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Shedding light on therapeutics in alopecia and their relevance to COVID-19

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Abstract As of July 9, 2020, there were more than 12 million confirmed cases of coronavirus disease 2019 (COVID-19) across the globe, with more than 550,000 deaths. Many European countries, including Belgium, the United Kingdom, Italy, and Spain, have had the highest numbers of fatalities per capita. This indicates the potential for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus to overwhelm even the most advanced health care systems despite extreme societal interventions. Since its emergence, SARS-CoV-2 has disseminated across the globe, affecting the structure of global societies, infrastructure, and economies. Patients with alopecia are a diverse group who, for various indications, are prescribed a number of antimicrobials and antiandrogen treatments in addition to immunomodulatory therapies such as hydroxychloroquine, oral corticosteroids, and a range of broad immunosuppressants. These drugs are being scrutinized for their capacity to potentially affect SARS-CoV-2 outcomes. We examine these treatments and highlight the critical role that patient registries will play in generating real-world evidence to assess their impact on COVID-19 outcomes.

Introduction and background

The first reports of a cluster of viral pneumonias originating from the wet animal markets in Wuhan, Hubei province, China emerged in late December 2019. The implicated novel RNA virus was formally designated as severe acute syn-

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drome coronavirus 2 (SARS-CoV-2). Since then, millions of people have contracted the virus.[1] The majority of those infected are believed to be asymptomatic or to display only mild symptoms; however, morbidity and mortality are considerable in the 15% of individuals who have severe disease and the 5% of individuals who require critical care.[2] Rapid progression from complications such as acute respiratory distress syndrome (ARDS) can lead to death.[3]

Despite unparalleled mobilization of the global medical and scientific communities against the pandemic, no fully effective treatment is available yet. The antiviral agent remdesivir has been shown to be modestly effective in a well-conducted clinical trial.[4] Likewise, preliminary results from a UK-based trial have suggested that dexamethasone, a corticosteroid, produces a moderate reduction of 28-day mortality in coronavirus disease 2019 (COVID-19) patients.[5] The rapid spread of SARS-CoV-2 across international borders highlights the need for a coordinated global response to improve outcomes.

The delicate balance of host and viral factors that appear to contribute to disease severity is similar to the closely related coronavirus infections severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. Experience from these epidemics and emerging evidence as COVID-19 spreads has stimulated drug trials exploring repurposing of existing medicines, including antivirals and immunomodulating therapies to attenuate the destructive cytokine storm associated with COVID-19. These repurposed therapies may be of benefit for SARS-CoV-2 at this time of immediate, acute, and widespread need, while we wait for targeted therapies to become available.

The factors that trigger severe disease in individuals are not yet well established. It is theorized that a pathologic excessive inflammatory response (including the so-called cytokine storm) may be a key player, and so this has led to trials of existing immunomodulatory drugs.[6,7] In addition, laboratory studies involving hydroxychloroquine and baricitinib have also identified antiviral properties. Interestingly, the reported higher prevalence of severe disease in men and a low incidence in prepubertal children suggests that androgens (and androgen receptor) could play a role in disease severity.[8] This highlights a possible role for antiandrogenic medications.[9]

Patient registries are a means of collecting data to monitor patients already taking immunomodulating and antiandrogen therapies that present an opportunity to establish the prevalence and severity of disease among this patient cohort. Patients being treated for various types of alopecia receive a wide range of therapies, including immunomodulating and antiandrogen drugs, and some will have been on long-term treatment. Data obtained from monitoring the outcomes of treated alopecia patients during the COVID-19 crisis will help clarify if modulating the immune-mediated and androgen pathways influences the disease course and improves or increases morbidity and mortality.[7,8] By simultaneously studying the outcomes of individuals suffering from alopecia currently not on these medicines, it will be possible to establish a large cohort of patients that can provide comparative data.

SARS-CoV-2 pathogenesis and host response

The main clinical features of COVID-19 are fever, dry cough, and dyspnea.[10] Anosmia and ageusia have also been widely reported. Approximately 80% of those infected run a mild disease course, 15% infected develop a severe illness, and 5% require critical care due to respiratory failure and ARDS.[2] These individuals may require mechanical ventilation and often multiorgan support. Those following a severe disease trajectory tend to be of older age with coexisting underlying disease,[10,11] although the virus can cause death in young people without comorbidities. The significant capacity for mortality, even in healthy individuals, has triggered broad scale and unprecedented public health interventions to curb the spread of SARS-CoV-2.

