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Review Article

Autoimmune Hepatitis-Like Liver Injury after COVID-19 Vaccination; Review of Molecular Underpinnings and Clinicopathologic Picture

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Abstract

Mass vaccination against COVID-19 infection has been able to substantially alleviate the consequent mortalities and the spread of the disease. The paced design and administration of novel mRNA-based vaccines paved the way for the production against cancers and acquired immunodeficiency syndrome. Various side effects, lethal in some instances, are described for COVID-19 vaccines, including the instigation of incidence or relapse of autoimmune disorders, including autoimmune hepatitis (AIH). Molecular mimicry with the spike protein S1 and cross-reactions, adjuvants-induced autoimmune/autoinflammatory syndrome, epitope spreading, and bystander activation are among the molecular mechanisms that are hypothesized to mediate vaccine-induced autoimmunity. Pathological and serologic evaluations of patients with liver injury following COVID-19 vaccination have displayed that most cases can be categorized as probable or definite for the diagnosis of AIH. AIH and AIH-like liver injuries following COVID-19 vaccination are generally manageable with the administration of corticosteroids and other immunosuppressive therapies if required. Data on the safety of subsequent vaccination is scarce; however, vaccination during maintenance therapy with steroids seems safe. More importantly, the recognition of asymptomatic cases with altered liver aminotransferase levels necessitates the design of prospective cohorts to assess the long-term consequences of sub-clinical liver dysfunction induced by COVID-19 vaccines.

Keywords: Autoimmune Hepatitis; COVID-19; Hepatology; SARS-CoV-2; Vaccination

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Introduction

In December 2019, many cases of an unknown respiratory disease were reported in Wuhan, Hubei province, China. By January 2020, it was corroborated that these cases were suffering from a new coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) later. (1). Coronavirus disease 2019 (COVID-19) is one of the most contagious infectious diseases (2). From that moment on, numerous preventive approaches, namely various types of vaccines (including inactivated virus vaccines, live attenuated virus vaccines, and protein and nucleic acid including vaccines) have been introduced (3,

4). Some of these designed vaccines (including mRNA-1273, BNT162b2, ChAdOx1 nCov-19, and Ad26.COV2.S) have exhibited considerable efficacy in alleviating the spread and mortality of SARS-CoV-2 (5).

Despite the considerable effectiveness of vaccines against COVID-19, this has come at the expense of various side effects, including lethal ones in some instances. Myocarditis (6), Guillain-Barré syndrome (GBS) (7), vaccine-induced thrombotic thrombocytopenia (VITT) (8), and post-vaccinal encephalitis (9) are some of these side effects. Autoimmune hepatitis (AIH) is one of the most noticeable side effects that has been reported in some cases (10). As of April 2022, five cases developed AIH after the injection of the Pfizer-BioNTech COVID-19 vaccine (BNT612b2) (11-15). Although the exact etiology of AIH is still unknown, the cardinal roles of the immune system in the pathogenesis and perpetuation of AIH are undeniable (16). The prevalence of AIH appears to be quite variable in different regions, as among the European population, it is reported to be 10 to 25 per 10000 people. The prevalence of AIH is reportedly 5 to 25 per 10000 in Asian-pacific regions (16, 17).

Regarding the fact that there are no specific tests to diagnose AIH, there is a scoring system in which different criteria are required for a definite or probable diagnosis (18, 19). According to this scoring system, serum immunoglobulin g (IgG) level, autoantibodies (including anti-nuclear antibodies [ANAs], anti-smooth muscle antibodies [ASMAs], anti-liver-kidney microsomal type 1 [anti-LKM1], and anti-liver cytosol type 1 [anti-LC1]), and tissue samples for microscopic assessment are required for the diagnosis. Other liver diseases (e.g., viral hepatitis) that may exhibit such serological and histological features must be excluded as well (19).

Due to the role of the immune system in the pathophysiology of AIH, some drugs are known to be effective against this disease. As the first-line therapy, the combination of prednisolone and azathioprine is effective in 80-90% of patients (19). As the second-line therapy, some alternative medications, such as mycophenolate mofetil (MMF) (20), calcineurin inhibitors (21), anti-tumor necrosis factor-alpha (TNF-α) agents (22, 23), and rituximab might be used as the third line of therapy (24). In addition, according to the estimations, the 10-year survival rate of untreated, moderate to severe AIH is approximately 10% (25), necessitating its proper diagnosis and management.

Therefore, the development of AIH after the COVID-19 vaccination should be monitored judiciously. This review article aims to delicately illustrate the prevalence of vaccine-induced AIH and its course among affected cases and to decipher the pathogenesis of vaccine-induced AIH, its correlation with SARS-CoV-2, and diagnostic and therapeutic approaches to this potentially lethal side effect.

COVID-19 immunopathogenesis

Cytokines

As a result of COVID-19 infection, patients often develop acute respiratory distress syndrome (ARDS), which is the leading cause of COVID-19-associated mortalities (26). It is believed that ARDS is the consequence of an exaggerated immunologic response that triggers cytokine release syndrome (CRS). CRS, also known as the cytokine storm, leads to multi-organ failure (27). SARS-CoV-2 pathogenesis and clinical manifestations appear to be associated with the host immune response, which is not confined to antiviral immune responses. It also includes proinflammatory cytokine release, leading to an irrepressible inflammatory response (28). Patients suffering from COVID-19 show impaired immune responses. It appears that the virus disrupts the patient's immune system (28). One of the main characteristics of immune system dysregulation is the excessive cytokine production found in severe cases (28). The majority of severe COVID-19 cases exhibit a significant rise in inflammatory cytokines, including interleukin-1beta (IL-1β), IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-CSF (GM-CSF), IFN-γ, TNF-α, monocyte chemotactic protein 1 (MCP-1), and macrophage inflammation protein-1α (MIP-1α) (29-32). Some studies have indicated that IL-1β, IL-6, and IL-10 are the three most imperative cytokines in severe cases (33, 34). It should be mentioned that other mentioned cytokines are also elevated in non-severe cases, but their concentrations are remarkably lower than

those in severe cases (29, 31, 35).

