The Impact of COVID-19 Vaccination on Pemphigus - A Review

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Submission: 13.02.2024 Acceptance: 04.04.2024 Publication: 31.05.2024

Abstract:

Background And Objectives:

Although the risk- benefit ratio of COVID-19 vaccination continues to be remarkably favourable, it is also crucial to know about the adverse reactions and contraindications of these vaccines. This review presents the evidence till date about the impact the COVID-19 vaccination had on prevalence of pemphigus and its treatment, and also discusses the mechanism triggering this immune response.

Materials And Methods:

PubMed database search was done using the following keywords and MeSH terms: (COVID 19 OR SARS Cov-2 OR Corona virus) AND vaccination AND (pemphigus). Only articles with individual patient data giving the required complete details were selected. Manuscripts regarding autoimmune diseases other than pemphigus were excluded.

Results:

32 articles with 52 individual case reports were selected. There were 34 new onset pemphigus in which 53% occurred after second dose, and in 18 cases with past history of pemphigus, 66.6% of symptoms occurred after first dose. Symptoms appeared within a median number of 7 days after dose 1 and 2. Symptoms resolved by treatments such as steroids and adjuvant therapy. There are no exact mechanism to establish a cause-effect relationship between vaccination and pemphigus, and there is a lack of strong evidence as most of the cases are from single case reports.

Conclusion:

Future studies should focus on large scale case control and cohort studies, and randomised controlled trials (RCT), to provide high level evidence regarding triggering of AID following COVID-19 vaccinations.

Keywords:

SARS Corona virus, mass vaccination, autoimmune disease, pemphigus, adverse drug reaction

Introduction

The outbreak of COVID-19 pandemic witnessed a paradigm shift in the field of Modern Medicine. The years 2020-2023 was a platform for innumerable researches in the field revolving in and around the virus, its complications, vaccination, and post- vaccination complications. One such area of concern was the management of patients affected with various autoimmune diseases (AID), their high chances of infectivity owing to the loss of integrity of skin barrier easily leading to pathogen colonization and immune dysregulation, and emergence of new onset auto immune diseases following COVID-19 vaccination. (1)

The COVID-19 vaccine emerged as a newly approved product and played the biggest role in containing the spread of the deadly virus through mass vaccination campaigns, globally. Although the risk- benefit ratio continues to be remarkably favourable, it is also crucial to know about the adverse reactions and contraindications of these vaccines, as

these can be equally fatal in certain individuals.⁽²⁾ Literature so far indicates an upsurge in various autoimmune dermatologic diseases such as psoriasis, ptyriasis rosea, pemphigoid, pemphigus, lichen planus, systemic lupus erythematosus, post vaccination.

Pemphigus, a group of autoimmune mucocutaneous blistering disorders characterized by acantholysis and formation of intraepithelial blisters, is induced by the binding of circulating autoantibodies to desmoglein 1 and desmoglein 3. There are numerous case reports in the literature showcasing onset of pemphigus following various classes of COVID-19 vaccination. The exact mechanism underlying this correlation is still uncertain, thus, the safety of these vaccines for such patients are questioned.

Pemphigus being one of the rare entities requiring multidisciplinary approach for management, is of interest to oral physicians as they play a pivotal role in diagnosing, treating, and providing supportive care to patients with oral manifestations. Thus, this review presents the evidence till date about the impact the COVID-19 vaccination had on prevalence of pemphigus and its treatment, and also discusses the mechanism triggering this immune response.

Materials And Methods

Information sources and search strategy

A literature search of the PubMed database from January 2020 to October 2023 was done using the following keywords and MeSH terms in combination with Boolean operators in the advanced search option: (COVID 19 OR SARS Cov-2 OR Corona virus) AND vaccination AND (pemphigus). Language filter of only English was applied.

Eligibility criteria

Examined manuscripts contained case reports, case series, observational studies, randomised controlled trials, and letters to the editor. Only articles with individual patient data giving complete details on the patient demographics, past medical history, vaccination details including vaccine name, number of doses, and onset of symptoms following the dosage, diagnosis of the lesion with histopathological or immunofluorescent report, and the treatment provided, were selected.