As a respiratory virus SARS-CoV-2 initially infects the lungs, targeting type 2 pneumocytes; however, the virus been found in many organs and tissues, including skin and testis. SARS-CoV-2 enters the cell by binding to the angiotensin-converting enzyme 2 (ACE2) surface receptor.[12] To enter the cell via ACE2 the viral spike protein must first be primed by the host protein transmembrane protease serine 2 (TMPRSS2).[13] To date, androgens are the only identified promoter for the *TMPRSS2* gene, binding to the androgen response element and promoting transcription of the gene.[14] Like TMPRSS2, ACE2 is also regulated by the androgen receptor (AR), although not exclusively.[15] As the primed spike protein is reliant on both TMPSS2 and ACE2 for pathogenesis, this highlights an association between androgens and SARS-CoV-2.[8]

Evidence suggests COVID-19 and its SARS and MERS predecessors are characterized by an hyperinflammatory response and cytokine storm syndrome.[6,16] This aberrant immune response likely contributes to lung damage and death.[17] Observational reports of COVID-19 patients indicate similarities between severe SARS-CoV-2 infection and other hyperinflammatory states like secondary hemophagocytic lymphohistiocytosis and macrophage activating syndrome.[17] Early reports of COVID-19 patients identified elevated interleukin-1β (IL-1β), interferon-γ (IFN-γ), interferon-γ inducible protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP1), activating type 1 T-cell responses.[10] In addition, higher levels of granulocyte colony-stimulating factor (GSCF), IP-10, macrophage inflammatory protein-1A (MIP1A), and tumor necrosis factor-α (TNF-α) were seen in those admitted to intensive care units.[10] In a separate study, levels of interleukin-6 (IL-6) and serum ferritin were higher in nonsurvivors and an increase in these markers correlated with severity of disease.[17]

Severely affected COVID-19 patients are those with underlying conditions that impair the immune response or cause chronic low-grade systemic inflammation, such as obesity, type 2 diabetes, and atherosclerosis.[18] In older adults, increased production of type 2 cytokines and age-dependent

defects in the function of T cells and B cells may lead to increased viral replication and a prolonged proinflammatory state, leading to a poorer outcome.[17] Similarly to MERS, the outcome of COVID-19 infection may depend on a balance of both host and SARS-CoV-2 induced immune signaling cascades.[16] Therapies that could modulate the interaction between the virus and the host responses may improve morbidity and mortality in COVID-19 patients.

Alopecia: Subtypes and current therapeutic landscape

Alopecia can be characterized as scarring or nonscarring. Nonscarring hair loss includes androgenetic alopecia (AGA; male pattern hair loss [MPHL] or female pattern hair loss [FPHL]), telogen effluvium, and alopecia areata. Although alopecia areata is believed to be among the most common autoimmune conditions in humans, with an estimated lifetime risk of 1.7-2.1%,[19,20] AGA is even more prevalent, progressively increasing with age. Half of all men and 30% of women are affected by the age of 50. Individuals with all forms of alopecia can find hair loss extremely distressing, because hair is seen as a core element of identity and culture. In women with breast cancer, chemotherapy-induced alopecia can be considered to be more emotionally difficult than the mastectomy.[21,22] In patients with alopecia areata, there is an association with suicidal ideation and youth suicide.[23]

Scarring alopecias include lichen planopilaris and its variants, frontal fibrosing alopecia, folliculitis decalvans, dissecting cellulitis of the scalp, discoid lupus erythematosus, and localized scleroderma. In contrast to nonscarring alopecia, scarring alopecias result in permanent hair loss. Prompt treatment with a broad range of immunomodulatory and systemic therapies is recommended to arrest the disease process.[24]

Recently, drugs that are used for hair disease, such as antiandrogens, antimicrobials and the immunomodulatory drugs hydroxychloroquine, corticosteroids, cyclosporine, and Janus kinase (JAK) inhibitors, have been considered for use in the treatment of COVID-19.[5,8,9,12,25-31] In particular, the use of hydroxychloroquine and corticosteroids has been controversial since the start of the pandemic. There are no data available yet on the value of methotrexate in COVID-19 disease, although it could be theorized that it is to be avoided given its association with pulmonary toxicity.[32]

Immunomodulatory drugs and COVID-19

Hydroxychloroquine

Hydroxychloroquine is often used to treat a number of cicatricial alopecias including discoid lupus erythematosus and lichen planopilaris.[33-35] Since the start of the outbreak, chloroquine and hydroxychloroquine have been under intense clinical scrutiny in scientific and mass media as possible therapeutic and prophylactic treatments for COVID-19. Hydroxychloroquine is generally considered to have a more favorable side effect profile than chloroquine, though both have raised concerns due to their arrhythmogenic potential.[28] Both drugs have an antiinflammatory role, because they reduce T-cell activation and alter the cytokine profile. They also have a synergistic antiviral role. They interfere with the glycosylation of the ACE2 cellular receptor of SARS-CoV and alter entry into the cell by increasing the endosomal pH, thereby limiting fusion.[36]

