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Recommendations on trichological treatments during COVID-19 pandemic

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ABSTRACT

COVID-19 is an infectious disease caused by the novel coronavirus SARS-CoV-2, which rapidly spreads via respiratory droplets and is the cause of the current pandemic. In this alarming situation, it is a delicate matter how to visit patients safely and how to manage their chronic treatments. The aim of this paper is to examine in detail the potential impact on SARS-CoV-2 infection of treatments routinely used in trichology and to provide a useful guide for the therapeutic management of trichological patients in this new COVID-19 era.

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Introduction

COVID-19 is an infectious disease caused by a recently identified coronavirus named SARS-CoV-2. This virus is highly contagious and spreads easily via respiratory droplets. Social distancing and sanitation protocols play a fundamental role in avoiding viral spreading. In this alarming situation, it is a delicate matter how to manage patients who are currently under chronic treatments. In trichological field, many diseases are characterized by a chronic relapsing course and usually require long-term treatments. These include not only on- and off-label drugs, with a systemic and/or topical administration, but also vitamins and dietary supplements.

The aim of this paper is to examine in detail the potential impact of treatments routinely used in the trichological field on infectious risks during COVID-19 era.

On-label treatments

Finasteride

Finasteride is one of the main pharmacological agents used in trichology. Its primary application is for the treatment of male androgenetic alopecia (AGA). Besides the FDA-approved systemic finasteride, an off-label topical formulation is also available, with positive effects on the treatment of both male AGA and female pattern hair loss (FPHL) and with a lower risk of side effects. Other trichological diseases taking benefit from the administration of systemic or topical finasteride are frontal fibrosing alopecia (FFA), fibrosing alopecia, lichen planopilaris (LPP), discoid lupus erythematosus (DLE).

It works by inhibiting 5-alpha-reductase II enzyme (5AR-II), which converts testosterone (T) to dihydrotestosterone (DHT). This molecule has a tenfold higher affinity to androgen receptors (AR) compared to testosterone.

Recently, Goner et al. (1) have hypothesized that androgens could play an important role in COVID-19 pathogenesis. SARS-CoV-2 pneumocytes infection depends on the priming of a viral

spike surface protein by transmembrane protease serine 2 (TMPRSS2). Interestingly, TMPRSS2 gene transcription is promoted by AR activation (2). Furthermore, literature evidence shows that angiotensin-converting enzyme 2 (ACE2) expression, which is largely linked to SARS-CoV-2 infection, is increased by androgens and decreased by estrogens (3).

Given this, the authors suppose that finasteride, blocking the 5AR-II enzyme with consequent T increase and DHT decrease, and indirect decrease of AR activity, may have a protective role against SARS-CoV-2 infection.

In our opinion, it should also be considered that the increase of T levels caused by finasteride may determine a T escape via two pathways. In women, because of their high expression of aromatase, the majority of T is converted to estrogens by aromatase. In men, in which the aromatase expression is usually low, finasteride-induced 5AR-II inhibition, with consequent T increase, may cause a T escape via 5AR-I, which is not inhibited by finasteride. Consequently, 5AR-I activation leads to the conversion of T in DHT, which lowers the efficacy of finasteride. Based on this consideration, finasteride may not have a protective role against SARS-CoV-2 supposed by Goner et al. (1).

As mentioned above, it has to be noticed that aromatase is much more expressed in women, suggesting that finasteride might be more protective against SARS-CoV-2 infection for females rather than males. This fact is of great importance if we consider that this drug is usually prescribed (off-label) only in postmenopausal women, which have a higher risk of developing severe COVID-19. However, all these considerations are theoretical and no data is available yet. To sum up, finasteride administration is currently not associated with a higher risk of contagion or disease severity and, therefore, patients should not be advised to interrupt their therapy.

Minoxidil

Another cornerstone of trichological therapy is minoxidil, a piperidine pyrimidine derivative with vasodilator properties.