Immune cells

Several studies have illustrated that lymphopenia occurs during the course of COVID-19 infection, particularly in severe cases that are admitted to the intensive care unit (ICU) and need mechanical ventilation or their fraction of inspired oxygen (FiO2) is more than 60% (36, 37). Moreover, it is shown that lymphopenia is an outstanding predictor of the severity of the disease and the development of ARDS (37). Patients also exhibit a significant decline in CD4+ T-cells, CD8+ T-cells, and NK cell counts (31, 38, 39). Nevertheless, it is shown that the B-cell numbers commonly remain within the normal range (28, 31), implicating that their dysregulations are not as critical as T-cells or NK cells during COVID-19 infection. Those patients suffering from lymphopenia are consequently more susceptible to microbial infection (28).

Humoral immune system

The humoral immune system has a protective role against SARS-CoV-2 infection (40). On the other side, it plays a prominent role in the COVID-19 severity, which is attributed to the deranged glycosylation pattern of anti-SARS-CoV-2 IgG antibodies (40, 41). Many studies have indicated that most patients produce virus-specific IgM and/or IgG antibodies within a short period after infection (42-45). In a study on 112 patients, both virus-specific IgM and IgG antibodies were positive in 51% of cases within 7-10 days after the disease onset (43). Another study illustrated that two weeks after the disease onset, anti-spike protein receptor binding domain IgG (anti-RBD) and anti-nucleocapsid protein IgG (anti-NP) are detectable in 100% and 94% of cases, respectively (45).

To find out whether these antibodies have any protective effects against the virus, some studies have been conducted, yet further studies are needed to reach robust conclusions (40). For instance, a study by Wang et al. reported that the virus-specific IgG could co-exist with the virus for a long time, which implies that antibodies may not be related to the virus clearance (46). Several studies identified antibodies that block the interactions of spike protein RBD with its receptors (neutralizing antibodies) in SARS-CoV2 and MERS-CoV-infected individuals (47, 48). Moreover, an investigation showed that some anti-SARS-CoV-2 spike RBD antibodies harbor neutralizing abilities and are detectable in affected individuals (49). Therefore, some of these antibodies have a neutralizing effect, but the rest of them are not proven to have protective functions.

When it comes to humoral immune responses, complement activation by virus-specific antibodies ought to be noticed, in addition to neutralizing activity. The activation of the complement system via different pathways has heterogeneous aspects that might be either protective or pathologic (41).

In fact, several studies have reported that certain virus-encoded proteins inhibit complement proteins, emphasizing the beneficial effects of complement pathway activation (50). In contrast, evidence shows that complement system activation might be pathological. A study by Magro et al. demonstrated that complement activation leads to microvascular injury and subsequent thrombosis in COVID-19 patients (51). Furthermore, it has been shown that C3-deficient mice demonstrate significantly less severe disease after infection with SARS-CoV (52). It has been shown that the blockade of C3a and C5a protects patients from coronavirus-induced lung injury. Besides, anti-C5a antibodies have a therapeutic effect against the induced impairments by MERS-CoV (including the degranulation of mast cells, induction of cytokine release, and enhanced permeability of vessels) that leads to acute lung injury (52, 53). Measuring the concentrations of complement proteins, such as the mannan-binding lectin (MBL) and mannose-binding protein-associated serine protease 2 (MASP-2) in the serum of patients seems to be beneficial, considering the fact that there is a direct correlation between the concentration of these proteins and the severity of the COVID-19 infection (41, 50).

Antibody-dependent enhancement (ADE) occurs when the binding of a non-neutralizing antibody contributes to the virus entering the cells and facilitates viral replication and virulence. This phenomenon is known to have a part in the pathogenesis of many viruses, particularly SARS-CoV-2 (54). In COVID-19, it is reported that antibodies against spike protein mediate this process (55, 56).

Cellular immune system

Contrary to the humoral immune system, data on the cellular immune system's involvement in the pathogenesis of COVID-19 is limited. As mentioned earlier, there is a remarkable decline in the numbers of CD4+ and CD8+ T-cells and NK cells in the peripheral blood of affected subjects (31, 38, 57). Unlike patients who do not respond to treatment, there is a significant increase in the numbers of CD4+ and CD8+ T-cells and NK cells in those who respond to treatment immediately after its commencement (57). Of note, the diminished counts of these cells do not necessarily implicate their suppressed activities. In a patient with low CD4+ and CD8+ T-cell counts immunophenotyping showed that these cells are hyper-activated. Such hyperactivation was indicated by the high expression of human leukocyte antigen (HLA)-DR/CD38, higher numbers of proinflammatory C-C motif chemokine receptor 6 (CCR6)+ T-helper 17 (Th17) cells, and higher production of cytotoxic proteins such as granulysin and perforin (expressed by CD8+ T-cells) (39). It should be noted that the exhausted state is the progressive loss of effector functions of cytotoxic T-cells and is the consequence of the expression of multiple inhibitory receptors such as programmed cell death protein 1 (PD-1), T-cell immunoglobulin mucin 3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), NKG2A (CD159), and CD39 on immune cells (58). This exhaustion phenotype is seen during COVID-19 infection and is thought to be caused by the overactivation of T-cells (34, 41, 59-62). It should be noted that in mild cases of COVID-19, Th2 cells maintain their normal function. On the opposite, some alterations occur in severe cases, leading to adverse responses in these cells (60). In COVID-19 survivors, memory CD4+ and CD8+ T-cells were found in 100% and 70% of convalescent cases, respectively (63).

Molecular structure of COVID-19 vaccines

Since the emergence of COVID-19, several vaccine approaches, including traditional approaches, inactivated viruses, live attenuated, and protein/adjuvant approaches, have been suggested. There are also some new and unlicensed approaches like viral vectors and nucleic acids (3). The generally approved vaccines against COVID-19 infection are outlined in **Table 1** (3, 64).