Manuscripts regarding autoimmune diseases other than pemphigus, and injection site reactions were excluded. Articles with incomplete case data, abstracts and indexes, and narrative reviews were excluded.

Results

On entering the key words in advanced search option, 67 articles were displayed. After title and abstract screening, 45 articles were selected. On full text screening and after applying the eligibility criteria, 13 articles were excluded. Finally, 32 articles with 52 individual case reports were selected for the review, which included 6 case reports, 8 case series, and 18 letters to the editor.

Out of 52 cases, 25 were male and 27 were female in an age range of 25-89 years (mean 57.4 years). There were 34 new onset pemphigus cases in which 53% occurred after second dose of vaccination, whereas among the 18 cases with past history of pemphigus, 66.6% of symptoms occurred after first dose. BioNTech Pfizer was the most commonly administered vaccine, followed by AstraZeneca and Moderna. Symptoms of pemphigus such as blisters, bullae or erosions appeared within the first month following dose 1 or dose 2 with median number of 7 days, whereas following dose 3, symptoms appeared within a median of 14.5 days. 30.7% of the cases were treated with systemic steroids, and were reported to have relief from the symptoms. Patients who were given immunomodulatory agents (Azathioprine, Mycophenolate mofetil, Intravenous Immunoglobulin, Methotrexate) and biologic therapy (Rituximab) were not responding to steroids alone, and had significant relief from the symptoms with the start of these adjuvant therapies.

The patient characteristics with vaccination and treatment details are given in Table 1.

| No. of Cases | 52 (%) | |
|-------------------|-----------|--|
| Age (years) | | |
| Range | 25-89 | |
| Mean | 57.4 | |
| Gender | | |
| Male | 25 (48) | |
| Female | 27 (52) | |
| Onset | | |
| New onset | 34 (65.3) | |
| Flare | 18 (34.6) | |
| Type of Pemphigus | | |
| PV35 | (67.3) | |
| PF | 13 (25) | |
| IgA Pemphigus | 1 (1.9) | |
| PE | 1 (1.9) | |
| P Veg | 1 (1.9) | |
| NS | 1 (1.9) | |
| Affected Tissue | | |
| Mucosal | 5 (9.6) | |
| Cutaneous | 18 (34.6) | |
| Mucocutaneous | 18 (34.6) | |
| Ns11 | (21.1) | |

| No. of Cases With Symptoms After Vaccination | | | | | | | | | |
|--|-----------|----------|----------|--|--|--|--|--|--|
| Vaccine | Dose 1 | Dose 2 | Dose 3 | | | | | | |
| BioNTech Pfizer (55.7%) | 9 | 13 | 7 | | | | | | |
| Oxford-AstraZeneca (15.3%) | 6 | 2 | 0 | | | | | | |
| Moderna (13.4%) | 4 | 3 | 0 | | | | | | |
| Sinopharm (9.6%) | 3 | 1 | 1 | | | | | | |
| Sinovac (3.8%) | 0 | 2 | 0 | | | | | | |
| Non specified mRNA vaccine (1.9%) | 0 | 1 | 0 | | | | | | |
| No. of Days To Onset | 3-30 | 1-30 | 3-92 | | | | | | |
| Median (days) | 7 | 7 | 14.5 | | | | | | |
| New Onset (n=34) | 10 (29.4) | 18 (53) | 6 (17.6) | | | | | | |
| Flare (n=18) | 12 (66.6) | 4 (22.2) | 2 (11.1) | | | | | | |
| Treatment Provided | | | | | | | | | |
| S | 16 (30.7) | | | | | | | | |
| S+A | 11 (21.1) | | | | | | | | |
| S+R | 10 (19.2) | | | | | | | | |
| S+MMF | 4 (7.7) | | | | | | | | |
| S+A+R | 1 (1.9) | | | | | | | | |
| S+A+IVIg | 1 (1.9) | | | | | | | | |
| S+IVIg | 1 (1.9) | | | | | | | | |
| S+R+MMF | 1 (1.9) | | | | | | | | |
| S+Mtx | 1 (1.9) | | | | | | | | |
| NS | 6 (11.5) | | | | | | | | |