Firstly approved for hypertension treatment, it is currently widely used as a first-choice topical treatment both for male AGA and FPHL, at 2 and 5% concentrations. Besides the hypotensive activity (4), minoxidil is able to modify the hair cycle by reducing the telogen phase and prolonging the anagen one. Furthermore, it increases VEGF production, and modifies prostaglandin activity, blocking the production of PGD2 and increasing those of PGE2 and PGF2, with a favorable outcome on hair regrowth. In addition to AGA, this agent is largely prescribed also in other conditions, including alopecia areata (AA), FFA, chemotherapy-induced alopecia (CIA), and telogen effluvium (TE).

No reports are currently available in the literature concerning possible relations between minoxidil and COVID-19. Interestingly, Smeitink et al. hypothesize that PGE2, whose production is increased by minoxidil, has a prominent role in COVID-19 pathophysiology (5).

However, the topical minoxidil effect on prostaglandins is not systemically relevant and, for this reason, therapy prosecution does not imply any risk.

Recently, low-dosage oral minoxidil has been increasingly used for the treatment of AGA and AA. Currently, no data is available to determine whether systemic minoxidil, increasing PGE2 levels, might increase the risk SARS-CoV-2 infection; given this, and also considering the low dosages utilized in trichological disorders, patients under treatment should not interrupt their therapy.

Off-label treatments

Dutasteride

The same considerations previously made for finasteride may be extended also to dutasteride. This off-label treatment for AGA is a selective and competitive 5AR enzymes suppressor, inhibiting both types I and II, while finasteride only blocks type II. Moreover, dutasteride 5AR-II inhibition is three times stronger than the one induced by finasteride (6), leading to a greater reduction of AR activity. Therefore, as suggested by Goner et al. (1), who suppose a protective role of finasteride against SARS-CoV-2 infection, these considerations may be extended also to dutasteride. In addition, by blocking both 5AR-I and -II, dutasteride avoids the risk of T escape previously mentioned as a possible consequence of finasteride. Hence, trichological patients under treatment with dutasteride can safely continue its assumption with no documented risks.

Estrogen and oral contraceptive

Other common off-label treatments used for those FPHL forms which are particularly associated with hormonal alterations, especially hyperandrogenism, are estrogen and oral contraceptive drugs containing estrogen or progestogen.

In our experience, also the topical application of off-label solutions containing 17 α -estradiol is associated with good results in FPHL. 17 α -estradiol is an isoform of 17 β -estradiol incapable to bind to estrogen receptors (ERs). It seems to exert its action by inducing aromatase expression, leading to increased testosterone transformation in 17 β -estradiol and androstenedione in estrone (7).

As mentioned above, ACE2 expression is decreased by estrogens and increased by testosterone, and this consideration

could partially explain why COVID-19 mortality is lower in females than males (3). A recent study proposed the conjugated estrogens drug Premarin as a possible valid therapeutic option for the treatment of COVID-19. As described by the authors, estrogens, by activating ERs, stimulate the immune system against respiratory virus infections (8).

Given this, no risks are associated with the administration of oral contraceptive estrogenic drugs, as well as estrogens contained in lotions, in the context of trichological disorders. On the contrary, we might hypothesize a possible protective role against severe forms of COVID-19.

Steroids

Steroids represent pharmacological agents of great importance for scalp diseases. Although many studies about COVID-19 acute phase treatment with corticosteroids have recently been published (9,10), very little is known about their role in SARS-CoV-2 risk of infection. The American Academy of Rheumatology suggests limiting steroid therapies to the minimum therapeutic dose, as high levels might lead to immunosuppression and increased possibility of infection. It is also recommended not to abruptly interrupt any therapy (11).

At present time, no literature evidence regarding topical steroids treatments and risk of COVID-19 is available but, given that systemic absorption is usually not clinically relevant and that application is usually prescribed for short periods or pulsed, we do not suggest any therapy discontinuing.

