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COVID-19: Important Updates and Developments
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Systemic steroids and risk of fecal-oral shedding and increased transmission of SARS-CoV-2 in pemphigus cases

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Abstract Pemphigus and its variants, viz., vulgaris, foliaceous, vegetans, Ig A pemphigus, paraneoplastic pemphigus and Senear-Usher syndrome are rare autoimmune blistering diseases of the skin and/or mucous membranes. The autoantibodies involved in the pathogenesis of pemphigus against desmoglein result in the breach of the skin and mucosal barrier, which acts as the first line of defence against pathogens. In this paper we underscore the importance of the integumentary system as a shield against the acquisition as well as transmission of SARS-CoV-2 virion. We have also made an attempt to delineate the various treatment modalities available and the viral-drug dynamics involved in choosing the optimum therapeutic modality.

To the Editor:

Coronavirus disease 2019 (COVID-19), a serious pulmonary illness caused by novel coronavirus SARS-CoV-2, has become a global pandemic. The outbreak of COVID-19 has made an impact on the management of various autoimmune skin diseases, including pemphigus vulgaris (PV). It is a general consensus that immunosuppressive or biologic treatment should be avoided in patients with active COVID-19 infection.[1] Rituximab, the only FDA-approved medication for moderate-to-severe PV, is considered first-line therapy for pemphigus; however, considering its irreversible effect on B-cells, which are active defense cells against COVID-19 infection, it is better to be avoided/postponed during this COVID pandemic.[2] Second option, which is still commonly practiced and considered as the first-line therapy in resource-poor settings, is corticosteroids—either in intravenous pulse doses or daily oral doses. As a result of a complete lockdown situation, patients with pemphigus do not have ready access to monthly pulse steroid therapy, and so they may be maintained on an effective daily regimen of oral steroids; however, there are a few concerns about systemic steroids in pemphigus and the risk of transmission of COVID-19.

Transmission

Severe or treatment-naïve cases of PV have mucocutaneous breaches that make them vulnerable to COVID-19 viral contagion, because angiotensin-converting enzyme 2, which is a cell receptor for SARS-CoV-2, is abundantly present in the cutaneous blood vessels and the basal cell layer.[3] Once a pemphigus patient is infected with COVID-19, there is a high