Abbreviations: PV Pemphigus vulgaris; PF pemphigus foliaceus; PE pemphigus erythematosus; P Veg Pemphigus vegetans; NS Non-specified; S steroids; A Azathioprine; R

Rituximab; IVIg Intravenous Immunoglobulin; MMF Mycophenolate Mofetil; Mtx Methotrexate

Extracted data from all the included articles are provided in Table 2.

| Type of Manuscript | S. No | Author | No of Cases | Age | Sex | Affected Tissue | H/o Pemphigus | Vaccination Name | Dose 1 | Dose 2 | Dose 3 | Diagnosis | Treatment |
|-----------------------|----------|--------------------------|----------------|-----|-----|---------------------------|------------------|--|--------|--------------|-----------------------|-----------|-----------|
| CASE REPORT | 1 | ARYANIAN ⁽⁴⁾ | 1 | 43 | M | ORAL AND SKIN | NA | Oxford-AstraZeneca | NS | 2 | 2 | PV | SR |
| | 2 | CALABRIA ⁽²⁾ | 1 | 60 | F | ORAL AND MUCOSAL | NA | Pfizer/BioNtech) | NS | 7 | | PV | S R |
| | 3 | KHALAYLI ⁽¹⁵⁾ | 1 | 50 | F | ORAL; GENITAL; SKIN | NA | mRNA COVID-19. vaccine | | 10 | | PV | S |
| | 4 | LANSANG ⁽¹⁶⁾ | 1 | 64 | М | SKIN | NA | ASTRAZENECA AND MODER NA | NS | 20 | IgA PEMP- HIGUS | | S |
| | 5 | ONG ⁽⁹⁾ | 1 | 46 | F | ORAL AND SKIN | YES | Moderna; J & J | 7 | NS | | PV | S R |
| | 6 | SINGH ⁽⁵⁾ | 1 | 44 | M | ORAL AND SKIN | NA | COVISHIELD (OXFORD Astra Zeneca) | NS | 7 | | PV | S A IG |
| | 7 | AKOGLU ⁽¹⁷⁾ | 3 | 69 | F | ORAL AND SKIN | NA | CoronaVac® (Sinovac) | NS | 7 | | PV | S Mtx |
| CASE SERIES | | | | 58 | F | ORAL; GENITAL; SKIN | YES | CoronaVac® (Sinovac) | NS | 7 | | PV | S IG |
| | | | | 31 | F | ORAL; GENITAL AND SKIN | YES | BioNTech/Pfizer | 7 | NOT TAKEN | | PV | S |
| | 8 | CORRA ⁽³⁾ | 5 | 61 | F | SKIN | NA | MODERNA; MODERNA; PFIZER | NS | NS | 3 | PV | S |
| | | | | 80 | M | SKIN | NA | BioNTech/Pfizer | NS | NS | 17 | PF | S R MMF |

Cont....

Extracted data from all the included articles are provided in Table 2.

