Tragedy and medical advances during the COVID-19 pandemic

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It is a pleasure to contribute to the 30th anniversary commemorative issue of the *Netherland's Journal of Dermatology and Venereology*. What a year this has been!

This past year could be dubbed the year of the virus and medical journals played a critical role in the vetting, dissemination and archiving of key knowledge about COVID-19. We demonstrated the range of cutaneous manifestations related to the virus and debated whether or not COVID toes are actually a specific viral manifestation. Authors in China also reported a high incidence of cutaneous injuries among healthcare workers related to personal protective equipment and alerted us that manual manipulation of the mask to shift the mask and goggles away from cutaneous erosions could reduce the effectiveness of protective measures. Prevalence of skin damage was 97.0% among frontline healthcare workers with the nasal bridge being the most commonly affected site and simple interventions, including more frequent work rotations and the use of adhesive barrier films could help prevent harm. [1] We also learned that androgen receptors may play a role in viral entry and adverse outcomes [2], and weighed evidence for and against continuation of biologics during the pandemic. [3]

Dirk Elston: "The past year has been a challenging one."

This year also provided us with game changing data on pharmacological interventions for hidradenitis suppurativa and reminded us of the key role surgery continues to play in the treatment of this debilitating disease. [4-7] Recent articles and guidelines address the approach to patients with this devastating disease, risks of medical therapy during the COVID-19 pandemic, current gaps in therapy and new data on agents reported to be effective in this condition. [8-13] While adalimumab has received the most press, high dose infliximab regimens similar to those used with inflammatory bowel disease represent a new treatment paradigm, and when efficacy is lost to neutralizing antibodies there is new evidence suggests that adjuvant therapy with methotrexate or sirolimus has the potential to restore responsiveness. [14-22] Other biologics that block Th17 T cells, IL12/23 or IL-23 alone also appear to have efficacy in this setting, and further studies are needed to determine relative efficacy of these biologic agents. [23-25] Short courses of antibiotics can be beneficial but emergence of resistance can complicate longer courses of treatment. [26,27] Cultures are of limited value as anaerobic bacteria predominate and are difficult to grow in culture. [28] Future studies should use molecular techniques to delve into the microbiome of hidradenitis. Topical antiseptics continue to be helpful, and those with less potential for antibiotic resistance are particularly valuable. [29,30] Drugs that affect neutrophils can also be helpful in this setting, including doxycycline, dapsone, anakinra and canakinumab, and antiandrogens including spironolactone can help with long-term control of disease. [31,32] Apremilast, on the other hand improves specific disease measures but an overall effect on quality of life was limited. [33,34] There have also been reminders that hidradenitis suppurativa can coexist with inflammatory bowel disease, and pyoderma gangrenosum, and may represent a systemic inflammatory disorder in the spectrum of autoinflammatory diseases. [35,36]

Important articles published this year demonstrated usefulness of dupilumab in the pediatric age group and