According to the published articles and trials on these vaccines' efficacy, among the three adenovirus vector vaccines, Gam-COVID-Vac has the highest efficacy (91.6%, 95%CI=85.6-95.2) (65). The second place belongs to ChAdOx1 nCoV-19 (70.4%, 95%CI=54.8-80.6)(66, 67), and is followed by Ad26.COV2.S (66.1%, 95%CI=55-74.8) (68).

To date, three studies have been conducted on the efficacy of mRNA vaccines (69-71). Two of them were conducted on BNT162b2. In the mentioned studies, the efficacy was calculated to be 95% (95%CI=90.3-97.6) and 92% (95%CI=88-95), respectively (69, 71). The efficacy of the mRNA-1273 vaccine in a randomized clinical trial was 94.1% (95%CI=89.3-96.8)(70).

An ideal vaccine can be applied to all age groups, even for immunosuppressed individuals, at a low price and with minimal side effects. Moreover, it should induce a persistent immune response by priming the immune system to produce protective neutralizing antibodies and diverse immune cells. (72, 73). Based on a study conducted by Zhang et al. (74), the effectiveness of BBIBP-CorV (Sinopharm) against hospitalization was 88.5% (95%CI=85.8%-90.7%). The effectiveness of NVX-CoV2373 was 89.7% (75). Based on three clinical trials carried out on CoronaVac, the efficacies against symptomatic infection were estimated to be 83.5% (95%CI=65.4%-92.1%) in Turkey (76), 65% (95%CI=20%-85%) in Indonesia (77), and 50.7% (95%CI=35.9%-62.0%) in Brazil (78). The effectiveness of BBV152 Covaxin was 93.4% (79).

Side effects of COVID-19 vaccines

The side effects of COVID-19 vaccines are extensively reported, and among the various registered side effects, some are serious and life-threatening, although in rare instances. There is firm evidence of the association between COVID-19 vaccines and the rare incidence of some complications, including anaphylaxis and allergic reaction, thrombosis with thrombocytopenia syndrome (TTS) (80), and GBS (81), which has led to the issuing of safety concerns. However, most

Table 1. Summary of the features and efficacy of commonly administered COVID-19 vaccines.

Vaccine name	Manufacturer	Manufacture location	Structure	Target antigen(s)	Efficacy	Number of doses
BNT162b2	Pfizer/BioNTech	Germany	Modified nucleoside mRNA	spike	95%	2
ChAdOx1 nCov-19 (AZD1222)	University of Oxford/AstraZeneca	UK	**Adenovirus vector vaccines**	spike	70.4%	2
BBIBP-CorV	Wuhan Institute of Biological Products/Sinopharm	China	Beta-propiolactone inactivated virus	Whole virus	88.5%	2
mRNA-1273	Moderna/NIAID	USA	mRNA	Stabilized Spike	94.1%	2
Gam-COVID-Vac rAd26/rAd5 (sputnik V)	Gamaleya Research Institute	Russia	Adenovirus prime boost	Spike	91.6%	2
CoronaVac	Sinovac	China	Beta-propiolactone Inactivated	Whole virus	83.5% (Turkey)	2
NVX-CoV2373	Novavax	USA	Recombinant nanoparticle vaccine	Spike	89.7%	2
Ad26.COV2.S	Janssen	USA, Belgium	Ad26 adenovirus vector	spike	66.1%	1
BBV152 Covaxin	Bharat Biotech	India	Inactivated virus	Whole virus	93.4%	2

reported complications are proposed based on mere temporal associations, and robust relationships are yet to be proven.

Based on these studies, complications are classified into short-term and long-term categories. Short-term side effects are further divided into local and systemic complications. Common local side effects include pain, redness, and swelling at the vaccination site. Common systemic side effects include fever, chill, fatigue, nausea, vomiting, headache, diarrhea, and arthralgia (64, 68, 82-88). Among the local side effects, pain at the injection site is reported as the most common symptom, while among systemic complications, fatigue and fever are the most prevalent ones in those who receive mRNA vaccines and adenovirus vector vaccines, respectively (64).

Until now, various studies have reported on subjects afflicted with long-term side effects secondary to COVID-19 vaccination, which have had significant morbidities and mortalities. One of the long-term side effects following adenoviral vector-based vaccines is VITT. VITT was first reported in a study conducted by D'Agostino et al. (89). Following this study, several VITT cases were reported secondary to adenoviral vector-based vaccines such as ChAdOx1 nCoV-19 and Ad26.COV2. S (90-93). Many of these cases were attributed to autoantibodies against the platelet factor 4 (PF-4) antigen (93-96), antibodies that are responsible for heparin-induced thrombocytopenia (HIT) (97).

Another rare yet fatal long-term complication of COVID-19 vaccination is myocarditis (98). Based on studies and reported cases, the incidence of post-COVID-19 vaccination myocarditis is estimated to be 2.13 cases per 100,000 BNT162b2 vaccine recipients (99). While the etiology is still unknown, the leading theory is molecular mimicry (discussed later) (100). It is assumed that the molecular similarity between COVID-19 spike glycoprotein and human proteasome might be responsible for this complication (101, 102). Moreover, it has been shown that there is a strong cross-reaction between antibodies against the S1 spike protein and multiple endogenous antigens such as F-actin and α-myosin (100, 103). Of note, his complication is much more prevalent after the application of mRNA vaccines (BNT162b2 and mRNA-1273) (98, 104).

There are also various reported neurological side effects following COVID-19 vaccination. Headache, transverse myelitis, GBS, and venous sinus thrombosis (VST) are remarkable neurological side effects of COVID-19 vaccination (105). Such complications may occur after the delivery of all available vaccines, but VST seems to particularly occur secondary to vector-based vaccines

(105).

A multitude of studies has revealed that diverse mucocutaneous side effects might happen following COVID-19 vaccination. Urticaria, flushing, angioedema, anaphylaxis, Stevens-Johnson syndrome, Rowell's syndrome, pityriasis rosea, purpuric lesions like immune thrombocytopenic purpura (ITP), and vasculitis-associated purpura are some of these mucocutaneous complications (106). More importantly, it is postulated that vaccination can lead to the reactivation of inflammatory diseases such as psoriasis, lichen planus, autoimmune inflammatory rheumatic diseases (AIIRD), Behçet's disease, and systemic lupus erythematosus (SLE) (106).

