose not to receive the vaccine.[11] Furthermore, the EAACI provided guidance on recognizing and treating vaccination-induced HSRs and proposed a workup to identify the responsible allergen.[11] The "Allergy and Its Impact on Asthma" (ARIA) group together with the EAACI recommended that allergic patients should be observed for at least 15 min after vaccination and that healthcare personnel involved in vaccination should be trained to recognize anaphylaxis and be

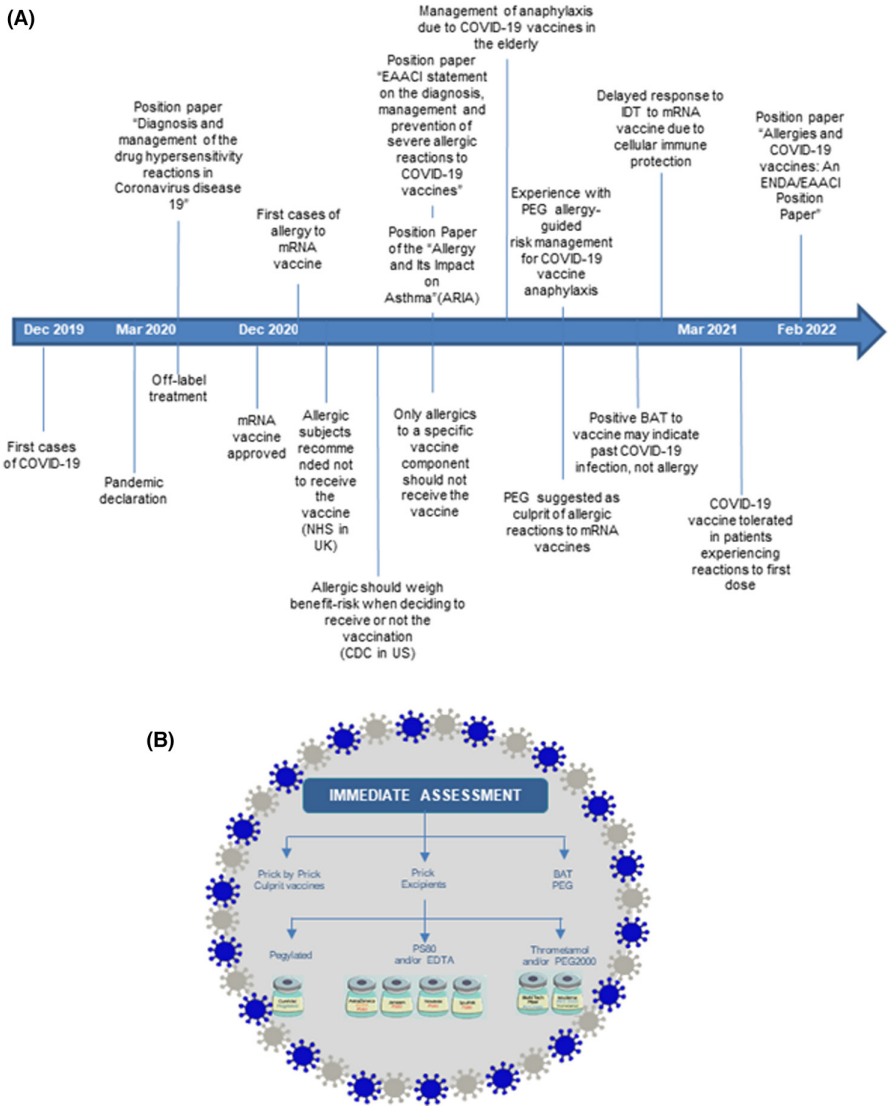


FIGURE 3 COVID-19 vaccines. (A) Chronological representation from the pandemic declaration to the present, emphasizing the most relevant contributions associated with the diagnosis, management, and prevention of severe allergic reactions (anaphylaxis) to COVID-19 vaccines. (B) Description of anti-SARS-CoV-2 vaccines including the main allergenic-containing excipients. The assessment for immediate reactions includes prick by prick with culprit vaccine, and prick test panel with excipients (pegylated, polysorbate 80, and PEG 2000) for diagnosis. Basophil activation test for Type-1 reactions to PEG can be considered

TABLE 2 Summary of main discoveries and perspectives for future research

HSR	Major milestones	Future researcher
In vitro tools	Nanoparticles-allergen for detection of HSRs to drugs.[2,15]	To develop diagnostic methods for allergic diseases based on nanoparticles
	Increase in the BAT sensitivity in HSRs to drugs.[3,17–21]	To improve the specificity and sensitivity of in vitro methods for allergic diseases
	LTT using DC improve the sensitivity of test and the proliferative response of effector cells.[4,23–25]	
	EliSpot assays can improve diagnosis in severe phenotypes and identification of culprit drugs.[5,26–29]	To improve the use of the EliSpot assays as diagnostic tool
	T-cell clones used as novel diagnostic tests to distinguish different disease.[30]	To understand better the use of the T cells clones as diagnostic tests
Biomarkers	New biomarkers can help identify patients with risk of breakthrough reactions and can be a useful diagnostic marker for HSR.[39,40]	To validate and standardize the use of novel biomarkers not only for drug allergy diagnosis, but also for prognosis and therapy monitoring
	New associations have been described between HSR and HLA and cPLA2 variants.[9,10,43]	
COVID-19 vaccines	HSR to COVID-19 vaccines are not as common as initially thought.[55]	To identify immunological mechanism for HSRs to COVID-19 vaccines
	HSR to COVID-19 vaccines seem to be mostly associated with certain excipients in the vaccine formulations, especially PEG-2000.[58,59]	
	HSR to PEG depend on its molecular weight.[59]	To develop effective in vitro methods on diagnosis of HSRs to the excipients of the COVID-19 vaccines
	BAT has shown to be useful to indicate a PEG allergy.[68]	