| | | | | 66 | F | SKIN | NA | BioNTech/Pfizer | NS | 28 | NS | PF | S MMF |
|--------------|-----|----------------------------------|---|----|---|---------------------------|---------|--|-------------|-------|----|-------|-------|
| | | | | 73 | F | ORAL | NA | BioNTech/Pfizer | NS | NS | 28 | PV | S R |
| | | | | 63 | F | ORAL AND SKIN | NA | Oxford-AstraZeneca | 28 | CW | | PV | S R |
| | 9 | COWAN ⁽¹⁸⁾ | 3 | 49 | F | | NA | BioNTech Pfizer | NS | NS | 92 | PV | |
| | | | | 32 | F | | YES | BioNTech Pfizer | NS | NS | 6 | PV | |
| | | | | 73 | M | | YES | BioNTech Pfizer | NS | NS | 15 | PV | |
| | 10 | GUI ⁽⁶⁾ | 2 | 25 | М | ORAL, GENITAL AND SKIN | NA | BioNTech Pfizer | NS | 28 | NS | P VEG | S MMF |
| | | | | 67 | F | SKIN | NA | MODERNA | NS | 14 | NS | PF | S |
| | 11 | HALI ⁽⁸⁾ | 2 | 50 | F | SKIN | NA | BioNTech Pfizer | NS | 15 | | PF | S |
| | | | | 58 | F | ORAL, GENITAL, SKIN | NA | BioNTech Pfizer | 30 | | | PV | S |
| | 12 | HATAMI ⁽¹⁹⁾ | 2 | 34 | М | ORAL | NA | Oxford-AstraZeneca | FEW DAYS | | | PV | |
| | | | | 61 | M | SKIN | YES | Oxford-AstraZeneca | 7 | | | PV | |
| | _13 | RASNER ⁽²⁰⁾ | 1 | 50 | F | SKIN | YES- PF | BioNTech Pfizer | 7 | NA | NA | PF | S |
| | 14 | SAFOURA ⁽²¹⁾ | 2 | 28 | F | MUCOCUT- ANEOUS | YES | SINOPHARM | 14 | NA | NA | PV | S R |
| | | | | 30 | F | ORAL AND MUCOSAL | NA | SINOPHARM | 16 | NA | NA | PV | S R |
| LETTER | 15 | AGHARBI ⁽²²⁾ | 1 | 72 | M | ORAL AND SKIN | NA | BioNTech Pfizer | NA | 7 | NA | PV | S A |
| | 16 | ALAMI ⁽²³⁾ | 1 | 44 | M | SKIN | NA | SINOPHARM | 7 | CW | | PF | S A |
| TO EDITOR | 17 | NASRABADI ⁽²⁴⁾ | 1 | 62 | F | SKIN | NA | AstraZeneca | 7 | CW | | PF | S MMF |
| | 18 | DAMIANI ⁽²⁵⁾ | 2 | 40 | M | SKIN | YES | MODERNA | 3 | NS | | PV | S MMF |
| | | | | 80 | M | SKIN | YES | BioNTech Pfizer | 3 | NS | | PV | S |
| | 19 | KNECHTI ⁽²⁶⁾ | 1 | 89 | M | ORAL AND SKIN | NA | BioNTech Pfizer | NS | 30 | | PV | S R |
| | 20 | KOUTLAS(27) | 1 | 60 | M | ORAL AND SKIN | NA | MODERNA | NS | 7 | | PV | |
| | 21 | LUA ⁽²⁸⁾ | 1 | 83 | M | SKIN | NA | BioNTech Pfizer | NS | 2 | | PF | S |
| | 22 | NORIMATZU ⁽²⁹⁾ | 1 | 86 | М | MUCOSAL AND SKIN | NA | BioNTech Pfizer | NS | 1 | | PV | S |
| | 23 | POURANI ⁽³⁰⁾ | 1 | 75 | M | SKIN | NA | SINOPHARM | NS | NS | 14 | PF | S R |
| | 24 | ROUTABI ⁽³¹⁾ | 2 | 70 | M | SKIN | NA | Corona Vac® (Sinovac); Corona Vac® (Sinovac; PFIZER | NS | NS | 7 | PF | S |
| | | | | 48 | M | | NA | AstraZeneca | 5 | | | PF | S |
| | 25 | SAFFARIAN ⁽³²⁾ | 1 | 76 | F | ORAL AND SKIN | NA | SINOPHARM | NS | 30 | | PV | S R |
| | 26 | SEBNEM ⁽³³⁾ | 1 | 65 | M | SKIN | NA | BioNTech Pfizer | 7 | 14 CW | | PF | S A |
| | _27 | SOLIMANI ⁽³⁴⁾ | 1 | 40 | F | ORAL AND SKIN | NA | BioNTech Pfizer | 5 | 3; CW | | PV | S A |
| | 28 | THONGP- ROSOM ⁽³⁵⁾ | 1 | 38 | F | ORAL | NA | AstraZeneca | 7 | | | P | S |
| | 29 | FALCINELLI ⁽³⁶⁾ | 1 | 63 | F | SKIN | NA | BioNTech Pfizer | | 2 | NA | PE | S |
| | 30 | AVALLONE ⁽³⁷⁾ | 1 | 46 | M | ORAL AND SKIN | YES | BioNTech Pfizer | 5 | 5; CW | | PV | SAR |
| | 31 | MARTORA (38) | 7 | 69 | M | | YES | BioNTech Pfizer | 5 | | NS | PV | S A |
| | | | | 64 | M | | YES | BioNTech Pfizer | | 7 | NS | PV | S A |
| | | | | 71 | M | | YES | BioNTech Pfizer | | 5 | NS | PV | S A |
| | | | | 61 | F | | YES | MODERNA | 6 | | NS | PV | S A |
| | | | | 68 | M | | YES | BioNTech Pfizer | | 8 | NS | PV | S A |
| | | | | 62 | F | | YES | MODERNA | 11 | | NS | PV | S A |
| | | | | 55 | F | | YES | BioNTech Pfizer | 7 | | NS | PV | S A |
| | 32 | REIS ⁽³⁹⁾ | 1 | 35 | F | SKIN | NO | BioNTech Pfizer | NS | 14 | | PF | S |