Pathogenesis of autoimmunity induced by COVID-19 and its vaccination

According to the published studies on the side effects of other vaccines, several mechanisms are presumed to be responsible for autoimmunity secondary to vaccination. The first possible mechanism is molecular mimicry and immune cross-reaction (107). Molecular mimicry is defined as the remarkable similarity between microbial antigens and host antigens. Immune cross-reaction happens when the immune system simultaneously destroys pathogenic agents and human antigens (107). It has been demonstrated that 13 out of 24 pentapeptides of the spike proteins of SARS-CoV-2 are similar to human surfactant proteins (102, 108).

A study showed that out of 50 human tissue antigens, 21 have significant cross-reactions with the SARS-CoV-2 antibodies (100). Some of these antigens, including transglutaminase 3 (tTG3), myelin basic protein (MBP), α-myosin, mitochondrial and nuclear antigens, thyroid peroxidase (TPO), and collagen, exhibited the strongest cross-reactivity (100). Intriguingly, among these antigens, mitochondrial and nuclear antigens are known to play a considerable role in immune-mediated liver cell injury (107). The detection of antimitochondrial antibodies (AMA) and ANA is an integral part of the diagnosis of primary biliary cholangitis (PBC) and AIH, respectively (107, 109).

The other mechanism that might be responsible for vaccine-induced autoimmunity is autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA), characterized by Shoenfeld and Agmon-Levin (110). Adjuvants are substances added to vaccines to make their influences more robust and durable. They simplify the process of the detection of foreign antigens by binding to Toll-like receptors (TLRs) (111, 112). They also improve dendritic cells, macrophages, and lymphocyte activities (113). The adjuvant that is used in mRNA-based COVID-19 vaccines is lipid nanoparticles (LNP). It has been shown that in mouse models, LNP can trigger the release of inflammatory cytokines and chemokines. It can also trigger the signaling of various inflammatory pathways (114). Therefore, LNP, as an adjuvant, can lead to ASIA.

The other implicated mechanism is epitope spreading and bystander activation (107). Epitope spreading refers to the phenomenon that epitope specificity alters from dominant epitope to cryptic epitope (115). This phenomenon leads to protection against pathogens and autoimmunity at the same time (116). Bystander activation is defined as the antigen-independent activation of T-cells and B-cells (117). It is thought that bystander activation has a significant role in the pathogenesis of AIH (118). It has been proposed that cryptic antigens of host tissues may be released by microbial agents (119). This phenomenon causes epitopes to spread, which may lead to autoimmunity.

AIH and immune system involvement

AIH is a relatively rare, chronic, and gradually progressive disease that is more prevalent in women. The etiology is still unknown, but various factors, such as genetic susceptibility, environmental insults, and dysregulated immune system activities, play key roles in its pathogenesis (120-122). It is believed that in the immunopathogenesis of AIH, adaptive immune cells lose their tolerance to liver cell antigens and subsequently attack them (123). Although the liver is an organ that is exposed to numerous antigens (such as toxins and true and potentially pathogenic organisms) via the portal system, it is a highly tolerogenic organ (122, 124). To prevent inappropriate inflammatory responses to these various antigens, the liver acts in such a way that, on the one hand, it fights against invading pathogens, and on the other hand, it strengthens the symbiosis of the

body and commensal agents (124). Therefore, the immune system of the liver must be tolerant to foreign antigens while responding appropriately to harmful agents.

Both central (which destroys autoreactive T-cells in the thymus) and peripheral tolerance play key roles in this phenomenon. As such, mutations in the autoimmune regulator gene (AIRE-1) lead to the development of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, which is closely related to AIH, and AIH can manifest as part of this syndrome (122). In addition, a study on mice revealed that the absence of the thymic medulla has a significant relationship with AIH and may contribute to the development of this disease (125). Nevertheless, multiple factors such as genetic predisposition, environmental insults (such as toxins, drugs, and infections), and defects in the regulatory mechanisms of the immune system are conducive to the pathogenesis of AIH. As a result, the loss of tolerance triggers hepatic cell damage mediated by cytotoxic T-cells, with extensive cooperation of different T-cell subsets and B-cells (126, 127).

When hepatocyte antigens are presented to naïve T-lymphocytes, there are three distinct pathways that can be activated, depending on the co-stimulatory molecules and local cytokines secreted by innate immune cells present in the hepatic tissue. In the first path, under the influence of IL-12, naïve T-cells differentiate into Th1 cells that secrete various immune mediators such as IL-2, IFN-γ, and macrophage migration inhibitory factor (MIF) (122). Also, these cells trigger macrophage and NK cell activation and cytotoxic CD8+ T-cell production. Ultimately, cytotoxic T-cells directly destroy liver cells (122). On the other hand, there are specialized T-cells called regulatory T-cells (Tregs) that express the IL-2 receptor (CD25) and inhibit autoreactive T-cells. As such, they are strongly stimulated and expanded by this cytokine (128). Therefore, IL-2 can stimulate cytotoxic T-cells and NK cells and expand Tregs. Recent studies have demonstrated that the administration of low-dose IL-2 has a therapeutic effect on AIH and some other autoimmune diseases (128-130). The point is that low-dose IL-2 stimulates Tregs expansion, while high-dose IL-2 has a stimulatory effect on cytotoxic CD8+ T-cells and NK cells (128). Multiple studies have revealed that the IFN-γ secreting Th1 cells are increased in the peripheral blood of AIH, compared to healthy individuals (131, 132). In addition, studies on mouse models have shown that IFN-γ produced by Th1 cells plays a crucial role in the progression of the disease (133-136).

