Caution in the management of SARS-CoV-2 infection in males

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Caution in the management of SARS-CoV-2 infection in males

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Abstract

The coronavirus 2 (SARS-CoV-2) pandemic carries clinical, economic and social burdens that are currently being disclosed. The key steps of virus life cycle have been recently clarified, highlighting the role of host type 2 angiotensin converting enzyme (ACE2) and TMPRSS2 serine protease in virus-cell binding and entry, respectively. Importantly, major concerns derive from the androgen-dependent tissue-expression of

both TMPRSS2 and ACE2, suggesting a differential clinical course of the infection between genders. In agreement with this model, available epidemiological data show that the disease in males has an higher risk to display an heavier pattern and associates with both an increased access to critical care unit and higher mortality rate.

In this opinion article, available evidence linking the androgen activity with the gender differences observed in SARS-CoV-2 infection are discussed, hypothesizing possible therapeutic approaches in male based on the disruption of androgen signaling. On these bases, gender-specific recommendations for the management of male patients affected by SARS-CoV-2 infection are warmly suggested, in order to improve the clinical course of the disease.

Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection disease (COVID-19) has rapidly risen as a novel breakthrough pandemic, spreading from the Hubei province in China to all around the world [1-4].

The cell-cycle of SARS-CoV-2 has been very recently clarified and, to this regard, two major host proteins have been involved in the cell-virus entry and triggering of the virus cell-cycle: type 2 angiotensin converting enzyme (ACE2) and serine-protease TMPRSS2, respectively [5]. In detail, by the use of replication-defective vesicular stomatitis virus (VSV) particles bearing SARS-CoV-2 spike (S) proteins, authors showed that anti-human ACE2 polyclonal antibodies were effective in specifically blocking viral entry in Vero cell line. In addition, authors demonstrated that SARS-CoV-2 protein undergoes to priming by cell endosomal in order to be internalization by host cells, however only TMPRSS2 serine-protease is essential for viral spread and pathogenesis, according to previous reports on SARS-CoV [6-9]. In agreement with the key pathogenic role in SARS-CoV-2 infection, the treatment with TMPRSS2 inhibitor *camostat mesylate* significantly reduced infection of primary human lung cells with SARS-CoV-2 [5].

A rising concern in regard of the SARS-CoV-2 infection is represented by the androgen-dependent tissue-expression of both TMPRSS2 and ACE2. Indeed, a highly compelling factor is represented by the androgen-dependency of TMPRSS2 activity, particularly at prostate level where this serine-protease is

expressed at the highest level compared to all other body tissues [10,11]. In fact, the androgen-responsive element is the only known transcription promoter for the TMPRSS2, although even estrogen and glucocorticoid can enhance the TMPRSS2 expression through the binding of their respective receptor to their responsive elements, accounting for both the persistent expression of TMPRSS2 in castrated men with a resistant form of prostate cancer, and for the severity of some forms of the COVID-19 infection in female patients subpopulations [12,13]. Moreover, the androgen-dependency of TMPRSS2 has been strongly associated with the acquired tumor growth and invasiveness of prostate cancer, particularly when TMPRSS2-ERG gene fusion is observed [14-17]. Of note, data from murine models showed that the androgenic control of TMPRSS2 expression is maintained also at lung level [18]. On the other hand, studies in animal models have also involved sex steroids with the regulation of blood pressure through the expression of the angiotensin-converting enzyme (ACE)/ACE2 system. In particular, the enzyme activity of ACE in lung is equally increased in both male and female upon gonadectomy, whilst both ACE and ACE2 activities showed significant downregulation in myocardial tissues of orchiectomized male rats, suggesting some tissue-specific androgenic control of this enzymatic system [19-20].