Discussion

Autoimmune disorders are a group of disorders that occur due to immune system dysfunction, and can be triggered by various factors such as drugs, malignancies, environmental change, viral infections, or vaccinations, in a genetically predisposed individual. [4] Pemphigus is one such AID that has been reported in the past following vaccination with rabies,

hepatitis B, influenza, and anthrax vaccines.^[5] It is evident from this review that, COVID-19 vaccine initiates or aggravates the course of pemphigus after the first or second dose and the disease develops within first 30 days. But, the etiopathogenesis of this occurrence is still not vivid.

Immunological mechanisms underlying pemphigus include T and B-cell dependent autoantibody production, T helper-2

cell predominant response with elevated levels of IL-6, IL-10, tumour necrosis factor- α and reduced levels of Interferon- γ , and immune dysregulation. [5] Several mechanisms proposed for the development of pemphigus after vaccination are:

- Molecular mimicry, in which a vaccine or its components resemble a self-antigen and induce immune crossreactivity and a break of self-tolerance, leading to development of autoimmunity following vaccination. [5,6]
- 2) Epitope spreading or bystander activation phenomenon, precipitated by immune dysregulation induced by vaccination, leading to recognition of self-antigens, and clonal expansion of T cells exhibiting SARS-CoV-2 reactivity. This causes transient immune activation in predisposed individuals with subclinical autoimmunity. [4,6,7]
- 3) mRNA vaccines may give rise to a cascade of immunologic events, ultimately leading to aberrant or non-specific activation of the innate and acquired immune system which can precipitate latent pemphigus in a susceptible individual.^[8]
- Upregulation of interferon-I following COVID-19 vaccination may induce autoimmunity and trigger the onset of AID.^[7]
- 5) Irrespective of being a Th2-dominant disease, some studies suggested a possible role of CD8+ T cells via Fas/Fas ligand pathway in the pathogenesis of pemphigus. Also, COVID-19 vaccines are known to have a high capability to elicit critical immune regulators like cytotoxic CD8+ T cells and memory cells which can also explain the occurrence of pemphigus.^[4]
- 6) In patients undergoing immunosuppressive therapy, stimulation of immune system after vaccination may disrupt the delicate balance achieved by therapy, leading to hyperimmune reactions exacerbating the disease. [9]

Despite all these hypotheses, a cause-effect relationship could not be established, although the presence of a temporal correlation may be suggestive of this occurrence. [2]