In the second path, the concomitant presence of IL-6 and transforming growth factor-beta (TGF-β) causes the differentiation of naïve T-cells into Th17 cells. The Th17 pathway is characterized by the production of inflammatory cytokines (including TNF-α, IL-6, IL-22, and IL-23) and leads to Th17-mediated liver cell damage. The concentration ratio of TGF-β and IL-6 is critical for Th17 differentiation, as in the case of TGF-β dominance, this pathway tends toward Tregs (122). Therefore, a balance between these cytokines is crucial in the pathogenesis of AIH. Some additional T-cell subsets are also known to participate in this process. The two major subsets are γδ T-cells and mucosal-associated invariant T-cells (MAIT), which are characterized by the expression of a special type of retinoic acid-related receptor that induces IL-17 production (122).

To illustrate the role of IL-17 in the development of AIH, some experimental studies have demonstrated that the deficiency of both IL-17 and IL-17 receptors is partially protective against liver cell injury (137, 138). Also, it has been proved that the number of Th17 cells is elevated in the blood and the hepatic tissue of these patients (139).

The other predisposing factor is polymorphism within the TNF-α gene, which should be considered an essential factor for the pathogenesis of AIH (140-143). In patients with AIH, the production of TNF-α by Th17 cells is significantly higher than that of healthy individuals (144).

As mentioned above, the densities of Tregs are lower in AIH cases than in healthy subjects (145-147). On the other hand, CD4+ T-cells are more resistant to the suppression by Tregs in AIH patients. In addition, there are some recently discovered co-inhibitory molecules (including PD-1 and CTLA-4) that are less active in AIH cases compared to healthy individuals (148).

In the third path, in the presence of IL-4, naïve T-cells differentiate into Th2 cells that secrete IL-4, IL-10, and IL-13. These cytokines induce the differentiation of B-cells into antigen-specific plasma cells. Besides, this pathway can activate

the complement system (122). Although T-cells are the main components involved in the pathogenesis of AIH, B-cells play at least two major roles. First, by presenting liver cell autoantigens to T-cells, they induce T-cell activation. Second, they produce autoantibodies, which are essential for the diagnosis of AIH (149). In addition, detecting these autoantibodies makes us able to distinguish between various types of AIH (122).

Reported cases of COVID-19 vaccine-induced AIH

Several studies have indicated that SARS-CoV-2 and autoimmunity are closely related (108, 150-152). It seems that the potential mechanism involved in this phenomenon is molecular mimicry (108). As mentioned, a study conducted by Vojdani et al. revealed that there is a high affinity between antibodies against the spike protein S1 and some endogenous proteins in the body (100). In addition, it is believed that vaccines against SARS-CoV-2 induce interferon pathways in the recipients and might be responsible for triggering interferon-mediated autoimmune conditions like AIH (123, 153). According to descriptions of earlier studies, different types of vaccines, such as hepatitis A and influenza vaccines, might be responsible for the development of AIH (154, 155).

Concerning the development of AIH and AIH-like liver injuries following COVID-19 vaccination, there are reports on 57 separate case reports(10-15, 156-181) (13 are represented in case series as well) and 140 cases (including six cases that are reported by both reports). Some are the same subjects presented in separate case reports) described by two case series (182, 183). The detailed characteristics of these cases are presented in Supplementary **Table 1** and **Table 2**, and the summary of the main findings are illustrated in **Table 3**.

In this study, we comprehensively summarized the demographic, clinical, and pathological characteristics of patients with liver injury with similarities to AIH following COVID-19 vaccination.

There was considerable heterogeneity in the timing of vaccination, delay from vaccination to the appearance of signs and symptoms, and presentations of the disease. In separate case reports, the age ranged between 21 and 85 years (median, 61), and 71.92% were female. The most common presentations in those with available data (n=37) were jaundice (67.56%), fatigue/malaise/weakness (37.83%), choluria (32.43%), and pruritis (29.72%). Of note, 16.21% of cases were asymptomatic during the course of their disease. 28.07% had a history of autoimmunity, and two had a positive history of the prescription of pegylated interferon, a suggested etiology for the development of AIH (184). In addition, some of the affected individuals had prior diagnoses that pose a risk for the incidence of AIH. For example, in two studies (166, 170), patients had a history of treated AIH and hepatitis C virus (HCV), and the latter is a putative risk factor for the development of AIH (184). The detection rate of other autoimmune disorders is reported to be higher in individuals with AIH compared to total incidence rates (185). As a result, a shared mechanism that predisposes to autoimmunity might underlie the susceptibility to the development of AIH following COVID-19 vaccination.

Drug-induced liver injury (DILI) is a paramount differential diagnosis for AIH (186). In separate case reports, only three patients were on statins therapy (a rare etiology for DILI) (186), and two had a history of the administration of another culprit for DILI/AIH, pegylated interferon (discontinued seven years ago in one case) (184). Of note, the dosage of the taken acetaminophen was unlikely to be responsible for hepatitis. In the Efe et al. study, six patients were receiving statins, and the drug was discontinued in three of them. In addition, one patient who was on pegylated interferon continued receiving the drug (183).

The main issue to be deciphered in this topic is the causal relationship between the COVID-19 vaccine and the incidence of AIH-like hepatitis. In separate case reports, 16 had a positive history of autoimmune disorders (Table 3), of whom five had AIH. While the instigation of a flare-up of previously unrecognized/treated hepatitis might be attributed to vaccines, this scenario is less consistent for most cases without a history of autoimmunity.

As mentioned, the histopathological patterns of liver injury can aid in better delineation of the causative relationship between COVID-19 vaccination and AIH. Among separate cases who underwent liver biopsy (n=50), lymphoplasmacytic

Table 2. Demographic and clinicopathologic features of patients with AIH-like liver injury following COVID-19 vaccination presented in case series.

