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LETTERS TO THE EDITORS

Correspondence Letter

Dear Editors,

Advice regarding COVID-19 and use of immunomodulators, in patients with severe dermatological diseases

Coronavirus disease 2019 (COVID-19) is the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as named by the International Committee on Taxonomy of Viruses (ICTV).

There is very limited evidence base to formulate specific advice for dermatology patients on immunomodulators with regard to COVID-19. The following is based on expert opinion, taking into account known risks of influenza (a negative-sense single-stranded RNA virus) and other, positive-sense single-stranded, RNA virus infections (such as SARS, MERS and the common cold). An Australia/New Zealand consensus document is in development.

This interim advice is for clinicians treating patients with severe inflammatory skin disorders managed on conventional and newer immunomodulators.[1] This includes systemic corticosteroids, azathioprine, ciclosporin, methotrexate and mycophenolate mofetil/mycophenolic acid, as well as the newer biologics for eczema and psoriasis including anti-TNF (e.g. adalimumab, certolizumab, etanercept, infliximab), anti-IL4/13 (dupilumab), anti-IL12/23 (ustekinumab), anti-IL17/23 (guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab), and small molecules such as PDE inhibitors (apremilast) and JAK inhibitors (abrocitinib, baricitinib, tofacitinib, upatacitinib).

There is no evidence of COVID-19 (or any RNA virus)-related harm from systemic retinoids (acetretin, alitretinoin, isotretinoin), so these do not currently need to be stopped/dose adjusted.

Currently, most people should continue taking their immunomodulator therapy, but this advice may change as more information becomes available.

IN A PATIENT WITH CONFIRMED COVID-19 DISEASE

Any patient with an inflammatory skin disorder being actively managed with an immunomodulator, who is diagnosed with COVID-19, should stop the immunomodulator (s) immediately, with the possible exception of systemic corticosteroids (see below). Whilst there is little specific evidence of COVID-19 infection being aggravated by immunomodulators as used in otherwise healthy dermatology patients, a precautionary approach is mandated, particularly as any secondary bacterial infection as part of COVID-19 may be aggravated by concurrent use of immunomodulators. Patients who are immunosuppressed appear to be at higher risk of a more severe infection or complications from COVID-19, although the extent of this risk is not known. Although median COVID-19 infection duration is in the order of 2 weeks, it would be sensible to discontinue systemic immunomodulators for at least 4 weeks, and until the patient has completely recovered.

IN A PATIENT WITH COLD/FLU-LIKE SYMPTOMS

In any patient with an inflammatory skin disorder being actively managed with an immunomodulator, who develops signs of a winter cold (e.g. mild coughing, sore throat, sneezing and runny nose), but who is not formally diagnosed with COVID-19 disease, it is reasonable to consider lowering the dose of any immunomodulator (see below) or temporarily stopping for 2 weeks. The possible exception is systemic corticosteroids.

PATIENTS AT HIGHER RISK OF SERIOUS OUTCOME SHOULD THEY DEVELOP COVID-19 DISEASE

Individuals over 60 years of age, patients with comorbid conditions including, but not limited to cardiovascular or chronic pulmonary diseases, chronic kidney diseases, diabetes, hepatitis B, hypertension and some cancers, are at significantly increased risk of developing a more serious course of the illness, including death. There is currently insufficient evidence to determine whether patients on systemic immunomodulators are at increased risk of becoming infected with COVID-19. Therefore, the benefit-to-risk ratio of any immunomodulator needs to be carefully assessed (see additional comments below).

1. **Patients with more severe skin disorders (e.g. severe psoriasis)[2] are inherently at increased risk of developing pneumonias of any cause.**
2. **Whilst a number of clinical trials of the newer biologics used in dermatology patients indicate a slight increased risk of developing upper respiratory tract infections (URTI), there does not appear to be a significant increase risk of developing influenza (flu). However, annual influenza vaccination is strongly encouraged (but avoid the live attenuated influenza nasal vaccine).**

3. **The COVID-19 pandemic is likely to continue for many months before being downgraded to seasonal epidemic status. This means a patient may have their immunomodulator withheld for many months.**

SYSTEMIC CORTICOSTEROIDS

Doses of predniso(lo)ne >20 mg/day are considered immunosuppressive, but sudden stopping, or significant reduction of dose, in patients on long-term systemic corticosteroids, is unwise, particularly if they have suddenly become physiologically stressed. Note that systemic corticosteroids are part of many adult respiratory distress syndrome (ARDS) protocols, but are not currently recommended for SARS-CoV-2, as there is weak evidence of harm when used in influenza-associated adult respiratory distress syndrome.