This literature review summarizes the cases of pemphigus following COVID-19 vaccination published so far, reporting demographic and clinical characteristics, vaccination details, and onset of the disease along with treatment provided. There was no gender or age predominance that was noted. One striking finding that was noted in our review is that majority (53%) of the new onset pemphigus occurred after the second dose of COVID-19 vaccination, whereas majority of the patients (66.6%) with known history of pemphigus were noted to have the recurrence after the first dosage. This may be attributed to the time taken for the cross reactivity or immunologic reactions to happen in healthy individuals,

compared to the patients undergoing treatment for pemphigus who may be easily susceptible to an imbalance in the immune system following the vaccination. This finding to the best of our knowledge is not alluded in the existing literature. The increased number of onsets of pemphigus following Pfizer administration can be attributed to the increased administration of these vaccines compared to the other vaccines.^[2]

There are multiple studies in the literature contradicting this correlation. In a prospective observational study done by Weschawalit etal^[10] assessing the cutaneous adverse events after COVID-19 vaccination, out of 7505 patients analysed only 92 patients had various cutaneous reactions following the vaccination. Among these, only 1 patient was reported to have affected with pemphigus foliaceus. This accentuates the rarity of occurrence of AID's and pemphigus following the vaccination.

Russo et al^[11] considers COVID-19 vaccine only as a possible trigger, but not as an independent cause of AID. They exemplified this statement by providing the incidence of AIDs in their regional referral center, which was 33 new cases in 2021, compared to 41 and 47 in 2020 and 2019 respectively.

Also, Kasperkiewicz et al^[12] in their case series of 24 patients including 12 post- COVID-19 individuals and 12 healthy individuals who were administered with two doses of Pfizer vaccination, were tested for autoantibodies to the main immunobullous autoantigens such as desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and type VII collagen. Results revealed that none of the 24 anti-SARS-CoV-2 IgG-positive subjects had concomitant antibody reactivity with any of the tested autoantigens, thus rejecting the theory of immune cross-reactivity. But the author also acknowledge the possibility of induction of symptoms in genetically predisposed individuals by the mechanism of bystander activation phenomenon.

In the systematic review by Kasperkiewicz et al^[13] including 30 papers, it was found that the vaccination possibly induce or trigger AIDs, albeit in a relatively small fraction of vaccinated subjects. They concluded that this causal relationship could be a pure coincidence, as the data is mainly derived from single case reports/ series with a low level of evidence.

Our review is also based on individual case reports, as well-conducted observational studies or randomised controlled trials were not available. In our results, the timing of pemphigus onset is the only element supporting a causal relationship. This correlation should be affirmed by support from higher evidence results from larger population-based studies. But physicians should be aware of the possibility of autoimmune blistering diseases following COVID-19

vaccination, thus showing the importance of including a history of recent vaccinations, while assessing patients with new onset or flaring of AID.^[3]

Current data supports vaccination completion even for patients that experienced disease flares after the first dose, as adequate control of AID can be achieved with appropriate treatment adjustments. All the cases in our review responded either to systemic steroid therapy alone, or with addition of other adjuvant therapies. Thus, considering the serious ill effects of SARS-Corona virus infectivity and rarity of occurrence of pemphigus and other AID's, it is very crucial to encourage vaccination in patients with AID, by adhering to the guidelines and recommendations of experts about COVID-19 vaccination in special categories. This helps in determining the timeline of scheduling vaccination to patients with AID based on their treatment plan especially Rituximab therapy.

Conclusion

Although the critical era of pandemic has ended, COVID-19 vaccination will continue in future.

Recommendations to Practitioners:

Knowledge about the rare but life threatening COVID-19 vaccine-associated adverse reactions is important for early diagnosis and management of such conditions. Considering the favourable risk — benefit ratio, these vaccines can be administered to patients with pemphigus by following the guidelines and recommendations.

Recommendations to Policy Makers and Researchers:

Future studies should focus on large scale case control and cohort studies, and randomised controlled trials (RCT), to provide high level evidence regarding triggering of AID following COVID-19 vaccinations. Guidelines and recommendations about COVID-19 vaccine in all AIDs can be updated based on such robust data.

Source of support: Nil

Conflict of interest: Nil

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