Study	No.	Median Age (range)	Sex	Hx of AI	Vaccines	Timing	Median latency (range)	Pattern of injury§	Hx liver disease	Symptoms	Peak AST/ULN	Peak ALT/ULN	Peak ALP/ULN	IgG>ULN	Autoantibodies	Probable/definite AIH	Treatment by steroid	Outcome
Efe et al. [183]*	87	48 (18-79)	55 F 32 M	24 (28%), including: AI thyroid disease 12 IBD 3 Sarcoidosis 3 AIH 2 SLE 2 Celiac 2 RA 1 MS 1 Pemphigus vulgaris 1 Lichen planus 1 PSC 1	Pfizer 51 (59%) ChAdOx1 nCov-19 20 (23%) mRNA-1273 16 (18%)	1st dose 40 (46%) 2nd dose 47 (54%)	15 (3-65)	Hepatocellular 73 (84%) Mixed 9 (10%) Cholestatic 5 (6%)	12, including: NAFLD 7 AIH 2 HCV 1 PBC 1 PSC 1 (liver transplantation)	Asymptomatic 7 (8%) Fatigue 65 (75%) Nausea 55 (63%) Jaundice 34 (39%)	15.4 (1.8-250)	16.7 (3.1-203.7)	1.3 (0.4-7.1)	53 (67%)	ANA 56 (67%) ASMA 15 (18%) AMA 5 (6%) Anti-SLA 1 (1%) Anti-LC-1 1 (1%)	58.2% (46/79)	Steroids 46 Plasma exchange 9 AZT 9 MMF 2 IVIg 1	Median time to NL labs 46 days (15-185). One transplantation was required.
Efe et al. [183]†	45	49 (30-76)	F 29 M 16	15 (33.3%)	NS	NS	NS	Hepatocellular 40 (88.9%) Mixed 3 (6.7%) Cholestatic 2 (4.4%)	4 (8.9%)	NS	18.1 (2.6-250)	18.8 (3.1-81.8)	1.3 (0.4-7.1)	NS	NS	100%	Steroids 32	Median time to NL labs 54 days (15-185)
Codoni et al. [182]‡	59	54 (19-92)	35 F 19 M	None	mRNA-1273 12 (20%) Pfizer 30 (51%) ChAdOx1 nCov-19 11 (19%) Sputnik V 5 (9%) Sinopharm 1 (2%)	1st dose 20 (34%) 2nd dose 37 (63%) 3rd does 2 (3%)	24 (1-74)	Predominantly lobular hepatitis 45 (76%) Predominantly portal hepatitis 10 (17%)	NR	NR	22.1 (3.0-169.1)	24.0 (5.0-111.3)	1.4 (0.5-8.2)	40 (68%)	ANA 23 (74%) ASMA 19 (61%) Anti-gastric parietal cells 8 (26%) Anti-LKM 4 (13%) AMA 4 (13%)	82% (simplified IAIHG criteria) and 92% (new histological criteria)	Steroids 52 (88.13%) AZT 7 (11.86%)	One transplantation was required.

*** New-onset liver injury defined as the increase in ALT or AST at least 5 times ULN and/or ALP at least two times ULN or ALT/AST at least 3 times UNL and bilirubin at least two times ULN.**

† Data of cases with immune-mediated hepatitis.

‡ Inclusion criteria were negative evidence for pre-existing liver diseases, transaminase levels at least five times ULN within 3 months after any COVID-19 vaccination, and availability of liver biopsy results. Six of the included cases are similar to those reported by Efe et al.

§ Hepatocellular, R $\left(\frac{ALT/ULN}{ALP/ULN}\right)$ **≥5; mixed, 2<R<5; cholestatic, R≤2.**

AI, autoimmunity; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ASMA, anti-smooth muscle antibody; AZT, azathioprine; Bili, bilirubin; F, female; Hx, history; HCV, hepatitis C virus; IAIHG, International Autoimmune Hepatitis Group; IVIg, intravenous immunoglobulin; IBD, inflammatory bowel disease; LC-1, liver cytosol type 1; LKM1, liver kidney microsomal; M, male; MMF, mycophenolate mofetil; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NL, normal; No, number; NR, not reported; NS, not specified; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SLA, soluble liver antigen; SLE, systemic lupus erythematosus; ULN, upper limit of normal.

Table 3. Summary of the features of cases reported by case report studies (n=57).

Feature	n (%)	Feature	n (%)
Age (median, range)	61, 21-85	**Drug history**	
Sex		Aspirin	5 (8.77)
Female	41 (71.92)	Statins	3 (5.26)
Male	16 (28.07)	Acetaminophen	3 (5.26)
Type of received vaccine		Pegylated interferon	2 (3.50)
BNT162b2	30 (52.63)	**Number of vaccinations before 1st notice of liver injury**	
mRNA-1273	18 (31.57)	1	39 (68.42)
ChAdOX1 nCoV-19	7 (12.28)	2	15 (26.31)
CoronaVac	1 (1.75)	3	1 (1.75)
Sinopharm	1 (1.75)	After completion of vaccination	2 (3.50)
Symptoms		**IgG levels**	
Jaundice	26 (45.61)	Elevated	33 (57.89)
NR	20 (35.08)	NR	15 (22.80)
Fatigue/weakness/malaise	14 (24.56)	NL	9 (15.78)
Choluria	12 (21.05)	**Biopsy findings**	
Pruritis	11 (19.29)	Lymphoplasmacytic infiltrates	43 (75.44)
Pain	7 (12.28)	Interface hepatitis	36 (63.16)
Asymptomatic	6 (10.52)	Necrosis	22 (38.60)
Anorexia	5 (8.77)	Eosinophilic infiltrates	17 (29.82)
Fever	3 (5.26)	Fibrosis	11 (19.30)
History of autoimmunity	16 (28.07)	Not taken	7 (12.28)
Hashimoto's thyroiditis	4	**Treatment(s)**	
Autoimmune hepatitis	5	Steroids	44 (77.19)
Vitiligo and pollen allergy	1	Azathioprine	12 (21.05)
Celiac disease	1	Ursodeoxycholic acid	6 (10.52)
Premature ovarian failure	1	None	7 (12.28)
Sarcoidosis	1	N-acetyl cysteine	4 (7.01)
Drug-induced liver injury	1		
Primary sclerosing cholangitis	1		
Sjogren's disease	1		

infiltrates were detected in 86%, while interface hepatitis was evident in 72%, and necrosis, eosinophilic infiltrates, and fibrosis presented in 44%, 34%, and 22% of samples, respectively.