During the earlier SARS-CoV-1 epidemic, *in vitro* studies of chloroquine and hydroxychloroquine had efficacy against the virus, and this has been mirrored in SARS-CoV-2.[37] In the SARS-CoV-2 pandemic, early clinical reports from China suggested positive outcomes in patients treated with chloroquine.[38,39] Hydroxychloroquine used alone or in combination with azithromycin suggested that the viral load may be reduced; however, the relevance of this in affecting disease severity is yet to be confirmed.[29,40] Unfortunately, these studies were not adequately powered and stemmed mainly from off-label use of the drugs.

More recently, a large-scale observational study of 96,032 COVID-19 patients taking chloroquine or hydroxychloroquine, with or without a macrolide, found no additional benefit and in fact reported a greater risk for in-hospital death and ventricular arrythmias.[41] This paper, published by *The Lancet* in May 2020, has since been retracted due to questions surrounding the validity of the data. The UK RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial reported that there was no clinical benefit in the use of hydroxychloroquine versus normal standard of care in hospitalized patients. High-dose hydroxychloroquine, 2.4 g administered in the first 24 hours and continued at a dose of 800 mg for 9 days, was found not to reduce mortality in COVID-19 patients.[42] The World Health Organization SOLIDARITY trial, another randomized controlled trial, has released preliminary data that confirm there is no reduction of death with the use of hydroxychloroquine.[43] Both the RECOVERY and SOLIDARITY trials have thus concluded that there is no benefit and have since stopped enrollment in the hydroxychloroquine arms of the trials.

The high-level endorsements of hydroxychloroquine's utility by some American and Chinese authorities led to shortages, which may affect the general availability of the drugs for approved use in hair disorders. Until further evidence emerges, widespread use of hydroxychloroquine cannot be recommended; however, it would be prudent to monitor alopecia patients currently taking these drugs, because this may provide further insight about the potential benefits of therapeutic or prophylactic use in the context of COVID-19.

Glucocorticoids

Glucocorticoids are used in inflammatory hair diseases, because they disrupt autoimmune mechanisms and cause a

widespread dampening down of immune responses.[34,44-46] Like hydroxychloroquine, the use of steroids has been controversial in the context of COVID-19. Although corticosteroids might presumably reduce the severe, immune-mediated lung inflammation seen in COVID-19 patients, they may also reduce host responses and so limit viral clearance.[47] They have commonly been used in ARDS, but they are not proven to reduce mortality due to variable results between individual trials.[48] In a review of six studies examining steroids and ARDS, there was insufficient evidence to support the use of corticosteroids.[48]

Corticosteroids were widely used during the earlier outbreaks of SARS and MERS. In one systematic review of SARS patients treated with steroids, 25 out of 29 studies were inconclusive and the remaining 4 reported possible harm.[49] In a retrospective study of MERS patients, those given steroids were more likely to have invasive interventions and had no difference in 90-day mortality.[50]

Despite considerable, but inconsistent evidence, steroids were used in China at the beginning of the COVID-19 outbreak. An expert consensus from the Chinese Thoracic Society, all of whose members were involved in treating COVID-19 patients, argues that a short course of low- to moderate-dose steroids for critically ill patients should not be ruled out.[51] Interestingly, a small retrospective cohort study of 201 patients from Wuhan identified that methylprednisolone appeared to reduce mortality in COVID-19 patients with ARDS.[52] Preliminary results from the UK-based randomized RECOVERY trial found that dexamethasone reduces 28-day mortality by 17% in hospitalized COVID-19 patients. The greatest benefit was seen in ventilated patients, reducing deaths by one third, and by one fifth in patients receiving oxygen only.[5] Taken together this suggests that corticosteroids may be of benefit in those with severe disease; however, current World Health Organization guidelines advise against the use of steroids in COVID-19.[47]

Cyclosporine

Cyclosporine (CYA), a calcineurin inhibitor, is a mainstay of steroid-sparing treatment in hair disorders and has a well-established side effect profile.[34,45,53,54] As an immunosuppressant, it limits the transcription of interleukin-2 (IL-2) and other cytokines in activated T cells.[55] Individuals taking cyclosporine are at risk for developing serious infections; however, it has an effect on cytokine profiles; in theory, it could be of benefit in preventing the pathologic hyperinflammation reported in COVID-19 patients. CYA had previously been used to treat the cytokine storm in secondary hemophagocytic lymphohistiocytosis, which has a similar cytokine profile to SARS-CoV-2 infection.[6,56] In contrast to targeted biologics, such as anti–interleukin-6 (IL-6) (which have been put forward as a treatment for the cytokine storm in COVID-19 patients), CYA is more affordable. *In vitro* studies reported that CYA at low doses inhibits MERS-CoV and SARS-CoV replication[57,58]; however, given the risk of serious complications, such as nephrotoxicity and hypertension in already compromised individuals, robust preclinical studies would need to confirm if CYA is beneficial in SAR-CoV-2 infection before its use.