Abbreviations: BAT, basophil activation test; DC, dendritic cells; HSR, hypersensitivity reaction; LTT, lymphocyte transformation test; PEG, polyethylene glycol.

prepared to treat it,[57] highlighting the adrenaline availability ready for administering, if necessary.

4.3 | Toward a precise diagnosis and management of COVID-19 vaccine allergic reactions

Although the culprit of the reported HSRs to COVID-19 vaccines has yet to be determined, excipients have been suggested as a potential cause.[58,59] Polyethylene glycol (PEG) has been clearly demonstrated to cause HSRs, both IgE and non-IgE-mediated.[60–63] Although PEG is widely distributed, sensitization occurs only rarely.[60,63] Recently, guidelines to manage patients at risk for HSRs to PEG indicate that SPT and intradermal testing (IDT) with different dilutions of PEG, BAT, and oral provocation testing are recommended.[12,64] However, it is not clear the use of skin testing to PEG prior to COVID-19 vaccination in patients reporting HSRs to drugs containing PEG, as such testing has unknown sensitivity/specificity in predicting severe allergic reactions.[64] Moreover, it has been reported that patients reporting HSRs to drugs containing PEG may tolerate the vaccine, maybe due to the fact that HRs seem not to be related to the excipient allergy history[65] or to a different molecular weight of PEG.[59] In addition to PEG, the role of other excipients such as polysorbate 80 (PS80) as relevant allergens in vaccines remains more questionable.[59,66] However, in case of severe reactions, excipients other than PEG should also be evaluated as causative agents.[66]

The utility of immediate readings of SPT and IDT with mRNA vaccines is very limited, as for cutaneous reactions no positive results have been reported for SPT, and positive delayed reactions have been described for IDT, even if patients tolerated subsequent doses of the same vaccine.[67] According to in vitro tests, BAT has shown to be useful to indicate PEG allergy.[68] A negative BAT to a vaccine should encourage vaccination with the tested vaccine; however, a positive BAT to vaccine may indicate a past COVID-19 infection instead of an allergy and may not contradict vaccine tolerance[68] (Figure 3B).

The practical recommendations for the management of patients having a suspicion of HSR to COVID-19 vaccines are that they should undergo risk stratification, weighing the benefits, and risks of subsequent dose vaccination. It has been proposed that a detailed clinical history would allow identifying those requiring PEG allergy workups and help to select the vaccination approach. Moreover, it has been reported that even PEG-allergic patients can tolerate COVID-19 vaccines as hypersensitivity depends on PEG molecular weight.[59]

Although the mechanisms of anaphylaxis associated with mRNA vaccines are currently unknown, a likely non-IgE-mediated mechanism has been proposed, and therefore, antihistaminic premedication may be helpful in improving tolerability of the subsequent dose, but not in cases with an IgE-mediated confirmed allergy to PEG.[69]

The European Network of Drug Allergies (ENDA) has harmonized protocols with recommendations for the management of patients suffering or having a suspicion of HSRs to COVID-19 vaccines[12] as

follows: (i) Allergy evaluation is recommended in subjects with suspected or confirmed allergy to compounds containing PEG or derivatives ot any mRNA; and with recurrent anaphylaxis of unknown cause; (ii) The allergological approach includes a prick-to-prick skin test with suspected vaccine; and SPT with PEG and PS80[12]; (iii) According to the results, if negative, vaccine with any COVID-19 vaccine is allowed; if positive to PEG but negative to PS80, vaccine with no PEG, but PS80 should be administered in an Allergy Unit; and if both PEG and PS80 are positive, it is recommended vaccination with fractionated doses in an Allergy Unit, or vaccination with a solution not containing PEG or PS80, or not vaccination.

5 | CONCLUSIONS

Many new studies have been reported in recent years regarding in vitro diagnostic methods for HSRs to drugs. However, more works are needed to improve the specificity and sensitivity of in vitro methods, and to validate and standardize the use of novel biomarkers not only for drug allergy diagnosis, but also for prognosis and therapy monitoring (Table 2).

Although after the initial round of vaccination against COVID-19, it was believed that IHSRs could be a common problem, the majority of patients reporting reactions to COVID-19 vaccine tolerated a subsequent vaccination. However, cases reporting HSRs to COVID-19 vaccines seem to be mostly associated with the presence of certain excipients in the vaccine formulations, such as PEG, being the allergological evaluation needed. In this context, the development of effective in vitro diagnostic methods is a particularly relevant area where the works reported this far have shown limited clinical utility. In addition, we have briefly included the main discoveries and perspectives for future research on HSR to drugs, in vitro tools, biomarkers, and COVID-19 vaccines (Table 2).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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