In Cao et al. report (158), the authors postulated that based on the detection of stage 2 hepatic fibrosis, the patient had undiagnosed AIH, and the vaccination exacerbated and unmasked the condition. Likewise, Torrente et al. and Izagirre et al. (167, 176) Reckoned that one of their reported cases had a history of manageably elevated aspartate aminotransferase (ASTO (122) and alanine aminotransferase (ALT) (157) since 2018, and four of them had predisposing HLA phenotypes (HLA-DRB1*03:01 and HLA-DRB1*04) for AIH, vaccination has been a trigger for the flare of the disease.

In Codoni et al. observations (182)Forty-five patients (76%) had a predominantly lobular involvement, with lymphocytic infiltrations, focal necroes, less-pronounced portal inflammation, and evident lobular cholestasis (cholestatic hepatitis) in five. Ten cases (17%) presented predominantly portal involvement, with lymphocytic infiltration, interface hepatitis (mild in two and more severe in others), and less-pronounced lobular inflammation (182). Of note, plasma cell infiltrations were observable in 62-80% of cases, while this was 40-50% for eosinophilic infiltrations. In addition, two other cases had evident cholestasis with bile casts, without notable necro-inflammatory alterations. As a result, according to the simplified International Autoimmune Hepatitis Group (IAIHG) criteria, 24% and 58% of samples classified as typical for or compatible with the diagnosis of AIH, respectively, while using the new histological criteria, 70% were likely, and 22% were possible for the diagnosis of AIH (182).

Codoni et al. further aimed to compare the clinicopathologic features of cases with predom-

inantly lobular versus portal involvement (182). Apart from the significantly higher AST/upper limit of normal (ULN), alkaline phosphatase (ALP)/ULN, total bilirubin/ULN, and the vaccination-presentation time in the lobular group, other parameters were similar between the two groups. The details of liver biopsy findings are not discussed in Efe et al. paper (183). Nevertheless, they tried to compare the features of cases with and cases without immune-mediated hepatitis. Excluding follow-up duration and steroid therapy, no significant differences were found; however, the former group had numerically higher peak AST, ALT, bilirubin, and proportions of autoimmune disorders and female sex.

From these findings, it can be concluded that patients with immune-mediated hepatitis (with a probable or definite diagnosis of AIH) present a more severe disturbance in liver functions and pathological findings. In addition, a high proportion of evaluated cases have had lymphoplasmacytic infiltrations and interface hepatitis as the hallmarks of AIH (20). Besides, the presence of eosinophils, rosette formation, and fibrosis, all favor a diagnosis of AIH instead of pure DILI (187). Hence, these data, along with the temporal associations between COVID-19 vaccination and AIH incidence, might point toward a causal relationship. However, there are also differences in the pathological picture of classical AIH and COVID-19 vaccine-induced AIH-like hepatitis. While advanced fibrosis is characteristic of classical AIH, both Codoni et al. (182) and Efe et al. (183) studies found that around 90% of evaluated samples had no or low-grade fibrosis according to the METAVIR (188) and modified Ishak's scoring systems (189), respectively. Based on these findings, Codoni et al. suggested that AIH-like DILI is a more appropriate term for the description of this condition (182).

Moreover, Boettler et al. (156) performed extensive analyses of the immune infiltrates of their case report. They found that contrary to the common pattern of classical AIH samples, the infiltrate was mainly composed of CD8+ T-cells, and the proportions of B-cells and plasma cells were lower. Furthermore, these granzyme-B positive CD8+ T-cells were also SARS-CoV-2 spike-specific and had a pan-lobular pattern of distribution, all implicating their fundamental roles in the induction of AIH-like hepatitis (156).

The therapeutic approach for the management of COVID-19 vaccination-induced hepatitis has been relatively homogeneous and simple. In case reports, 77.19% of cases received steroids, 21.05% received azathioprine, and 24.56% did not need any treatments at their first presentation, seven of them subsequently received steroids due to relapses (156, 161, 172, 177, 190).

Likewise, in Efe et al. report (183), 71.1% of immune-mediated versus 38.2% of non-immune-mediated cases received steroids, and in their entire sample, azathioprine and plasma exchange were each prescribed for 10.3% of cases. Moreover, 47.12% showed spontaneous resolution of liver injury, without any specific therapy. In this series (183), immunosuppressive therapies were discontinued in 12 patients, and none of them revealed signs of relapse. Another 34 were on immunosuppressive therapies at the last follow-up (183).

In the Codoni Et al. study (182), seven cases (11.86%) did not receive any treatments, of whom two presented with a steroid-requiring relapse after re-exposure to COVID-19 vaccines. In 16.94%, the immunosuppressive therapies were successfully withdrawn, while in 6.77%, the withdrawal was not successful. In 38.98%, the immunosuppressive discontinuation is still ongoing, and of note, in 20.33%, despite improvements in clinicopathologic parameters, no remission ensued with immunosuppression (182).

Overall, the prognosis of AIH-like hepatitis due to COVID-19 vaccination was favorable in the separate case reports; only two patients died (160, 173) because of liver failure, and one of them was not able to receive liver transplantation due to economic restraints (173).

In the Shroff et al. report (174), of 16 reported cases, four had a prior diagnosis of AIH. Among the remaining 12 cases, only one had a probable diagnosis of AIH according to the IAIHG criteria. In addition, the prognosis of these cases was favorable. Despite the hospitalization of ten cases, only three had an easy-to-treat acute liver injury (defined as an international normalized ratio [INR]>1.5), and none had an acute liver failure (ALF) (174). In addition, six cases did not receive any relevant therapies. Moreover, all the cases with provided pathologic samples (n=10) had

portal inflammation that was composed of significant plasma cell infiltrations in five. Last but not least, in 12 cases, the presentations of liver injury appeared after the 2nd dose of vaccines (174).

Similarly, in other reports on five cases (167, 176), one of them did not require any specific therapies, and none developed ALF. Only one of them presented with a total bilirubin level of 14 mg/dL during follow-up, which required hospitalization (167, 176). In another study (177), the patient had presentations of jaundice, hepatomegaly, and abnormal liver function tests (LFT), which was slightly more pronounced after the 2nd dose, and led to the decision to administer prednisolone. Nevertheless, the pathologic picture of liver injury was similar to other cases (with marked interface hepatitis with eosinophilic and plasma cell infiltration and liver necrosis), and the response to therapy has been satisfying.