JAK inhibitors

Using Benevolent AI(artificial intelligence) software, researchers at the Imperial College, London, identified baricitinib, a JAK inhibitor, as a potential treatment for COVID-19.[59] SARS-CoV-2 enters cells through clathrin-mediated endocytosis via the ACE2 surface protein. The numb-associated kinases, AP2-associated protein kinase 1 (AAK1) and cyclin G–associated kinase are known regulars of endocytosis. AAK1 and cyclin G–associated kinase are potential therapeutic targets, preventing the virus from entering the cells via receptor-mediated endocytosis. Baricitinib, a JAK inhibitor, currently in a phase 3 clinical trial for the treatment of severe alopecia areata, is a high affinity inhibitor of AAK1 and binds cyclin G–associated kinase.[31,59] It was granted breakthrough therapy status for alopecia in March 2020 by the FDA.[60] Originally six potential AAK1 inhibitors were identified by artificial intelligence, but baricitinib, given its once-daily dosing and acceptable side effect profile, was considered the most favorable therapeutic option.[31]

Baricitinib exerts its anti-inflammatory properties via the JAK1/2 pathway and is approved for use in rheumatoid arthritis. The anti-inflammatory properties may limit the hyperinflammatory response and subsequent cytokine storm in SARS-CoV-2 infection. A randomized controlled trial currently being conducted by the National Institutes of Allergy and Diseases aims to explore this further. In ACCT 2 (Adaptive COVID-19 Treatment Trial), baricitinib will be combined with remdesivir, an antiviral that has been tested already in COVID-19 patients (ACTT) by the National Institutes of Allergy and Diseases. Preliminary results from ACTT indicates a 31% faster time to recovery in those receiving remdesivir versus placebo in COVID-19 patients.[4] It is postulated that these drugs act synergistically to reduce viral entry, replication, and hyperinflammation without interacting with the relevant CYP drug-metabolizing enzymes.[59]

Methotrexate

Methotrexate is a longstanding immunosuppressive drug used in a number of dermatoses, including those affecting the hair follicle.[45,46,61-63] Along with other immunosuppressants, patients currently taking methotrexate are in theory more susceptible to serious infections including COVID-19. The guidelines from the British Association of Dermatologists recommend that patients currently taking immunosuppressant drugs self-isolate and, if they contract COVID-19, temporarily stop methotrexate use.[64] Methotrexate, a folate analogue, exerts its antiinflammatory effects by increasing intracellular adenosine. In addition, it reduces homing of T

cells and decreases the production of proinflammatory cytokines.[65]

At present, there is no scientific evidence examining the interaction between SARS-CoV-2 and methotrexate. It is possible that the immunosuppressive effects of methotrexate could prevent the virus-induced cytokine storm by inhibiting the expression of certain cytokines; however, because a known side effect of methotrexate is pulmonary toxicity, it is not currently a drug being investigated for repurposing.[32] Monitoring patients with alopecia on methotrexate during the pandemic is important, because it will allow clinicians to determine if there is an increased risk of contracting the virus and if this is associated with a worse outcome.

Antiandrogens in alopecia and COVID-19

Androgenetic alopecia hair loss is due to a genetically determined sensitivity to androgens. Higher expression of the AR may correlate with increased disease severity in COVID-19 patients.[8] Evidence for this comes from epidemiologic studies, as well as reports of AR in TMPRSS and ACE2 expression.[13,15]

Severe disease in COVID-19 patients has shown a greater male versus female predominance (52% versus 48%). Prepubescent children are at very low risk of severe disease, representing only 0.6% of cases in a study of 1099 patients in China.[66] Ethnic differences in the outcomes of COVID-19 have also been reported, with more African Americans having worse outcomes compared with Caucasians. Although confounding factors are likely to contribute to these differences, genetic variations of the AR between different ethnic groups could explain the increased susceptibility to severe complications of COVID-19; likewise, genetic variants in AR expression in women and children could explain the lower rate of severe COVID-19 seen in these populations.[9] For example, polymorphisms in the CAG repeat in exon 1 of the AR may account for some of these racial and gender differences because CAG polymorphisms correlate with the incidence of other androgen-mediated diseases, such as androgenetic alopecia and prostate cancer.[67,68] Studies of expression of CAG polymorphisms in hospitalized COVID-19 patients could be of value in determining whether this hypothesis is true.[9]