Cetirizine

An off-label treatment for AGA and LPP is represented by systemic or topical cetirizine, which is a second-generation histamine-H1 receptor antagonist. Like minoxidil, it inhibits PGD2 with a consequent relative increase in PGE2 and PGF2 (12).

Topical cetirizine should not interfere with COVID-19 pathogenesis, as we previously suggested regarding minoxidil. Concerning the systemic formulation, no data support possible infective risks associated with its assumption. For this reason, trichological patients can safely continue their assumptions for hair and scalp diseases.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is a quinine derivative, prescribed for years as an antimalarial agent and currently used for autoimmune diseases, based on its well-known immunomodulatory and anti-inflammatory properties. In trichological field, HCQ is used for discoid lupus erythematosus (DLE) of the scalp, LPP, and FFA. Recently, it has been successfully used for COVID-19 treatment for its antiviral activity (13).

Consequently, its assumption is not associated with any risk and should not be interrupted.

Antibiotics

Systemic antibiotics are commonly administered in trichological diseases. Minocycline, doxycycline, and azithromycin are used for the treatment of folliculitis decalvans (FD), Dissecting Cellulitis (CD), and scalp furunculosis.

Curiously, both minocycline and doxycycline have been proposed as COVID-19 therapy, in consideration of their anti-

inflammatory activity exerted by suppressing various cytokines including IL-6, which plays a key role in COVID-19 pathogenesis (14,15).

Azithromycin has been largely used to treat COVID-19 in combination with HCQ, but a recent review assesses there is no evidence supporting its use outside of clinical trials (16).

However, no risks are associated with the antibiotic assumption for trichological disorders during COVID-19 pandemic.

Retinoids

Retinoids are commonly used for the treatment of LPP and FD. In fact, besides their well-known activity on keratinocytes proliferation and differentiation, they present an important immunomodulatory action. Interestingly, retinoids possess *in vitro* antiviral effects, which have been observed on human herpesvirus-8, human immunodeficiency virus type 1, herpes-simplex virus 1, polyomavirus, hepatitis B virus, hepatitis C virus. However, their effect on SARS-CoV-2 is unknown (17). Since the lack of evidence concerning retinoids and COVID-19, and considering the hypothesized antiviral properties of retinoids, their administration can be considered safe in trichological patients.

Anti-TNF- α drugs

Anti-TNF- α drugs are used off-label as a treatment for DC (18). These agents have been proposed as a treatment for SARS-CoV-2 infection, in consideration of TNF- α high levels observed in blood and tissues of patients affected by COVID-19 (19).

A recent letter published by Lebwohl et al., regarding biological drugs used for psoriasis, assesses that respiratory infection rates were comparable to placebo during the pre-COVID-19 era (20).

Consequently, its administration for trichological conditions can be normally prosecuted during the pandemic.

Janus kinase inhibitors

An important emerging treatment for AA is represented by Janus Kinase (JAK) inhibitors. These oral drugs interfere with the JAK-STAT pathway, decreasing cytokines production and blocking the positive feedback loop between follicular cells and cytotoxic CD8+ NKGD+T cells, which is at the base of AA pathogenesis (21). Tofacitinib, baricitinib, and ruxolitinib have been proposed and studied for the treatment of AA, with positive results, and good tolerability, even if randomized, double-blind, placebo-controlled trials are currently ongoing (21). JAK inhibitors' main adverse effects are represented by reactivation of latent infections, particularly those affecting the upper respiratory tract (21). Other complications are urinary tract infections, tuberculosis reactivation, herpes zoster, hyperlipidemia, leukopenia, and transaminases alterations.

Stebbing et al. (22) discuss the possible use of baricitinib as a treatment for SARS-Cov-2 infection. Baricitinib is a numb-associated kinase (NAK) inhibitor, with high affinity for AAK1, which is an important regulator of clathrin-mediated endocytosis, inhibiting cells viral entry. Besides this antiviral effect, the authors observe that this drug might be indicated in COVID-19 acute phase treatment because of its important anti-inflammatory properties (22).