The presentations and medical and drug history of reported cases exhibit substantial differences. In some reports, affected patients were entirely asymptomatic, and the suspicion for AIH has been made due to abnormal LFT and liver biopsy findings. This might implicate a higher prevalence of AIH following the COVID-19 vaccine that is missed due to the lack of the acquisition of LFT. Of note, the long-term outcome of such cases is of great importance, which necessitates the design and conduction of prospective cohorts and trials.

In the Efe et al. series (183), of 87 cases with liver injury following COVID-19 vaccination, 79 had available serologic and/or histologic evaluations for the detection of AIH, and 46 (58.2%) had a probable or definite diagnosis. Of note, the prescription rate of steroids and the follow-up duration were significantly higher in those with a diagnosis of AIH. In addition, among 52 with previous aminotransferases assessment, 48 had normal results, and among 6 cases with elevated tests, 4 had NAFLD. Last but not least, in Efe et al. report, there was no difference in the vaccination type for the incidence of acute liver injury (183).

Concerning the safety of subsequent COVID-19 vaccination, data from case reports are scarce. In these reports, a patient who developed mild symptoms at first exposure to the mRNA-1273 vaccine (without receiving therapies) presented with more serious disturbances in LFTs, which required steroid therapy (169). Another case of deranged LFTs following 1st dose of vaccination with mRNA-1273 had an intensification of jaundice after receiving the 2nd dose, which led to the initiation of prednisolone (191). A treated case of AIH (by liver transplantation) had a sole ALT rise of 85 after receiving the 2nd dose of Pfizer, while the 3rd one was associated with exaggerated LFT abnormalities, which led to the administration of pulsed intravenous methylprednisolone (170). The booster dose was received without problems (170). Another case had choluria and acholic stools after the 1st dose of vaccination with CoronaVac (190). The patients did not receive any therapies, and after the 2nd dose of vaccination, generalized pruritus and jaundice appeared, and ursodeoxycholic acid, methylprednisolone, and azathioprine commenced (190). In Ferronato et al. study (161), one case had mild a 2-fold increase in ALT before Pfizer vaccination, after receiving the 2nd dose, ALT increased to 4.7 times ULN, and after the 3rd dose, a diagnosis of genuine AIH was put; however, the patient did not receive therapies. Following the administration of the booster dose of mRNA-1273, ALT showed a 12.7 times increase, and steroid therapy began (161).

However, six cases received their subsequent doses of mRNA-1273, Pfizer, and ChAdOx1 nCov-19 without evident problems (Five on immunosuppressive therapy) (170, 174, 176, 181). In Codoni et al. report (182), among 15 individuals who were re-exposed to COVID-19 vaccines, only three exhibited signs of relapse, and all were re-exposed to the same vaccine that was administered prior to the development of hepatitis. Of note, and quite similar to the Efe et al. descriptions (183), the sole patient in Codoni et al. report that required liver transplantation was a 53-year-old man that was re-exposed to the BNT162b2 vaccine (182).

In Efe et al. report (183), three cases with mild liver injury after 1st dose of vaccination experienced a more severe disease after receiving the second dose of the same vaccine. One of these cases was the only patient who developed hepatic encephalopathy and liver failure and presented with a mild liver injury after receiving the first dose of the BNT162b2 vaccine. However, the second dose-related extreme liver injury was not responsive to steroid therapy and plasma exchange, which necessitated liver transplantation. In this

series (183), two cases with liver injury after vaccination with ChAdOx1 nCov-19 received their subsequent doses by switching to Pfizer-BioNTech, and no complications developed.

Among case reports, two patients had a flare-up after treatment (15, 156); in one, it was two weeks after the discontinuation of prednisolone (15), and in another case, despite initial response to budesonide, systemic steroids, and ursodeoxycholic acid were necessary to re-normalize LFTs (156). In the first case, the liver function tests normalized again with the reinstitution of prednisolone (15). In another case, despite spontaneous remission after 1st dose of BNT162b2 vaccination, a relapse occurred after exposure to the 2nd dose of the BNT162b2 vaccine. Hence, oral budesonide was initiated, but after an initial decrease, the LFT tended to worsen again, and systemic steroids and UDCA were needed to normalize LFT.

Fortunately, the outcome of COVID-19 vaccination-induced AIH seems to be favorable. Among the individual case reports, as mentioned, only two patients developed liver failure and died because of sepsis. All other cases are either recovered or have exhibited substantial alterations in their symptoms and laboratory values toward normalization. In the Efe et al. series (183), apart from the previously discussed case, another patient displayed low-grade hepatic encephalopathy, but the condition was responsive to plasma exchange and corticosteroid therapy, and transplantation did not become necessary.

Conclusion

According to the mechanisms discussed above, the phenomenon of autoimmunity following the COVID-19 disease and the vaccination is predictable. Excluding AIH, various autoimmune diseases induced by the COVID-19 disease and vaccination have been reported. These studies reported Graves' disease (192, 193), subacute thyroiditis (194), immune thrombocytopenia (195-197), thrombotic thrombocytopenia (198), autoimmune hemolytic anemia (196, 199, 200), aplastic anemia (201), reactive arthritis (202), immune complex and IgA vasculitis (203, 204), GBS (205), myasthenia gravis (206), SLE (207), polymyositis (208), microscopic polyangiitis (209), and giant cell arteritis (210), as complications of COVID-19 and COVID-19 vaccines (157, 167). The outcome of COVID-19 vaccine-induced liver injury with features of AIH is generally favorable. Only two cases deceased as a result of hepatic failure, and two others required liver transplantations. However, the long-term outcome of asymptomatic cases is not illustrated, and the design of prospective cohorts is prudent to decide on the necessity of the acquisition of screening liver function tests after vaccination.

Conflict of interest

The authors have no conflicts of interest.

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