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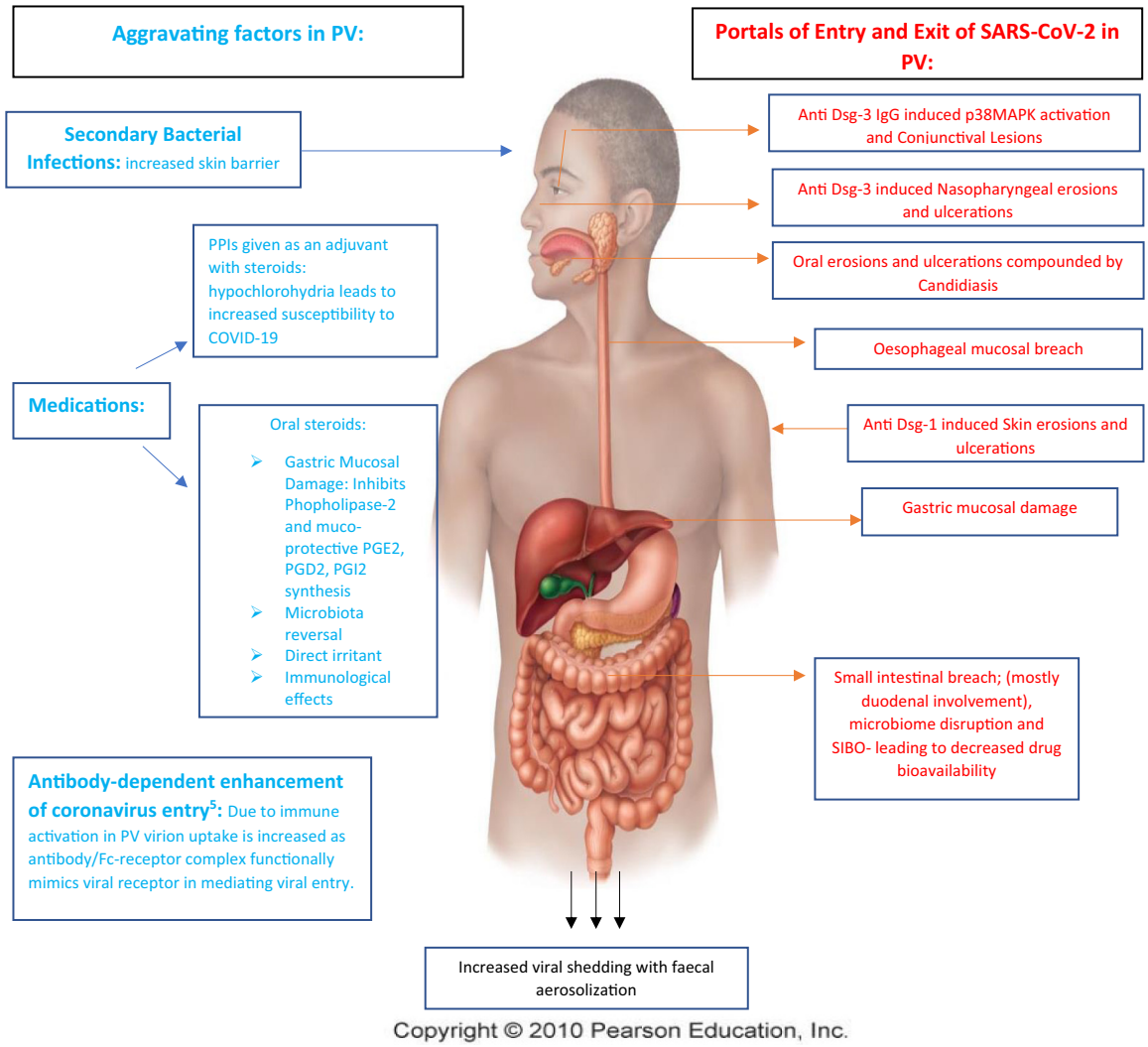

Fig. 1 Proposed model for faeco-oral transmission and perpetuation of COVID-19 with altered pharmacodynamics in pemphigus vulgaris; Digestive system outline sourced and modified from: https://www.thinglink.com/scene/784445306325434368; graphical illustration courtesy: Rahul Dalia, M. Tech., MBA).

chance of increased viral shedding due to both gut barrier dysfunction and increased viral transmission, associated with "aerosolization" of infected fecal matter.[4] Recently, a theory for coronavirus entry into cell has been proposed, that is, antibody-dependent enhancement, in which a neutralizing antibody binds to the surface spike protein of coronaviruses like a viral receptor, triggers a conformational change of the spike, and mediates viral entry into cells expressing IgG Fc receptors through canonical viral-receptor-dependent pathways. We speculate that the already primed immune system in PV with increased and marginalized T-cell and B-cell populations at the active sites of PV may increase the virion uptake. Conversely, COVID-19 may increase the *epitope spreading* phenomenon in PV, leading to increased severity and hence a more vicious circle.[5] Managing pemphigus patients with a high viral load of COVID-19 may also increase the chances of nosocomial spread to health care workers.