REDUCING IMMUNOMODULATOR DOSE

The immunomodulating actions of conventional systemic agents are dose-related. Whilst there is no hard data to make firm recommendations, consider the following lower dosages.

- Azathioprine: reduce to ≤0.5 mg/kg/day
- 'Biologics: no specific data available, but as their half-lives are considerable, they may better be modify on a case-by-case basis
- Ciclosporin: reduce to ≤1 mg/kg/day. Some *in vitro* evidence of potential benefit in COVID-19 disease
- Methotrexate: reduce to ≤10 mg/week
- Mycophenolate mofetil: reduce to ≤1 gm/day (mycophenolic acid to ≤720 mg/day)
- Retinoids: no need for dose adjustment
- Systemic corticosteroids: reduce to ≤10 mg/day predniso(lo)ne equivalent.

Marius Rademaker[1] | Christopher Baker[2,3] | Peter Foley[3,4] | John Sullivan[5,6] | Charlie Wang[3]
[1]Waikato Hospital - Waikato Clinical Campus, University of Auckland's Faculty of Medical and Health Sciences Hamilton, Hamilton, New Zealand, [2]The University of Melbourne – Dermatology, Fitzroy, [3]Skin Health Institute, Carlton, Victoria, [4]The University of Melbourne, Melbourne, [5]Kingsway Dermatology & Aesthetics, Miranda and [6]Sutherland Hospital - University of New South Wales, Caringbah, New South Wales Australia,

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Correspondence Letter

Dear Editor,

Granular parakeratosis is a reaction pattern in hyperkeratotic flexural erythema

We read with interest the well-illustrated article on granular parakeratosis by Shen S et al in the AJD.[1] We would like to draw the attention of the authors to our recent publication on the same morphological entity where we proposed that granular parakeratosis should be considered a reaction pattern due to epidermal perturbation triggered by variety of causes.[2] In our experience, the clinical morphology described in the recently reported case by Shen S et al also occurs in people who have not used any benzalkonium chloride-containing laundry detergents, and some cases of hyperkeratotic flexural erythema do not show the histopathological features of granular parakeratosis at any given time. Therefore, we proposed the term hyperkeratotic flexural erythema (HKFE) to encompass all cases of this clinical entity. Granular parakeratosis is often a feature, but not an essential feature to diagnose this condition. The disordered keratinisation of hyperkeratotic flexural erythema appears to be due to a change in the flexural microbiome due to irritants or other causes. A parallel to this situation is the skin changes of confluent and reticulated papillomatosis (commonly postulated to be triggered by an actinomycete), which responds to minocycline. As we reported previously, the skin lesions of hyperkeratotic flexural erythema rapidly improve within a few days, if a course of amoxicillin–clavulanic acid is given.[2] This we believe is due to an effect on the skin microbiome of the flexures. A comprehensive study of pathogenic as well as traditionally 'non-pathogenic' bacteria would be required to identify any putative causative organisms.

This paper as well as a few other publications highlight the detrimental effects of using benzalkonium chloride in laundry detergents and bath oils.[3–5] This would be an opportune moment for the Australasian College of Dermatologists and other similar scientific bodies to bring this to the notice of the public, detergent industry stake holders and relevant government agencies, with a view to stopping the practice of adding unnecessary antifungal and antibacterial additives to laundry detergents. Such additives do not have any proven benefit in preventing infections. If a person has a true fungal infection, it should be appropriately treated with standard medications.

Sujith Prasad Kumarasinghe[1] | Veena Chandran[2] | Edward Raby[3] | Benjamin Wood[4]
[1]Fiona Stanley Hospital, Murdoch, WA Australia, [2]Royal Perth Hospital, Perth, WA Australia, [3]Fiona Stanley Hospital, Murdoch, WA Australia and [4]Pathwest, QE2 Medical Centre, Perth, WA Australia