Favalli et al. (23) counter the hypothesis advanced by Stebbing and coauthors. In fact, it is important to consider that

JAK inhibitors, such as baricitinib, determine profound alterations of cytokine production, including interferon. The latter is a major component of innate immunity, playing a pivotal role in the prevention of viral infections. Consequently, its impairment could facilitate viral infections, including herpes viruses and coronaviruses. Thus, Favalli et al. suggest that the use of these agents should be cautiously evaluated and eventually discontinued in susceptible patients (23).

Given actual controversial studies, we suggest these drugs should be discontinued in trichological patients.

Platelet-rich plasma

A further common trichological treatment is platelet-rich plasma (PRP) therapy, which consists of local intradermal injections of an autologous blood-derived preparation, rich in cytokines, growth factors, stimulating stem cells proliferation and tissue regeneration (24). In trichology, PRP is frequently used for the treatment of conditions such as AGA, FFA, and LPP.

In our opinion, considering that PRP is an invasive technique, it might be associated with the risk of local infections and virus auto-inoculation, even if such complications are rarely reported (25). Furthermore, we may speculate on a possible risk of infections linked to air pollution. Some reports describe the association between viral respiratory disorders and air pollution (26). Hence, coronavirus may be conveyed through air pollutants and be deposited on the scalp, with subsequent risk of intradermal inoculation in case of procedures such as PRP injections. On bald cutaneous areas, this risk is easily avoided through accurate disinfection of the region, but at the scalp, the local sterilization may be more difficult because of hair. Additionally, PRP might represent a risk of infection for the healthcare professional while performing the procedure. Consequently, PRP treatments should be suspended during this pandemic and replaced with medical therapies. The same advice applies to other invasive treatments for trichological diseases, including needling and mesotherapy.

Vitamins and dietary supplements

Antioxidant agents are often employed in the treatment of hair and scalp diseases as dietary supplements. SARS-CoV-2 is able to elicit cytokine storm and immune-cell infiltration *in vivo*. This leads to the production of a great number of reactive oxygen species (ROS) (27–29), which may damage not only virus-infected cells but also normal cells, driving to multiple organ failure. Many authors reported the use of antioxidant molecules as an adjuvant treatment in patients affected by COVID19, with the aim of reducing ROS-induced damages (30).

Below, we discuss the most commonly prescribed supplements in the trichological field. In all cases, no risks are associated with their assumption and they can be safely administered during COVID-19 pandemic.

Vitamin C

Vitamin C is reported to be an effective trichological treatment thanks to its antioxidant proprieties and its anti-inflammatory and immune-modulator activities.

Moreover, reducing neutrophils accumulation and activations, it is reported to be effective in reducing respiratory distress and in eliminating lung fluids (31). These hypothesis seems to be

confirmed by a recent randomized controlled trial carried out in the United States that showed how the administration of ~15 g/day of intravenous vitamin C for 4 days decreased mortality in patients with sepsis-related Acute Respiratory Distress Syndrome (ARDS) (32). Other studies are currently ongoing (33).

Vitamin D

An important treatment largely prescribed for AA, LPP, and AGA, is vitamin D. Vitamin D is a steroid hormone and a fat-soluble vitamin. Besides its well-known role in bone mineralization, it regulates both innate and acquired immune response by binding to its receptor (VDR) expressed on immune cells like lymphocytes and macrophages. In fact, vitamin D deficiency is a possible trigger for autoimmune diseases. Furthermore, this hormone regulates the proliferation and differentiation of keratinocytes and hair follicle cells influencing hair growth and hair follicle morphogenesis. Its deficiency has been related to alopecia (34).

Grant et al. hypothesize a protective role of vitamin D against influenza viruses and SARS-CoV-2. In fact, vitamin D stimulates cathelicidins and defensins activity, reducing viral replication rates. Moreover, it reduces pro-inflammatory cytokines, which contribute to alveolar damage, leading to pneumonia, and increases anti-inflammatory cytokines levels (35).