The gut mucosal damage triggered by corticosteroids may increase the susceptibility of PV patients to COVID-19, as feco-oral transmission has been established as a route of transmission of SARS-CoV-2.[4,6] Corticosteroids are also linked to a disruption of microbiome leading to a breach in the protective gut biological mantle. These protective bacteria serve as a biologic shield to combat the contagion.[6] Systemic steroids may cause breach in the biologic, physical, or even immunologic barriers of the gut, eventually leading to a so-called leaky gut, from which the viral particles can disseminate into the bloodstream (Figure 1). Opposed to this concept, the bioavailability and thus efficacy of oral steroids in pemphigus patients with mucosal involvement may be impaired due to gut mucosal disintegrity and gut dysbiosis.[6,7] Pemphigus patients with severe upper gastrointestinal and oral mucosal involvement may experience troublesome swallowing and associated decreased compliance.[7] (See Table 1).

Table 1 Summary of available treatment options for pemphigus vulgaris[11-13].

Drug	Washout Period (Increased Susceptibility Period For COVID-19)	Pros	Cons	Expert Guidelines (During COVID)[14]
Rituximab	1 year (earliest 5-6 months)	• First-line adjuvant (EADV guideline) and second line therapy (BAD recommendation) • Steroid sparing • Gold standard therapy in non-resource limiting settings • Can be stopped abruptly • Specific immunosuppression,i.e., humoral immunity suppression • Few adverse effects, especially lower incidence of metabolic side effects. • Few follow ups required	• Infusion-related adverse effects • Mucocutaneous reactions • Hepatitis B reactivation with fulminant hepatitis; progressive, multifocal leukoencephalopathy; other viral and opportunistic infections • Cardiac arrhythmias; renal toxicity; bowel obstruction and perforation; • Hematologic disturbances, such as lymphopenia, neutropenia, and anemia • Contraindicated in pregnant or breast-feeding women and in individuals with hepatitis B or C, HIV, or sepsis • B cell depletion: increased susceptibility to infections • Risk of thromboembolism • Might decrease the efficacy of future COVID-19 vaccine • Expensive. Not the first line in resource poor set ups	• Definite high risk[#] patients: require shielding[§]
Oral corticosteroids	2 weeks	• First line therapy in all settings. • Rapid disease control • Cheaper • Recent study indicates the potential reduction of mortality in severe COVID-19 cases by using low dose dexamethasone.[17]	• Non-specific immunosuppression • Adrenal suppression • Requires careful tapering • Metabolic side effects precludes long term use	• Corticosteroid dose of ≥ 20 mg (or 0.5 mg/kg) prednisolone (or equivalent) per day for more than 4 weeks: definite high risk-need shielding[§] • Corticosteroid dose of ≥ 5 mg prednisolone (or equivalent) per day for more than 4 weeks plus at least one other immunosuppressive medication, biologic/monoclonal or novel small molecule immunosuppressants (e.g. JAK inhibitors): definite high risk-need shielding[§]
Azathioprine	3 months (approx.)	• First-line adjuvant • Steroid sparing	• Measurement of TPMT activity before initiation • Regular monitoring required • Myelosuppression • Hepatotoxicity, pancreatitis, and arthralgia. • Long-term: increases the risk of infections and neoplasia.	• If patient has co-morbidities * or any immunosuppressant or biologics/monoclonals or novel small molecule immunosuppressants combined: Definite high risk[#] – to be advised to shield[§]