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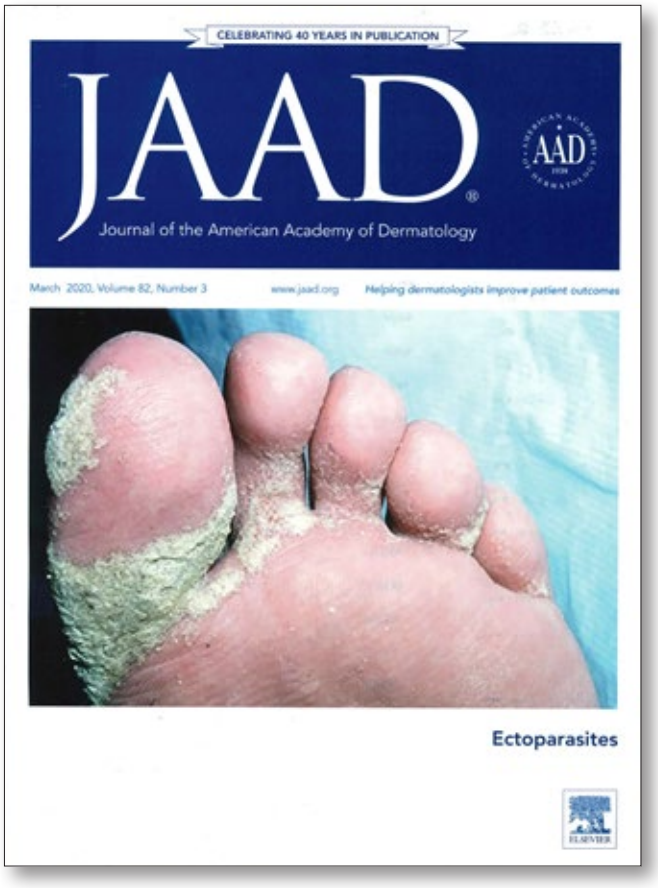
new potential roles for dupilumab in the treatment of hand dermatitis, idiopathic dermatitis, nummular eczema, bullous pemphigoid and prurigo nodularis, but also raised awareness that persistent dermatitis in patients on dupilumab may be related to Pityrosporum or contact dermatitis, especially to cocamidopropylbetaine in soaps and shampoo. [37-46] We also received an important warning about the potential for fatal progression of cutaneous T-cell lymphoma (CTCL) in patients treated with dupilumab. [47,48] Authors from UCSF and Northwestern University described seven patients given dupilumab for clinically presumed atopic dermatitis or to treat refractory pruritus in cutaneous CTCL. While six of the seven patients experienced transient improvement, all subsequently demonstrated disease progression and fatalities occurred. [49,50] Dupilumab remains a valuable agent in our therapeutic armamentarium, but physicians should be vigilant for signs of CTCL in patients on dupilumab therapy and the physical examination during follow-up visits should include the buttocks, groin, thighs, and limb girdle areas as these are common sites for the appearance of CTCL. Other authors have reported CTCL following use of dupilumab and more research is needed to determine the magnitude of the risk and contributing factors [51,52] Pathogenesis is likely complex as targeted cytokines appear to modulate lymphomas and can exert a beneficial or negative response in various settings. Dupilumab modulates signaling of both the IL-4 and IL-13 pathways, and interleukin 13 in particular may play a role in progression of various forms of lymphoma.



Scarring alopecia remains one of our most difficult disease categories and many patients with alopecia have multifactorial disease leading to confusion and suboptimal outcomes. It is important to remember that pattern alopecia affects almost half of adults of European decent. By extension, this means that roughly half of the patients of European descent whom we treat for scarring alopecia also have a background of pattern hair loss and addressing both conditions can lead to better treatment outcomes. [53] Topical minoxidil has a defined role in the treatment of pattern alopecia, but recent studies have focused on the effectiveness and tolerability of low dose minoxidil administered orally. [54-60] Antiandrogens such as spironolactone and cyproterone acetate may also be helpful to treat background pattern alopecia and improve hair density in women, and patients should also be evaluated for papulosquamous disease, thyroid disorders and dietary issues that may contribute to superimposed telogen effluvium.
Targeted therapy has led to dramatic improvement in many conditions, including JAK-inhibitor therapy for alopecia areata, vitiligo, granuloma annulare, lichen planopilaris,

sarcoidosis, and chronic eczema and rituximab therapy for immunobullous diseases. [61-67] As dermatologists prescribe more of these agents, it is important to remain vigilant for potentially lethal side-effects of therapy. JAK inhibitors can cause cytopenias, lipid abnormalities and an increase thrombotic risk with the associated risk of fatal pulmonary embolism. Patients should be monitored appropriately and counseled about the risks, early recognition of complications, and preventive strategies.

Covid-19 has not been the only infectious disease that gained focus this year. Patients on immunosuppressive agents should be assessed for the presence of any underlying disease prior to the initiation of therapy. In particular, those on rituximab must be monitored for reactivation of hepatis B with massive hepatic necrosis.

All clinicians should be aware of issues with screening for hepatitis B, in particular the removal of core IgG antibody from acute hepatitis panels reducing our ability to screen for latent infection in patients who are surface antigen-negative. The core IgG antibody must be ordered separately and patients should be monitored for signs, symptoms and laboratory evidence of hepatitis. In our patients with immunobullous disease, glucocorticoids are often used concurrently with rituximab or other steroid-sparing agents and can mask hepatitis reactivation. Prompt intervention is key and some evidence suggests that rituximab therapy may be possible in patients with latent infection if given together with antiviral prophylaxis. Physicians should also be aware that false-positive serological and DNA testing for hepatitis can occur in patients who have been recently vaccinated. Careful evaluation of patient history is key.

The past year has been a challenging one and few of us well be sad to see it go, but we should remember the remarkable advances in disease treatment and prevention that have emerged during this year. Covid-19 has been a potent reminder that we are all in this together and physicians play a key role not only in disease treatment, but also in prevention, public policy and as important role models. It is an honor and a privilege to serve society in the role of physician and healer. May we all carry those banners proudly and live up to the sacred calling we accepted. Keep well so you can continue to serve your patients.

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