These data are supportive of the observed sex-related severity of SARS-CoV-2 infection. Several studies have reported a higher rate of severe cases in adult males compared to females, ranging from 58% to 67% [21,22]. According to the last available sex-related analysis from Italian "Istituto Superiore di Sanità" [23] on 25,058 patients, the infection rate is barely different between males and females (48.8% and 51.2%, respectively). However, the lethality rate accounts for 7.9% in men and 4.1% in women, with 70% of total deaths being men (Italian Ministry of Health (2020) https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_22aprile%20ITA.pdf). Data from retrospective cohort-studies in China also showed that male gender is a major risk factor for higher disease severity, unimprovement and mortality [24]. These data are confirmed by the global information from intensive care services, showing an average access to intensive care units doubled for males compared to females, and suggesting some kind of gender-related factor worsening factor of the SARS-CoV-2 infection [22,25,26].

On these bases, if the expression of ACE2 and TMPRSS2 represents a key factor for the infection and spreading of the SARS-CoV-2, an attractive therapeutic strategy to improve the treatment of virus infection could be then represented by the downregulation of both ACE2 and TMPRSS2 expression at lung level. Given the aforementioned androgenic control of these two enzymes, this effect could be achieved by the androgen deprivation therapy (ADT). Indeed, ADT is associated with efficient prostate cancer cell death and downstream reduction of TMPRSS2 expression through the disruption of androgen signaling [27,28]. Importantly, the same pattern is observed also in extra-prostate tissues, since the application of ADT in *ex vivo* rat model of lung culture associates with the reduction of tissue TMPRSS2 transcriptions [18]. Taken together, these evidence suggest that the same ADT used as adjuvant therapy in prostate cancer may

represent a suitable strategy to downregulate the host SARS-CoV-2 receptors at lung level and to control the observed clinical complications of the viral infection in males. In a recent study, Cava et al. provided some support to this working hypothesis. By the use of a computational approach, authors evaluated the protein-protein interaction network of ACE2 in epithelial lung cells with the aim to identify potential drugs supposed to interfere with SARS-CoV-2 cell cycle. Strikingly, the androgen receptor antagonist flutamide emerged among the 36 drug candidates, based on the regulatory role of AR on ACE2 [29].

Importantly, the aforementioned tissues-specific androgenic control of ACE2 should be taken into consideration since, in murine kidney, the chronic treatment with flutamide significantly altered the renin-angiotensin system without affecting expression ACE2 [30]. However, a possible confirmation of the proposed model has been provided by a very recent study from Montopoli et al. [31]. Through a population-registry based approach conducted on the Veneto Italian Region, authors showed that whether the underlying cancer disease represents a mortality risk factor for SARS-CoV-2, the administration of ADT in prostate cancer patients with SARS-CoV-2 infection was associated with a fourfold lower risk of death compared to those patients that did not received ADT. A similar pattern of protection was observed also from the comparison between prostate cancer patients receiving ADT and patients with any other type of cancer, showing a fivefold lower risk of death associated with the administration of adjuvant ADT.

Currently, the application of ADT to non-cancer patients with SARS-CoV-2 infection retains an exclusive theoretical nature. Several pharmacodynamic and pharmacokinetic concerns have to be addressed since the known markers of anti-androgen drug response may take several days to be achieved, which is rather in contrast with the typical acute treatment of a SARS-CoV-2 patient [32]. Individual upregulation of ACE2 expression has also been hypothesized as possible compensatory response to long term ADT, in analogy to what recently observed in other classical target tissues of androgens such as skeletal muscle [33]. In addition, men receiving ADT are at higher risk of long-term exacerbation of other life threatening comorbidities such as cardiovascular disease, diabetes, obesity and osteoporosis [34]. However, there is a vast experience in the management of the anti-androgen therapy which today can count on a variety of molecules and protocols already validated in the treatment of prostate cancer [27]. To this regard, the likely future scenario could be represented by an adjuvant anti-androgen treatment associated with an acute anti-viral therapy with *camostat mesylate*, whose clinical efficiency in the treatment of SARS-CoV-2 infection is currently under investigation with a specific randomized control trial [https://clinicaltrials.gov/ct2/show/NCT04321096].

Based on these considerations it is strongly suggested that National Health Agencies quickly draft straightforward recommendations for the clinical management of male patients affected by SARS-CoV-2 infection. In addition, physicians should adopt gender-specific therapeutic approaches in order to improve the clinical course of the disease.

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