	Drug	Washout Period (Increased Susceptibility Period For COVID-19)	Pros	Cons
Mycophenolate mofetil	3 months (approx.)	• First-line adjuvant • Steroid sparing	• Contraindicated in Pregnancy and breast feeding • Gastrointestinal disturbances • Genitourinary symptoms • Hematologic abnormalities • Opportunistic infections • Requires continuous monitoring • Cost	• If patient has co-morbidities * or any immunosuppressant or biologics/ monoclonals or novel small molecule immunosuppressants combined: Definite high risk – to be advised to shield [§]
Cyclophosphamide	3 months (data extrapolated from Azathioprine/ MMF)	• Second-line adjuvant (EADV guideline) • Third-line therapy (BAD guideline) • Steroid sparing • Used in unresponsive or recalcitrant cases	• Poor safety profile • GI disturbances • Skin, hair and nail changes • Hemorrhagic cystitis • Transitional cell carcinoma of urinary bladder • Azoospermia, and infertility • Pregnancy Category D and contraindicated in breastfeeding	• If patient has co-morbidities * or any immunosuppressant or biologics/ monoclonals or novel small molecule immunosuppressants combined: Definite high risk [#] – to be advised to shield [§]
Cyclosporine	3 months (data extrapolated from Azathioprine/ MMF)	• Steroid sparing	• Both humoral and cellular immunity suppression. • Insufficient data for efficacy in PV-not recommended by BAD and EADV guidelines	• If patient has co-morbidities * or any immunosuppressant or biologics/ monoclonals or novel small molecule immunosuppressants combined: Definite high risk [#] – to be advised to shield [§]
Dapsone	1-2 week	• Second-line adjuvant • Useful in mild cases • Established safety profile	• Questionable efficacy • Hemolytic anemia. • Requires regular monitoring	• Does not warrant high risk status [€] in absence of comorbidities. • Social distancing as with normal population.
Methotrexate	2-3 days	• Second-line adjuvant	• GI, haematologic side effects • Infections, including pneumonia and reactivation of tuberculosis. • Pregnancy category X	• If patient has co-morbidities * or any immunosuppressant or biologics/ monoclonals or novel small molecule immunosuppressants combined: Definite high risk – to be advised to shield [§]
IVIG	Not applicable as no immunosuppression	• Second-line adjuvant (EADV guidelines) • Third-line therapy by the BAD guidelines. • Safest option	• Questionable efficacy • Infusion reactions	• Does not warrant high risk status [€] in absence of comorbidities.
Hydroxychloroquine (HCQ)	90 days (not applicable)	• Reports of efficacy against and as a preventive therapy for COVID-19	• Retinopathy • Asian patients: Occular toxicity outside of macula: visual field testing be	• Does not warrant high risk status [€] in absence of comorbidities.

Table 1 (*continued*)

Drug	Washout Period (Increased Susceptibility Period For COVID-19)	Pros	Cons	Expert Guidelines (During COVID)[14]
		• Can be used pregnancy (Category C) • Cheaper • Easy availability • Long record of Drug safety	performed in the central 24 degrees instead of the central 10 degree • Cardiac Effects, including Cardiomyopathy and QT prolongation • Proximal Myopathy and Neuropathy • Neuropsychiatric events, including suicidality • Hypoglycemia • Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine.	• Preventive and therapeutic in COVID-19 [$,18]
Plasmapheresis	Not applicable	• Second-line adjuvant • Safer • Helpful as an adjuvant in acute phase	• Efficacy not well established • Invasive • Expensive • Available only in tertiary centres	• Does not warrant high risk status [€] in absence of comorbidities. • Therapeutic in COVID-19 [$,19]
Immunoadsorption	Not applicable	• Same as plasmapheresis	• Same as plasmapheresis • Only added advantage being avoidance of substitution fluids	• Does not warrant high risk status [€] in absence of comorbidities.
Rilzabrutinib (formerly *PRN 1008*) : Phase 3 trial	Not disclosed	• Highly targeted therapy: Agammaglobulinaemia tyrosine kinase inhibitors • Oral administration	• Phase 3 • No long term data • Cannot be used in pregnant/lactating women • Expensive • Non-availability	• No available guidelines; by extrapolation: If patient has co-morbidities * or any immunosuppressant or biologics/monoclonals or novel small molecule immunosuppressants combined: Definite high risk [#] – to be advised to shield
Tocilizumab	Cocentration dependent and not applicable here	• Phase 2 trial for COVID pneumonia • Useful in paraneoplastic pemphigus • Anecdotal reports inPV	• Efficacy not established in PV • Reports of toclizumab induced pemphigus[15]	• No available guidelines.
Other Investigational Drugs: Ofatumumab	Not disclosed			• No available guidelines.
Veltuzumab		Type 1 anti-CD20 monoclonal antibodies Type I humanized anti CD20 monoclonal antibody: administered subcutaneously, resulting in lower side effects than intravenous RTX		• By extrapolation: If patient has co-morbidities * or any immunosuppressant or biologics/monoclonals or novel small molecule immunosuppressants combined: Definite high risk – to be advised to shield [§]
Obinutuzumab		Type II humanized anti-CD20	Investigational drugs No data for clinical use at present	