To better understand if there is an association between AR expression and severity of COVID-19 infection, it is important to record the outcomes of individuals with increased AR expression/sensitivity, such as men with androgenetic alopecia.[9] If true, several classes of drugs used in androgenetic alopecia may be of use in SARS-CoV-2 infection. Examples of such androgen receptor antagonists include spironolactone,[69,70] flutamide,[71] bicalutamide,[72] cyproterone acetate,[73] and the 5-α-reductase inhibitors finasteride and dutasteride.[74-78] These drugs, which are widely available and have a well-understood safety profile, could be rapidly repurposed for use in COVID-19 patients.

Conclusions

SARS-CoV-2 is a newly emergent pathogen, about which relatively little is known currently. It is associated with considerable morbidity, mortality, and profound socioeconomic disruption. As such, there is a critical need for effective therapies to become available on a large scale. As measures designed to limit its spread are gradually withdrawn, the threat of a second, more devastating, wave of illness looms, highlighting the continued need for worldwide research and collaboration.

The rapidly evolving nature of COVID-19 disease and the manner in which new therapies and novel applications of existing therapies could be applied (ie, beyond their conventional use), stresses the need to collect data in a harmonized manner. The role of patient registries is fundamental to enabling this. The emergence of a number of collaborative, international patient registries is of significant interest, including for alopecia (SECURE-Alopecia; securederm.com/secure-alopecia/).[79] These registries focus on collecting anonymized data regarding outcomes of patients with specific conditions, such as inflammatory bowel disease, cirrhosis, atopic dermatitis, psoriasis, and all forms of alopecia, who have contracted COVID-19.[80] This will generate relatively well-harmonized data sets in a large cohort of patients who have contracted COVID-19 while on immunomodulatory therapies. Such an initiative will allow us to compare outcomes with alopecia patients who have not been treated. Data collected will provide real-world evidence to assess the safety and effectiveness of the potential treatments described in this contribution.

The emergence of three highly infective SARS coronaviruses in the last 20 years has shown the value of international networks and the necessity for coordinated rapid responses. Identifying and repurposing approved therapies with known pharmacokinetics, proven safety profiles, and acceptable side effects could be of paramount importance, until such time as an effective vaccine is available.

Therapies used for alopecia may have a positive effect on the outcomes of COVID-19. Immunomodulators such as hydroxychloroquine, ciclosporin, and the JAK inhibitor baricitinib may augment the cytokine storm and pathologic lung inflammation leading to death. Hydroxychloroquine and baricitinib may also exert an antiviral effect in SARS-CoV-2 infection. Recently, the positive effect of hydroxychloroquine proposed in earlier studies has been questioned, because more data have indicated that there is no benefit. Official reporting of two large prospective, randomized, placebo-controlled clinical trials is currently awaited. The role of the AR in the severity of COVID-19 disease needs to be elucidated further. If proven, antiandrogens, such as finasteride and spironolactone, could be used to reduce the risk of severe disease. Until recently, evidence for the use of glucocorticoids was inconclusive or even suggested harm; however, the results of the UK RECOVERY trial have disputed this, suggesting a benefit for the use of dexamethasone in COVID-19

patients. Methotrexate, although an immunomodulator, is not currently a candidate drug for repurposing in SARS-CoV-2 infection given its potential pulmonary side effects.

Patients with alopecia are a diverse group, for whom a wide range of systemic therapies are prescribed. They offer a meaningful opportunity to collect real-world data that will better inform the global community, through pooled observations from multinational real-world patient registries, and so not only help inform care of alopecia but also offer a chance to establish risk factors and candidate interventions that may modulate disease course and save lives.

Conflicts of Interest

Desmond J. Tobin is a director (secretary) of the National and International Skin Registry Solutions (NISR). Alan Irvine is Chairman of National and International Skin Registry Solutions (NISR). He has acted as a consultant for Pfizer, Sanofi, Regeneron, Novartis, and AbbVie, but not in relation to any products discussed in this contribution. Dmitri Wall has received personal fees (honoraria) from Janssen and Eli Lilly (consultancy fees) and nonfinancial support (travel fees/grant) from Pfizer. He has received personal fees for consultancy from the charity National and International Skin Registry Solutions.

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