Consequently, we suggest that vitamin D supplementation in trichological patients is safe and may be continued, with no higher risk of COVID-19 infection. Actually, based on literature considerations, it might also be considered protective.

Serenoa repens

Serenoa Repens is a plant of the *Arecaceae*'s family, also known as *Sabal serrulata*. It is a natural competitive nonselective inhibitor of 5AR-I and -II, and for this reason, it is used as a treatment of male AGA (36). In consideration of the activities, *Serenoa Repens* shares with dutasteride, the same discussion previously advanced for the latter is valid also for *Serenoa Repens*. Consequently, its assumption is safe with no risks related to infections.

Epigallo-catechin3 gallate and flavonoids

Another molecule with antibacterial, antiviral, and antioxidative activities is epigallo-catechin3 gallate (EGCG), which is contained in green tea. It seems that EGCG may have an immune suppressive role and may also inhibit epithelial-mesenchymal transition EMT (37). Flavonoids are able to block NF- κ B translocation, inhibiting the influenza virus and toll-like receptor signaling (38,39).

Seafood and fish oil extracts

Seafood and fish oil extracts are prescribed in a wide range of inflammatory trichological diseases.

They contain docosahexaenoic acid and eicosapentaenoic acid, which are involved in the inhibition of leucocytes chemotaxis, adhesion molecule expression, and eicosanoid production. Their action seems to be mediated by the interaction with PPAR- γ , with the consequent inhibition of NF- κ B translocation into the nucleus. This leads to the down-regulation of its target genes, among which there are many inflammatory proteins (40).

Turmeric

Turmeric is largely employed in the treatment of many inflammatory disorders, also in trichology (41). Curcumin is the phytochemical component of turmeric. It is able to regulate the expression of numerous transcription factors, cytokines, adhesion molecules, and enzymes related to inflammation (42), and it inhibits TNF- α expression by inducing PPAR- γ up-regulation (41,43).

Also, curcumin reduces PGD2 levels, with a relative increase of PGE2, as previously discussed also for minoxidil and cetirizine.

Melatonin

Melatonin is largely used as a dietary supplement for hair disease because of its beneficial effect on hair. Because of its anti-oxidant and DNA repair inducer properties, melatonin acts as a cytoprotective factor for the high metabolically and proliferatively active anagen hair bulb cells, inducing the anagen phase (44,45).

For the same reasons, melatonin seems to be useful in preventing or reducing the severity of SARS-CoV-2 infection. Indeed, because of its anti-inflammatory, anti-oxidant, and immunomodulant actions, it has a supportive role in the case of sepsis or other critical conditions.

In particular (46,47) it is reported that melatonin suppresses the pro-inflammatory molecule NF- κ B; it stimulates NF-E2-related factor 2 (Nrf2), which seems to be crucial in protecting from lung injury; it causes a reduction in pro-inflammatory cytokines and an increase in anti-inflammatory IL-10 levels; it regulates NOD-like receptor 3 (NLRP3) inflammasome; it improves the proliferation and the maturation of natural killer cells, T and B lymphocytes, granulocytes and monocytes; it also improves antigen presentation by macrophages; moreover, melatonin may reduce the massive and prolonged stress, anxiety and sleep deprivation, which derives from the COVID-19 societal crisis (46,47).

Conclusion

In this paper, we thoroughly examined the most common drugs used in the trichological field, with the aim of discussing their safety and of assessing their possible impact on SARS-CoV-2 infection. Based on our experience and on careful research of the current literature, in the majority of cases, we considered the trichological therapeutic agents safe, with no specific infectious risks associated with their assumption. However, in some cases, their administration should be carefully evaluated and eventually suspended. We hope that this work could represent a useful guide for the therapeutic management of trichological patients in this new COVID-19 era.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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