	Drug	Washout Period (Increased Susceptibility Period For COVID-19)	Pros	Cons
Belimumab		monoclonal antibody Monoclonal human IgG1 antibody bwhich target BAFF and a proliferating-induced ligand (APRIL)		
Atacicept		Human recombinant fusion protein, which target BAFF and a proliferating-induced ligand (APRIL) Ty		

* Co-morbidities: Age >60 years, pregnancy, chronic smokers or tobacco chewers, diabetes mellitus, severe hypertension, any pre-existing ischemic heart disease, respiratory system compromise, liver disease, kidney disease, internal malignancies.

§ Shielding: Individuals at highest clinical risk from coronavirus (COVID-19) should:

- ➢ Stay in home isolation for as long as possible with not more than one stint outside per day.
- ➢ Exercise extra precautions to minimise contact with others by keeping 2 metres apart if they opt to go out.
- ➢ Interaction to be limited to members of their own household or at the most one person/essential caretaker (same person everytime) from outside (maintain a social bubble).
- ➢ Should not attend and avoid gatherings.
- ➢ Strictly avoid contact with symptomatic and/or known cases of COVID-19.
- ➢ Essential carers coming to home or other members of family should:
  - follow advice on good hygiene and frequent hand washing for 20 seconds or sanitiser; avoid touching face.
  - At home also practice social distancing by keeping 2 meters or 3 steps away.
  - Minimise the time other people living with the patient spend in shared spaces such as kitchens, bathrooms and sitting areas, and keep shared spaces well ventilated with frequent cleaning.
  - Try and sleep in a different bed where possible.

  (Public Health England guidance published on 21 March 2020.)[16]

€ Advised to shield (moderate risk) only if other concerns or high-risk circumstances/co-morbidities *, however, those not requiring shielding, on immunosuppressant therapy, are termed 'vulnerable person' advised to be particularly stringent with certain social distancing measures.

Definite high risk: As delineated in the table some agents confer high risk stratification.

$ These agents have either been used or have a potential to be used in the treatment of COVID-19. Some drugs like HCQ might have a preventive role in COVID-19 infection.

Corticosteroids

Corticosteroids can be considered a double-edged sword in the COVID-19 situation. Systemic steroid-induced immunosuppression impairs induction of Interferon Type 1 (IFN-1) responses to various respiratory viruses, including COVID-19.[8] In opposition, steroids have shown some beneficial effects in hyperinflammatory conditions associated with COVID-19, that is, cytokine storm, acute respiratory distress syndrome, and sepsis. In any event, abrupt cessation of corticosteroids is not advised due to the risk of adrenal suppression.[9]

A recent international registry has shown that patients with inflammatory bowel disease treated with corticosteroids had increased severity of COVID-19, compared with patients receiving such tumor-necrosis-factor-alpha antagonists as adalimumab (Humira).[10] Physicians should assess risks versus benefits on a case-by-case basis before commencing/continuing systemic steroid in pemphigus cases. Corticosteroids should be one of the last therapeutic options for pemphigus, given the possible association between increased severity of COVID-19 in the patients receiving corticosteroids. We recommend that oral steroids be prescribed at the lowest possible yet effective doses, and tapered in a gradual manner. If therapy is prolonged for more than a month, such patients should be categorized as extremely being vulnerable and a high risk as suggested by NHS and should be home quarantined for 12 weeks.

Declaration of competing interest

No conflict of interest.

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